

THE EGYPTIAN UROLOGICAL GUIDELINES

1st Edition – 2021

A collaboration of The Egyptian Society for Urologic Research
& The Supreme Council of University Hospitals

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Acknowledgement

It is my pleasure to express my sincere appreciation to all the hard work and diligent effort that have been put into the completion of the “Egyptian Urological Guidelines”.

It was a persistent hard work and effort in the field of Urology that has given us a fruitful result that eventually came to light by the hands of a group of brilliant professors and field experts under the supervision of the Editorial Board.

These guidelines represent the first Egyptian medical guidelines which will not only be the cornerstone for the standardization of health care but also will allow to provide a safe, evidence-based, and effective health services.

Eventually we would like to extend our appreciation to everyone who shared in the construction of such work which will pave the way for other Egyptian medical guidelines to follow.

Professor Dr Khaled Abdel Ghaffar
Minister of High Education

Forward



It gives me immense pleasure to witness the creation of the Egyptian guidelines for Urology which is of a great importance and would be the reference for the Egyptian Urologists.

I would like to express my sincere gratitude to the “Egyptian Urological Guidelines Board members for their dedication, hard work and their willingness to contribute their time and commitment to excellence the creation of these valuable guidelines which will be related to the university hospital facilities.

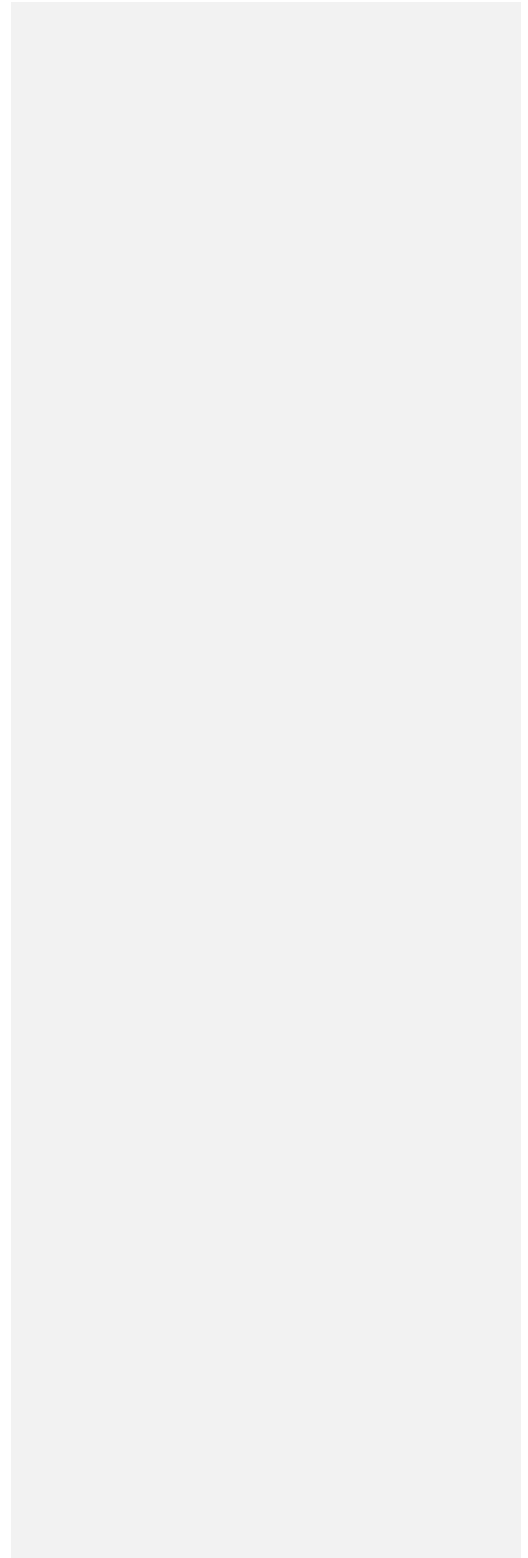
This will be an authorized landmark for the future practice of Urology in Egypt.

I extend my best wishes for all our Egyptian doctors and professors.

Professor Dr Hossam Abdel Ghaffar
Secretary of the Supreme Council
of University Hospitals

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Preface



It is a real honor to be appointment as the board director of the “Egyptian Urological Guidelines”. We at the board value the trust given to us by the “Minister of High Education” and the “Secretary of the Supreme Council of University Hospital” to take over this mission.

This critical mission was a real challenge to create a subject that is already available by other international societies. The important edition was to fashion the already existing guidelines to the Egyptian culture, the doctors training levels and the different ranges of hospitals equipment.

The board played a major role in the assignment of the chairs and members of each committee and in achieving our methodology of research and writing. The 14 committees included more than 80 experts from every city of Egypt who were selected according to their pre-eminence in their topic area.

The “Egyptian Urological Guidelines” is a very important tool that will be used by all the Egyptian urologists as a reference to their practice in different hospitals, either in the governmental or in the private sectors.

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Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS)



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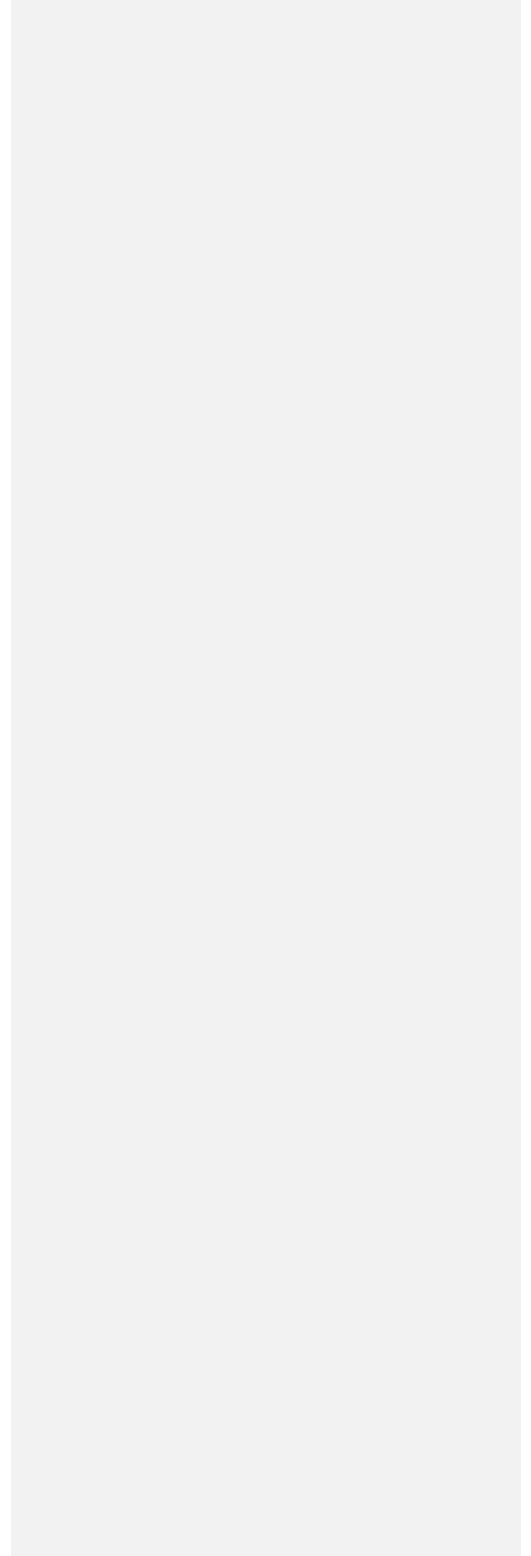


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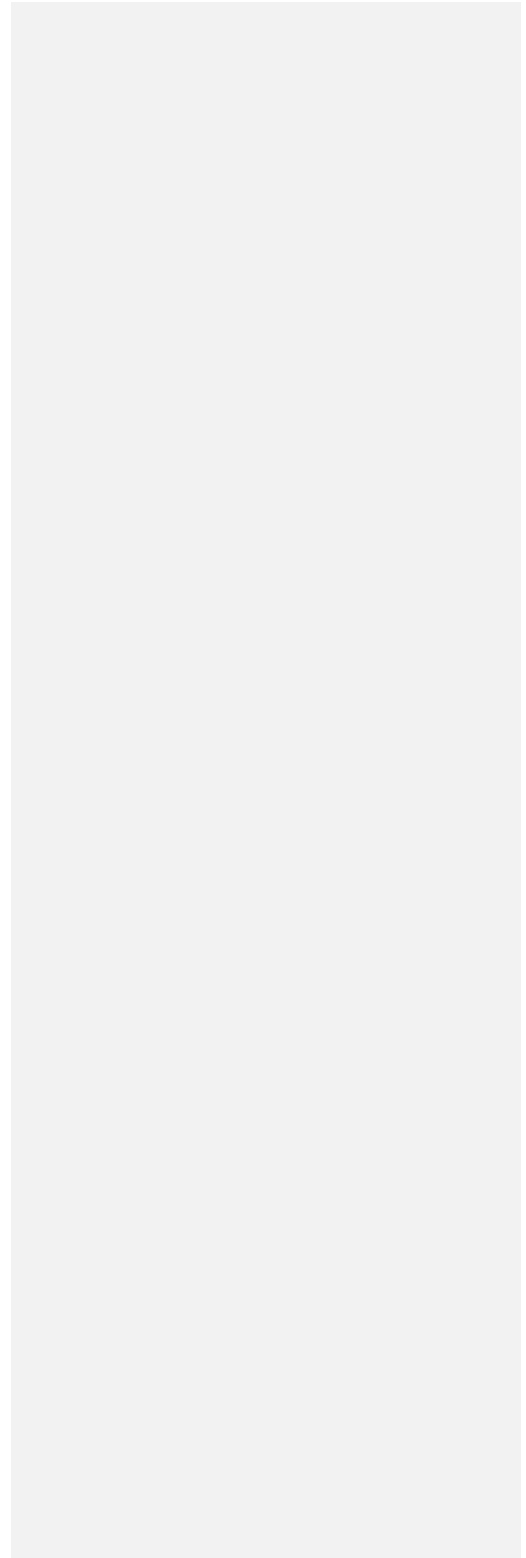


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Egyptian Urological Guidelines on Male Non-Neurogenic LUTS



and Male Incontinence



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1 List of Abbreviations

5-ARIs	5 α -Reductase Inhibitors
AUA	American Urologic Association
AUR	Acute Urinary Retention
AUS	Artificial Urinary Sphincter
B-TURP	Transurethral Bipolar Resection of Prostate
BEP	Bipolar Enucleation of the Prostate
BOO	Bladder Outlet Obstruction
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
BVP	Bipolar Vaporization of Prostate
CAM	Complementary and Alternative Medicines
CAU	Canadian Urologic Association
CKD	Chronic Kidney Disease
CPU	Conformal Planning Unit
CT	Computed Tomography
DHT	Dihydrotestosterone
DO	Detrusor Over activity
DRE	Digital Rectal Examination
EAU	European Urological Association
eGFR	Estimated Glomerular Filtration Rate
EjD	Ejaculatory Dysfunction
EUG	Egyptian Urological Guidelines
FVC	Frequency Volume Charts
HoLEP	HoLmium Laser Enucleation of Prostate
ICS	International continence society
IFIS	Intra-Operative Floppy Iris Syndrome
IPP	Intravesical Prostatic Protrusion
IPSS	The International Prostate Symptom Score
IPSS-Arb	Arabic version of the IPSS
KTP	Potassium-Titanyl-Phosphate
LBO	Lithium Triborate
LUTS	Lower Urinary Tract Symptoms
M-TURP	Monopolar Transurethral Resection of Prostate
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health Care Excellence
OP	Open Prostatectomy
OP	Open Prostatectomy
PAE	Prostatic Artery Embolization

PCa	Prediction Of Carcinoma Of The Prostate
PDE5Is	Phosphodiesterase 5 Inhibitors
PFS	Pressure flow study
PMD	Post Micturition Dribble
PPI	Post-prostatectomy Urinary Incontinence
PSA	Prostate-Specific Antigen
PUL	Prostatic Urethral Lift
PVP	Photoselective Vaporization of Prostate
PVR	Post-Void Residual Urine
QoL	Quality of Life
ThuLEP	Thulium Laser Enucleation of Prostate
TRUS	Transabdominal or Transrectal US
TUIP	Transurethral Incision of The Prostate
TUMT	Transurethral Microwave Therapy
TUNA	Transurethral Needle Ablation
TURP	Transurethral Resection of The Prostate
UDS	Urodynamic studies
UTI	Urinary Tract Infection
VGUG	Voiding Cystourethrogram

2 Abstract.

2.1 Objective

This overview represents the updated recommendations for diagnosis and management of non-neurogenic male lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). It also provides an updated scheme for the management of male urinary incontinence. This document integrates recent international guidelines with local experts' opinions based on Egyptian healthcare and socioeconomic circumstances.

2.2 Method

Databases searched included Medline, Cochrane Libraries, EAU guidelines, ICS recommendations, 6th ICI recommendations, AUA and NICE guidelines, from January 2018 to September 2020.

Review of several meta-analyses, leading institutional protocols and relevant Egyptian publications were taken into consideration. All statements were graded according to strength of recommendation. Each statement was given a strength rating (strong or weak).

2.3 Result

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

2.4 Conclusion

The understanding of the LUT as a functional unit, and the multifactorial aetiology of associated symptoms, means that LUTS now constitute the main focus, rather than the former emphasis on BPH. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

3 Introduction

- This overview represents the updated recommendations for diagnosis and management of non-neurogenic male lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). It also provides an updated scheme for the management of male urinary incontinence.
- It must be emphasized that the Egyptian guidelines can never replace the clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions, taking in consideration the personal values, expectations, preferences and individual circumstances of patients and the physician's preferences.

3.1 Methodology

- Our recommendations are the outcome of integrating 3 resource categories:
 - Five guidelines (including their latest updates), namely, European Urological Association (EAU), American Urologic Association (AUA), National Institute for Health Care Excellence (NICE) and Canadian Urologic Association (CAU) and International continence society (ICS) ⁽¹⁻⁵⁾.
 - Review of several guides, recommendations, position statements, meta-analyses and leading institutional protocols.
 - Relevant Egyptian publications.
- All statements were graded according to strength of clinical practice recommendations, expressed as strong or weak. While this was guided by other guideline recommendations, it was modified to suit the Egyptian environment dominated by a rich bioecological environment, specific demographics and social constraints and limited financial resources.

3.2 EPIDEMIOLOGY

- LUTS in elderly men due to BPH are very common. El-Gilany et al. ⁽⁶⁾ in their study found that despite the high prevalence of severe symptoms among the targeted elderly, only 16% of them sought medical advice. Little is known about the quality of life (QoL) of these elderly males with BPH in Egypt, and there is no community-based studies on the magnitude of the problem of BPH among elderly men in Egypt.

-

4 DIAGNOSTIC EVALUATION (Medical History)

- Full medical history is the cornerstone in the diagnosis of the causes, identifying the complications and comorbidities and knowing patients' expectations and QoL. During this step, physicians must focus on neurologic symptoms, drugs intake [especially anticoagulants] and previous surgeries. Patient's erectile function and sexual history should be reviewed thoroughly ^(6,7).

4.1 DIAGNOSTIC EVALUATION

- Symptom score questionnaires are important in quantifying patient's symptoms and in detection of the predominant symptoms. They are not disease specific, but they can be used to monitor and follow-up treatment outcomes. These include:

4.1.1 The International Prostate Symptom Score (IPSS)

- It is based on the answers of seven questions concerning urinary symptoms and one question concerning QoL. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increased severity of the particular symptom. The answers are assigned points from 0 to 5. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic). The IPSS score is categorized as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderately symptomatic' (8-19 points), and 'severely symptomatic' (20-35 points).

4.1.2 Arabic version of the IPSS (IPSS-Arb)

- An Arabic version of the IPSS (IPSS-Arb) was developed through a series of translations and modifications. The validity and reliability were assessed. The IPSS-Arb is shown to be a reliable and valid instrument for patients with BPH. It can be used in patient assessment, follow-up, and in research involving Arabic-speaking patients. ⁽⁸⁾

-

5 DIAGNOSTIC EVALUATION (Assessment of erectile function)

- Male erectile function has significant impact on QoL especially in those who are suffering from BPH. There is a strong correlation between the severity of sexual dysfunction and the severity of LUTS. It should be taken into consideration that all treatment options of BPH affect sexual function. Medical, surgical, and minimally invasive treatment options differ in their effect on erectile function, ejaculation, and sexual satisfaction. Choice of treatment modality takes into account baseline sexual function and patient expectations. ^(1,2)

5.1 Diaries

- Urinary diaries include frequency volume charts (FVC) and bladder diary. Frequency volume chart is a simple recording of the voided urine volume and time of the void [day and night]. Bladder diaries include more details such as fluid intake, episodes of incontinence, number of pads and possible associated symptoms. Bladder diary of at least 48 hours seem to be the most defensible policy ⁽⁹⁾.

5.2 Physical examination, digital rectal examination (DRE) and focused neurologic examination.

Examination for BPH includes abdominal, digital rectal and a focused neurological examination. Abdominal examination is done to detect palpable bladder [in cases of urinary retention] and other abdominal masses. The DRE starts with assessment of perianal sensation, anal tone, prostate size and contour. DRE is a good test for identifying enlargement above a threshold value, as occurs in benign and malignant disease; it has not yet proved to be a good quantitative measure of prostate gland enlargement ⁽¹⁰⁾

5.3 Urine Analysis

It is a simple, rapid and low-cost test that can detect microscopic hematuria, urinary tract infection (UTI), glycosuria and other pathologic conditions of the urinary tract.

5.4 Renal function measurement

Serum creatinine or estimated glomerular filtration rate (eGFR) are the commonly used methods for renal functions' assessment. Eleven percent of men with LUTS shows renal insufficiency, diabetes mellitus or hypertension which usually lead to elevated renal functions. ⁽¹¹⁾ Hong et al. ⁽¹²⁾ showed that in hypertensive patients who presented with LUTS, low Qmax was associated with chronic kidney disease (CKD). The risk of post-operative complications is higher in patients with renal impairment ⁽¹³⁾.

5.5 Prostate-specific antigen (PSA)

The role of PSA assessment in male with LUTS due to BPO (benign prostatic obstruction) includes prediction of prostatic volume ⁽¹⁴⁾ and Prediction of BPO-related outcomes. Serum PSA is a good predictor of prostate growth ⁽¹⁵⁾, changes in symptoms, QoL/bother, and maximum flow-rate (Qmax) ⁽¹⁶⁾, clinical progression ⁽¹⁷⁾, the risk of acute urinary retention (AUR) and BPE-related surgery risk for treatment [higher in men with a baseline PSA of > 1.4 ng/ml] ⁽¹⁸⁾.

5.5.1 Prediction of carcinoma of the prostate (PCa)

The potential benefits and harms of screening of serum PSA to diagnose PCa in men with LUTS should be discussed with the patient.

5.6 Post-void residual urine [PVR]

Noninvasive method for assessment of PVR is the transabdominal Ultrasound (bladder scan), while catheterization is considered an invasive method. In cases of high PVR volumes, bladder outlet obstruction (BOO) and/or detrusor underactivity should be considered ⁽¹⁹⁾.

Large PVR may indicate a poor response to medical treatment and changes in PVR over time can detect increased risk for AUR, with elevated chances when prescribing anti-muscarinics for these patients. ⁽²⁰⁾

PVR value represents clinical and medical research challenge, as its value is extremely variable and no known cut-off PVR thresholds have been correlated to various diagnostic or surgical outcomes.

5.7 Uroflowmetry

It is an initial non-invasive test to give crude estimate of the voiding phase. It entails measuring the voided volume, Qmax, flow pattern and PVR. Low Qmax means BOO, DUA or an under-filled bladder. Uroflowmetry should be repeated if voided volume is less than 150 ml. ⁽²¹⁾

Qmax of 10 mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for diagnosis of BOO. If Qmax is > 15 mL/s, the result is considered equivocal and BOO cannot be excluded. Uroflowmetry can be used for following up of the treatment outcomes and quantifying patient's symptoms. ⁽²¹⁾

5.8 Imaging

5.8.1 Upper urinary tract imaging

Ultrasound allows for assessment of renal masses, hydronephrosis and simultaneous evaluation of the bladder, PVR and prostate size and morphology. It can be used for the evaluation of haematuria, or urolithiasis. Ultrasound is of lower cost, radiation free ⁽²²⁾, however it is operator-dependent.

5.8.1.1 Imaging of the Prostate

Prostate imaging is mostly done by transabdominal or Transrectal US [TRUS]. Other imaging modalities include computed tomography (CT), and magnetic resonance imaging (MRI). Prostate volume predicts symptom progression and the risk of complications. ⁽²²⁾

It's important to assess prostate size and shape prior to treatment with 5 α -reductase inhibitors (5-ARIs) and before choosing the surgical treatment modality [open prostatectomy (OP), enucleation techniques, transurethral resection, transurethral incision of the prostate (TUIP), or minimally invasive therapies]. Transrectal US is superior to transabdominal route for assessment of volume of prostate ⁽²³⁾. Median lobe enlargement is considered a contraindication for some minimally invasive treatments.

5.8.1.2 Urodynamic (UDS)

Pressure flow study (PFS) and filling cystometry are performed to assess male LUTS due to BPO. The role of urodynamic testing in male LUTS due to BPO includes identifying the pathophysiologic events in patients with LUTS during voiding, predicting the outcomes of treatment especially when invasive surgical intervention is considered and making causal diagnosis in patients with inconclusive other tests. Urodynamic tests also differentiate between bladder outlet obstructions [BOO], detrusor underactivity and detrusor overactivity. ⁽²⁴⁾

5.8.2 Non-invasive tests in diagnosing BOO in men with LUTS

These tests include prostatic configuration/intravesical prostatic protrusion (IPP) ⁽²⁵⁾, Bladder/detrusor wall thickness and ultrasound-estimated bladder weight ⁽²⁶⁾. Other non-invasive urodynamic testing includes penile cuff method (external condom), Prostatic urethral angle and Resistive index ⁽²⁷⁻²⁹⁾ are not validated for use in the assessment of male LUTS.

Table 1: Recommendations for diagnosis of male non-neurogenic LUTS

Recommendation	Strength Rating
1. Take a complete medical history from men with LUTS	Strong
2. Use IPSS or its validated Arabic form in the primary assessment of male LUTS, monitoring treatment response and for research purposes	Strong
3. Consider assessment of patients' sexual function before starting any modality of active treatment for BPH [medical, surgical or minimally invasive]	Strong

Recommendation	Strength Rating
4. Advise the BPH patient to record a bladder diary for at least 48 hours	Strong
5. Perform physical examination, DRE and focused neurological examination for male patients with LUTS	Strong
6. It is crucial to perform urinalysis for male patients with LUTS.	Strong
7. Assess renal functions if: -Evidence of Renal impairment (based on history and clinical examination) -Hydronephrosis -Before surgical treatment for male LUTS.	Strong
8. PSA measurement is important if it helps in the diagnosis or selecting treatment option for LUTS due to BPO.	Strong
9. Measure prostate-specific antigen (PSA) if a diagnosis of PCa will change management. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient.	Strong
10. Measure PVR in the initial assessment of male LUTS and before prescribing medical treatment for BPH, using transabdominal ultrasound	Strong
11. Perform uroflowmetry in the initial assessment of male LUTS.	Weak
12. Perform uroflowmetry before starting medical or invasive treatment and for follow-up to assess the treatment outcomes.	Strong
13. Perform ultrasound of the upper urinary tract in men with LUTS if there is elevated renal functions	Strong
14. Perform prostate imaging when considering 5-ARIs treatment for male LUTS or considering surgical treatment	Strong

Recommendation	Strength Rating
15. Voiding cystourethrogram (VGUG) is not recommended in the routine diagnostic work-up of men with BPH	Strong
16. Retrograde urethrography may additionally be useful for the evaluation of suspected urethral strictures	Strong
17. Urethrocystoscopy should be performed in men with LUTS before invasive or minimally invasive treatment if the endoscopic findings may change the treatment option	Strong
18. Patients with history of microscopic or gross hematuria, urethral stricture, or bladder cancer who present with LUTS should undergo urethrocystoscopy during diagnostic evaluation	Strong
19. Pressure-flow studies (PFS) should be individualized according to certain indications prior to invasive treatment: 1. In men who have had previous failed invasive treatment for their LUTS 2. In men undergoing invasive treatment for their LUTS and cannot void > 150 mL. 3. In men with bothersome voiding LUTS considering invasive treatment and high Qmax > 10 mL/s or high post void residual > 300 mL. 4. In men with bothersome voiding LUTS considering invasive treatment with aged < 50 years or > 80 years. 5. In men with BPH and known or suspected neurological diseases (multiple sclerosis, Parkinsonism, lumbar disc prolapse, diabetes mellitus) considering invasive treatment	Strong
20. Do not offer non-invasive diagnostic tests as an alternative to pressure-flow studies for diagnosing BOO in men	Strong

6 Conservative treatment (*Watchful waiting, WW*)

Minority of the men who are not bothered by their LUTS may occasionally progress to AUR and complications, however hand most of them (about 79 %) usually remain stable for many years⁽³⁰⁾.

Studies comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed that the surgical group had improved bladder function (flow rates and PVR volumes), especially in those with high levels of bother. 36% of WW patients crossed over to surgery within five years, leaving 64% doing well in the WW group⁽³¹⁾. Increasing symptom bother and PVR volumes are the strongest predictors of clinical failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW, which is a type of strategy in which the patient is receiving no treatment but on the other hand he is regularly followed- up by his health care provider⁽³²⁾

Table 2: Recommendations for conservative treatment of male non-neurogenic LUTS due to BPH.

Recommendations	Strength Rating
1. Patients should share in decisions about their care and treatment with their healthcare providers.	Strong
2. Men who are troubled by their symptoms should be assessed prior to treatment to establish symptom severity and detect complications (most patients are uncomplicated and mild to moderate symptoms)	Strong
3. Watchful waiting (active surveillance) should be offered as the preferred option in: - All patients with mild symptoms of LUTS secondary to BPH (AUA-SI score <8) - Patients with moderate or severe symptoms (AUA-SI score ≥8) who are NOT bothered by their LUTS	Strong
4. Drug treatment can only be offered when conservative therapy has failed or is not appropriate	Strong

Recommendations	Strength Rating
5. Lifestyle advice, behavioural and dietary modifications are part of WW. This entails education about the natural history of the disease, reassurance (that BPH is not precancerous) and periodic monitoring (first time after 6 months, then yearly as long as there is no deterioration of symptoms and/or appearance of new complaints. Lifestyle advice includes: I. Restriction of fluid intake at specific times e.g., at night or when going out in public) II. Avoidance/moderation of intake of caffeine or cola, which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia III. Use of double-voiding techniques IV. Urethral milking to prevent post-micturition dribble V. Reviewing the medications and optimising the time of administration or substituting drugs for others that have fewer urinary side effects V. Treatment of constipation	Strong

7 Pharmacological treatment

7.1 Alpha Blockers

The prostate and bladder neck have α -adrenergic innervation which is responsible for the “dynamic” component of bladder outlet obstruction. The bladder neck and trigone receptors and also the receptors in the prostate capsule are mainly alpha-1A. Alpha blockers are thought to work by relaxing smooth muscles thereby reducing this resistance and improving symptoms and flow rate ⁽³³⁾

α 1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events. ⁽³⁴⁾

Alpha-1-blockers can reduce both storage and voiding LUTS. IPSS reduction and Qmax improvement during α 1-blocker treatment appears to be maintained over at least four years ⁽³⁵⁾

Indirect comparisons and limited direct comparisons between α 1-blockers demonstrate that all α 1-blockers have similar efficacy in appropriate doses ^(36,37)

Selective alpha 1-A blockers (Tamsulosin and Silodosin) are as effective as older non-selective alpha blockers (Alfuzosin, doxazosin, terazosin), however with less likely cardio-vascular events that are common with the non-selective alpha blockers (postural hypotension, dizziness and ECG changes).

Neither prostate size nor age correlate with α 1-blocker efficacy in short term (less than one year) follow-up studies, however α 1-blockers seems to be more effective in patients with smaller prostates (< 40 mL) in longer-term studies ⁽³⁸⁾. Until recently Alpha 1-blockers seemed to have no effect on AUR prevention in long-term studies, however, recent evidence suggests that their use may improve resolution of AUR ⁽³⁹⁾.

The first report on intra-operative floppy iris syndrome (IFIS) was in cataract surgery in 2005. Meta-analysis showed that patients using α 1-blockers, whatever the type, has IFIS increased risk. However, the risk for IFIS was much higher for tamsulosin. ⁽⁴⁰⁾ Ejaculatory dysfunction (EjD) seems to be reported more common with α 1-blockers than with placebo. Tamsulosin and silodosin reported statistically high incidence of EjD than placebo. On the other hand, both doxazosin and terazosin were associated with less incidence of EjD ⁽⁴¹⁾.

7.2 5- alpha reductase inhibitors

The androgen that nourishes the prostate gland is dihydrotestosterone (DHT), which results from reduction of testosterone by the enzyme 5 α -reductase.

5-alpha reductase has two-types:

Type 1: predominant expression and activity in the skin and liver (finasteride)

Type 2: predominant expression and activity in the prostate (dutasteride)

The main effect of 5 α -reductase inhibitors is inducing apoptosis of prostatic epithelial cells ⁽⁴²⁾, thus reducing the prostate volume by about 18-28% after six months. They also cause a decrease in circulating PSA levels of about 50% after six to twelve months of treatment ⁽⁴³⁾. Contrary to alpha blockers, in the PLESS study, finasteride reduced the relative risk of AUR by 57% and need for surgery by 55% (absolute risk reduction 4% and 7%, respectively) at four years, compared with placebo ⁽⁴⁴⁾. Furthermore, finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation. ⁽⁴⁵⁾

The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, erectile dysfunction and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume. They may also cause gynecomastia and breast tenderness.

7.3 Muscarinic Receptor Antagonists

Bladder contraction is mediated via the parasympathetic cholinergic nerves. Anticholinergics may also reduce the sensation of urgency during bladder filling and therefore increase the functional bladder capacity. Antimuscarinics (anticholinergics) improve the storage component of male LUTS whether due to BPH or not. Antimuscarinics reduce frequency, urgency, and urgency incontinence episodes ⁽⁴⁶⁾. They may be used in elderly men and those with significant BOO. There is little evidence of safety in men with high PVRs, however some guidelines prefer cut-off value of 150 ml ⁽¹⁾ while others suggest 250 ml ⁽⁴⁾. Evidence shows that alpha-blockers combination with antimuscarinics can improve men with both voiding and storage symptoms ⁽⁴⁷⁾.

Adverse events include dry mouth, dizziness, cognitive affection, dry eyes, constipation and theoretical risk of urine retention in males with increased PVR. They should not be used in patients with narrow-angle glaucoma.

7.4 Phosphodiesterase 5 inhibitors

The exact mechanism of PDE5Is on LUTS is not completely understood. Many theories have been suggested including reduced smooth muscle tone of the detrusor, prostate and urethra, while others suggest alleged altered reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder. Increase blood perfusion and oxygenation in the LUT have also been suggested, together with an anti-inflammatory effect on the prostate and bladder ^(48,49).

Clinical trials of several selective oral PDE5Is have been conducted in men with LUTS and all of them showed good efficacy in treatment of LUTS due to BPH, however only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS due to its longer half-life. The noted reduction in LUTS was not correlated to age, pre-treatment testosterone level or prostate volume ⁽⁵⁰⁻⁵²⁾. PDE-5 inhibitors are contraindicated in patients who have had a recent myocardial

infarction, unstable angina pectoris or stroke, or those using the non-selective α 1-blockers doxazosin and terazosin, nitrates, potassium channel opener nicorandil. Phosphodiesterase 5 inhibitors improve IPSS, QoL and IIEF score, but not Qmax.

7.5 Beta-3 agonists

Beta-3 adrenoceptors are the main beta receptors distributed in smooth muscle cells of the detrusor and when stimulated, detrusor relaxation occurs ⁽⁵⁴⁾. It has been shown that this category of drugs significantly improves all OAB symptom score items and also improves the storage sub-score of the IPSS when studying their add-on effect to alpha blockers ⁽⁵⁵⁻⁵⁶⁾.

7.6 Phytotherapy or Complementary and Alternative Medicines (CAM)

Many studies and Cochrane meta-analyses report no statistically significant improvement in IPSS, Q max, PVR, QoL and prostate volume between different phytotherapies compared to placebo ^(57,58).

7.7 Combination therapies

Many authors have tested the efficacy of combination therapy of an α 1-blocker, 5-ARI or placebo alone and shown that combination therapy was superior to monotherapy in most of the measured parameters, however the frequency of adverse events was more in combination therapy ⁽⁵⁹⁻⁶¹⁾.

Combination treatment with α 1-blockers and antimuscarinics or beta-3 agonists is effective for improving LUTS-related QoL impairment. These combinations are more effective for reducing urgency, UII, frequency, nocturia, or IPSS compared with α 1-blockers or placebo alone for up to one year ⁽⁶²⁻⁶⁴⁾.

A combination of PDE5Is and α -blockers has also been recently studied and showed that the combination is better than α -blockers alone ⁽⁶⁵⁾. The combination of PDE5Is with 5 alpha reductases have been also studied but to a lesser extent ⁽⁶⁶⁾.

7.8 Desmopressin

As per table 3.

7.9 Post micturition dribbling

Post void urethral milking is a technique used to eliminate post micturition dribble (PMD), which is not associated with obstruction but may be caused by the urethra being emptied incompletely by the muscles surrounding it. This technique involves drawing the tips of the fingers behind the scrotum and pushing up and forward to expel the pooled urine ⁽⁶⁸⁾.

Table 3: Recommendations for pharmacological treatment of male LUTS due to BPH

Recommendations	Strength Rating
1. Offer alpha 1-adrenergic blockers (Alpha Blockers available in Egyptian market: alfuzosin, doxazosin, terazosin, tamsulosin and Silodosin) as the first line treatment option for patients with bothersome, moderate to severe LUTS secondary to BPH (AUA-SI score ≥ 8),	Strong
2. Offer alpha 1-adrenergic blockers for those who failed conservative treatment as a first line treatment	Strong
3. Give the patient a period of 2 weeks to fully appreciate the clinical effect of the prescribed alpha blocker, however significant efficacy over placebo can occur within hours to days.	Strong
4. Offer alpha 1- blockers to improve the two components to LUTS (storage and voiding), which appears in significant improvements in IPSS and Q max, which is mostly maintained for about 4 years.	Strong
5. Do not offer alpha 1-blockers with the aim of reduction of prostate size	Strong
6. Titrate the dose of Doxazosin and Terazosin and monitor blood pressure when offering these alpha blockers for treatment of BPH	Strong
7. Warn the patients of ejaculatory disorders when prescribing selective alpha-1A blockers such as Tamsulosin and Silodosin	Strong
8. The choice of the alpha blocker should put into consideration the patient's comorbidities, side effect profiles, tolerance and economic issues.	Weak
9. Offer treatment with any of the two types of 5-ARIs (type 1 and 2) in men with moderate-to-severe LUTS with prostate volume more than (30 - 40 mL) and/or elevated PSA concentration (> 1.4 - 1.6 ng/mL).	Strong

Recommendations	Strength Rating
10. Do not offer 5-ARIs for immediate relief of LUTS due to the slow onset of action ranging from 3-6 months.	Strong
11. Offer 5-ARIs to decrease the prostate volume on long term use. They can also prevent the risk of AUR and need for surgery.	Strong
12. Offer 5-ARIs as treatment alternative for refractory hematuria due to prostatic bleeding, and also preoperatively in BPH cases that present with hematuria	Weak
13. Prescribe muscarinic receptor antagonists as a single treatment, however cautiously, in management of male voiding LUTS	Weak
14. Offer antimuscarinics only if residual urine volume is estimated to be less than 150 ml	Weak
15. Regularly evaluate PVR urine in BPH patients on antimuscarinics	Strong
16. Advise patient to discontinue medication if worsening voiding LUTS or urinary stream is decreased after initiation of therapy	Strong
17. Use long-acting phosphodiesterase 5 inhibitors as a single treatment for patients with bothersome, moderate to severe LUTS secondary to BPH (AUA-SI score ≥ 8) whether they suffer from erectile dysfunction or not.	Strong
18. Do not prescribe PDE-5 inhibitors in patients using nitrates, potassium channel opener nicorandil, or the $\alpha 1$ -blockers doxazosin and terazosin, in patients who have unstable angina pectoris, and those who have had a recent myocardial infarction or stroke	Strong
19. Combination therapy using alpha blockers and PDE-5 inhibitors seem better than either alone	Weak

Recommendations	Strength Rating
20. Offer beta-3 agonists alone in men with moderate-to-severe LUTS who present mainly with storage symptoms (frequency, urgency and urgency incontinence)	Weak
21. Prescribe beta-3 agonists only if residual urine volume is estimated to be less than 150 ml	Weak
22. Monitor PVR in patients on beta-3 agonists regularly	Weak
23. Do not offer beta-3 agonists in patients with severe uncontrolled hypertension	Strong
24. Do not offer dietary supplement or combination phytotherapeutic agents as standard therapy for the management of LUTS secondary to BPH	Strong
25. Offer combination treatment with an α 1-blocker and a 5 α -reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong
26. Offer patients successfully treated with combination therapy the option of discontinuing the alpha-blocker after 6 months. If symptoms recur, the alpha-blocker should be restarted (conditional recommendation based on moderate-quality evidence).	Weak
27. Offer antimuscarinics or beta-3 agonists to alpha blockers in patients with persistent storage LUTS during α 1-blocker monotherapy treatment	Strong
28. Use the combination of PDE5Is and α -blockers for those not responding well to the use of either of the drugs as a monotherapy, especially those with erectile dysfunction	Strong
29. Offer Low-dose Desmopressin as a therapeutic option in men with LUTS/BPH with nocturnal polyuria if other medical causes	Strong

Recommendations	Strength Rating
have been excluded as a cause of nocturnal polyuria and if patients did not benefit from other treatments ⁽⁶⁷⁾	
30. Monitor serum sodium 3 days after the first dose. Re-check again after one month. If serum sodium is reduced to below the normal range, stop desmopressin treatment.	Strong

8 Surgical treatment

This includes the followings: Monopolar Transurethral Resection of Prostate (M-TURP)

TURP is the standard surgical treatment for BPH since many decades. It has been proven to be efficacious with durable outcomes in terms of decreased I-PSS score, elevated Qmax, improved QoL and decreased PVR urine levels ⁽⁶⁹⁾.

Intraoperative and short-term postoperative complications include TUR syndrome (0.8-2.5%), blood transfusion (2-4.4%), clot retention (4.9-7.2%) and significant UTI (4-6%). Mid to long term complications include retrograde ejaculation (55-85%), stress urinary incontinence (0.6-1.5%), bladder neck contracture (2-3%) and urethral stricture (3.4-4%). The procedure has overall relatively low incidence of morbidity, which increases with increased prostate size ⁽⁶⁹⁻⁷²⁾.

8.1 Transurethral Incision of Prostate (TUIP)

Incising bladder neck down to the verumontanum has been used as alternative to conventional TURP with prostate size around 30 g, showing comparable LUTS improvements and increased Qmax ⁽⁷³⁾. An Egyptian RCT comparing TUIP and TURP in prostate size < 30g found no significant differences in terms of I-PSS score, need for blood transfusion and reoperation. TUIP showed favorable results over TURP concerning sexual complications (ED 8% vs. 20%, retrograde ejaculation 30% vs. 70% respectively) ⁽⁷⁴⁾

8.2 Transurethral Bipolar Resection of Prostate (B-TURP):

With the advent of bipolar trans urethral technology, resection could be carried out in isotonic saline, where the closed circuit of the current is situated locally at the resection site, with no need for returning pole as the grounding pad.

Short term results proved to be comparable to M-TURP in terms of efficacy, with more favorable safety criteria and reduced side effects (blood transfusion, clot retention and TUR syndrome) ⁽⁷³⁾. Long term results showed comparable results in terms of efficacy and complications as well ⁽⁷³⁻⁷⁵⁾. This technique could be used safely in patients with large prostates and other comorbidities such as cardiac patients and bleeding tendencies.

8.3 Transurethral Bipolar Vaporization of Prostate (BVP):

Although short term results show comparable efficacy with TURP and more favorable safety profile, with lower perioperative morbidity, data still is lacking to identify mid to long term efficacy and complications ⁽⁷⁵⁾

8.4 Transurethral Bipolar Enucleation of the Prostate (BEP):

It has comparable efficacy and safety profile with HoLEP in substantially large prostates more than 80 g ⁽⁷⁵⁻⁷⁷⁾

8.5 Open Simple prostatectomy:

Open prostatectomy could be performed by either trans vesical (Freyer's) approach or retro pubic (Millin's) approach. This is the most invasive surgical treatment option for substantially large prostates more than 80gm. Other less invasive endoscopic procedures such as enucleation procedures as HoLEP & BEP proved to have comparable short to mid-term efficacy with open procedures but with superior safety profiles ^(76,77).

Table 4: Recommendations for Surgical Treatment of BPH

Recommendations	Strength Rating
31. Indications of prostatectomy (whatever the technique) include: • Recurrent or refractory urinary retention • Recurrent urinary tract infections due to BPH • Bladder stones or diverticula due to BPH • Treatment-resistant recurrent haematuria due to BPH • Upper urinary tract dilatation due to BPO, with or without renal insufficiency. • Unsatisfied patients with QoL because of LUTS despite conservative or pharmacological treatments	Strong
2. Both monopolar and bipolar TURP can be used for endoscopic removal of prostates in men with BPH and prostate size 30-80 g.	Strong
3. Offer bipolar TURP when prostate volume is larger than 80 g, but still, this depends on surgeon's expertise and resection speed. Offer bipolar TURP in cardiac patients or patients with bleeding tendencies or patients on anticoagulants	Weak
4. Junior staff may use cut-off value of prostate size up to 60 g for M-TURP and B-TURP for prostate size 60-80 g until achieving adequate learning curve	Weak

Recommendations	Strength Rating
5. Offer TUIP to treat properly indicated men with BPH when prostate size < 30 g, and no middle lobe enlargement	Strong
6. BVP may be used as alternative to TURP in prostate size 30-80 g, whenever available and by trained urologists	Weak
7. In absence of endoscopic enucleation possibility, consider simple open prostatectomy for treating large prostates more than 80 g in properly indicated patients	Strong

8.6 Laser transurethral prostatectomy

8.6.1 HoLmium Laser Enucleation of Prostate (HoLEP)

HoLEP is considered the endoscopic equivalent of open prostatectomy (OP). Its outcome is comparable to OP in terms of IPSS and Qmax improvement in large prostates ⁽⁷⁷⁾. HoLEP has less incidence of blood transfusion, shorter hospital stay and shorter catheterization time compared to both TURP and OP ^(77,78). HoLEP has been safely used in patients on anticoagulants and anti-platelet therapy ^(78,96).

8.6.2 Green light Laser (Photoselective) Vaporization of Prostate (PVP)

PVP utilizes one of 3 different forms of laser of the same wavelength (532 nm) with different power and different fibers design: 80W KTP, 120W LBO and 180W XPS Lasers.

Mechanism of action: The Potassium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. Laser energy is absorbed by haemoglobin, but not by water. Vaporization leads to immediate removal of prostatic tissue. Three “Greenlight” lasers exist, which differ not only in maximum power output, but more significantly in fibre design and the associated energy tissue interaction of each. The standard Greenlight device is the 180-W XPS laser, but the majority of evidence is published with the former 80-W KTP or 120-W LBO laser systems.

Laser vaporization of the prostate using either 80-W KTP, 120- or 180-W LBO lasers is a good option for the treatment of BPH patients who are indicated for surgical intervention with a prostate size of 30-80 g. PVP can be offered as a modality of BPH treatment for those patients on anticoagulants or anti platelet therapy.

1. 80W KTP

It has proven equivalent efficacy to TURP at 12 months' follow-up in terms of Qmax and I-PSS. KTP PVP showed inferior results to TURP concerning incidence of bladder neck contracture, urethral stricture, residual adenoma and need for reoperation ⁽⁷⁹⁻⁸¹⁾.

2. 120W LBO

Short to mid-term objective and subjective outcomes proved to be comparable to TURP with more favorable perioperative complications rate towards PVP concerning blood transfusion, clot retention, duration of catheterization and hospital stay ⁽⁸²⁾.

3. 180W XPS

Goliath study showed non-inferiority of 180W PVP to TURP in both functional and subjective outcomes as well as in complications rate ⁽⁸³⁾.

8.6.3 Diode laser treatment of the prostate

Diode lasers with a wavelength of 940, 980, 1318 and 1470 nm (depending on the semiconductor used) are used for either vaporization or enucleation of the prostate. A limited number of low-quality RCTs are present in the literature ⁽⁸⁴⁾. Worth of notice, this modality is still not available in Egypt.

8.6.4 Thulium Laser Enucleation of Prostate (ThuLEP)

Long term results of ThuLEP are similar to TURP in terms of PVR, Qmax, I-PSS and QoL. Post-operative results favored ThuLEP over TURP concerning catheter duration, hospital stay and blood loss ⁽⁸⁵⁻⁸⁶⁾.

Table 5: Recommendations for Laser transurethral prostatectomy

Recommendations	Strength Rating
32. Offer HoLEP as a surgical option for men with moderate to- severe LUTS provided that the endoscopic skills and equipments allow for it	Strong
33. Offer HoLEP for treatment of large prostates more than 80 g in patients on anticoagulants or antiplatelet therapy	Weak
34. Consider ThuLEP in treating properly indicated men with BPH and large prostates as an alternative to simple open prostatectomy and HoLEP, provided that the endoscopic skills and equipments allow for it	Strong

Recommendations	Strength Rating
35. Consider PVP (if available) using 120- or 180-W LBO lasers as an option for the treatment of BPH patients with a prostate size of 30-80 g.	Weak
36. Offer HoLEP, PVP, and ThuLEP in patients who are at higher risk of bleeding such as those on anti-coagulants	Weak

9 Minimally invasive procedures.

9.1 Prostatic Urethral Lift (PUL)

This procedure depends on decompressing the prostatic urethra by lateralizing away the prostatic lobes using a cystoscopically-held device, which implants permanent sutures in the lateral lobes. Although PUL showed lower improvements in Qmax and I-PSS when compared to TURP, The QoL score was the same at 2 years' follow-up as well as need for retreatment due to bothersome symptoms. PUL was superior to TURP in preserving erectile and ejaculatory functions (87). PUL can be offered as an alternative to TURP in patients not fit for this invasive procedure or those willing to preserve their sexual function with prostates less than 70 g and no middle lobe. Worth of notice, this modality is still not available in Egypt.

9.2 Transurethral Microwave Therapy (TUMT)

It uses a specialized catheter to emit electromagnetic waves to prostate for thermos-ablative effect. The available data are considered inconsistent with no evidence of long-term efficacy and high retreatment rates (88). Worth of notice, this modality is not available in Egypt.

9.3 Transurethral Needle Ablation (TUNA)

It uses an endoscopic catheter through which needles are inserted in the prostate to emit radiofrequency waves to create thermal necrosis. There is no sufficient evidence to support the use of TUNA in the continuum of BPH treatment (89). Worth of notice, this modality is not available in Egypt.

9.4 Prostatic stent

No sufficient evidence to support its use in treating BPH attributed LUTS. It has high incidence of adverse events as migration, faulty insertion and worsening irritative symptoms (90).

9.5 Intraprostatic injection of Botulinum Toxin A

No evidence to support its use in treating BPH attributed LUTS. All data from the literature has proven that it has no role for treatment of BPH.

9.6 Water vapour thermal therapy

Water vapor thermal therapy (also referred to as transurethral destruction of prostate tissue by radiofrequency generated water thermotherapy) (Rezüm[®]) may be offered to patients with LUTS attributed to BPH provided prostate volume <80g. It may be offered to eligible patients who desire preservation of erectile and ejaculatory function. Three-year results showed sustained improvements for the IPSS, IPSS-QoL and Qmax⁽⁹¹⁾.

9.7 Aquablation

Aquablation surgery uses a robotic handpiece, console and conformal planning unit (CPU). The resection of the prostate is done via a water jet from a transurethrally placed robotic handpiece. Pre-treatment transrectal ultrasound is used to map out the specific region of the prostate to be resected with a particular focus on limiting resection in the area of the verumontanum. After completion of the resection, electro-cautery via a standard resctoscope or traction from a 3-way catheter balloon are used to obtain hemostasis.

Aquablation may be offered to patients with LUTS attributed to BPH provided prostate volume 30-80g. It has a theoretical advantage in preservation of erectile function or ejaculation as conductive heat (and its potential damage of erectile nerves) is not used to remove prostate tissue⁽⁹²⁾.

9.8 Prostatic Artery Embolization (PAE)

PAE is a newer, largely unproven minimally invasive modality for BPH. High level evidence remains sparse, and the overall quality of the studies is low. Results also differed between the trials regarding improvements in Qmax. Two trials reported lower flow rates with PAE compared with TURP⁽⁹³⁻⁹⁵⁾, and one trial reported similar flow rates between groups⁽⁹⁴⁾. Mean prostate volumes were significantly higher in the PAE group compared with the TURP group at all follow-up time points^(94,97).

Table 6: Recommendations for Minimally invasive procedures for BPH

Recommendations	Strength Rating
1. Consider prostatic stent placement as an alternative to indwelling catheters in patients with BPH attributed refractory urinary retention and not fit for invasive procedures	Weak

Recommendations	Strength Rating
2. Do not offer intraprostatic Botulinum toxin-A injection as a treatment option for patients with male LUTS due to BPH	Strong
3. Do not offer PAE for the treatment of LUTS secondary to BPH. PAE is not recommended outside the context of clinical trials.	Strong

10 Post-prostatectomy Urinary Incontinence (PPI)

Table 7: Recommendations for Post Prostatectomy Urinary Incontinence

Recommendation	Strength Rating
37. Inform patients undergoing radical prostatectomy of all known factors that could affect urinary continence	Strong
38. Inform patients undergoing radical prostatectomy that urinary incontinence generally returns to near baseline by one year postoperatively, but may persist and require treatment	Strong
39. Instruct patients to perform pelvic floor muscle exercises (pelvic rehabilitation) before radical prostatectomy and six months postoperatively to hasten recovery of urinary continence	Weak
40. Exclude the presence of detrusor overactivity (DO) as a cause of PPI	Strong
41. Exclude the presence of anastomotic stricture or contractures leading to overflow incontinence. Perform PVR estimation and office cystourethroscopy to confirm the findings	Strong
42. Order pressure flow study (PFS) before proceeding to any invasive treatment modality for PPI to exclude other causes of urinary incontinence; at least six months to one year postoperatively	Weak
43. Offer duloxetine ONLY to hasten recovery of urinary continence after prostate surgery. It should not be offered as a therapeutic option for PPI due to sphincteric derangement	Weak
44. Offer bulking agents to men with mild PPI ONLY with the intent of temporary relief of their urinary incontinence and after meticulous counselling of these patients	Weak
45. Offer male slings to men with mild-to-moderate PPI as a treatment option. Patients should be counselled about the possible adverse events of erosion and the possible need for use of CIC	Weak

Recommendation	Strength Rating
46. Avoid the use of male slings in PPI in the presence of any of the following: severe incontinence, prior pelvic radiotherapy or urethral stricture surgery	Weak
47. Offer artificial urinary sphincter (AUS) to men with moderate-to-severe PPI. Patients should be counselled about the possible side effects of infections and malfunctions. AUS implantation should be offered ONLY in expert centres	Weak
48. Counsel patients undergoing AUS implantation that AUS will likely lose effectiveness over time, and reoperations are common	Strong
49. Offer patients with persistent or recurrent stress urinary incontinence after male slings AUS implantation	Weak

11 Conclusion

The understanding of the LUT as a functional unit, and the multifactorial aetiology of associated symptoms, means that LUTS now constitute the main focus, rather than the former emphasis on BPH. It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

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Committee II

Neurogenic Lower Urinary Tract Symptoms (NLUTS)



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13 Abbreviations

ANLUTD	Adult Neurogenic Lower Urinary Tract Dysfunction
AUDS	Ambulatory Urodynamics
AUA	American Urological Association
AUS	Artificial urinary sphincter
AD	Autonomic Dysreflexia
BPO	Benign Prostatic Obstruction
BP	Blood Pressure
BM	Bowel Management
BCR	Bulbocavernosus Reflex
CVS	Cerebrovascular Stroke
DLPP	Detrusor Leak Point Pressure
DSD	Detrusor Sphincter Dyssynergia
DUA	Detrusor Underactivity
DM	Diabetes Mellitus
DRE	Digital Rectal Examination
DMSA	Dimercaptosuccinic acid
ED	Erectile Dysfunction
EAU	European Association of Urology
FDA	Food And Drug Administration
FVC-BD	Frequency-Volume Chart Bladder Diary
GFR	Glomerular Filtration Rate
IPD	Idiopathic Parkinson's Disease
ICI	International Consultation on Incontinence
ICS	International Continence Society

IPSS	International Prostate Symptom Score
LUT	Lower Urinary Tract
LUTS	Lower Urinary Tract Symptoms
MAG3	Mercaptoacetyl triglicine
MESA	Microsurgical Epididymal Sperm Aspiration
MS	Multiple Sclerosis
MSA	Multiple System Atrophy
NB	Neurogenic Bladder
NBSS	Neurogenic Bladder Symptom Score
NLUTD	Neurogenic Lower Urinary Tract Disease
OAB	Overactive Bladder
PS	Parkinsonian Syndrome
PDE5Is	Phosphodiesterase Type 5 Inhibitors
PMC	Pontine Micturition Center
RCTs	Randomized Controlled Trials
SB	Spina Bifida
SCI	Spinal Cord Injury
TESE	Testicular Sperm Extraction
TENS	Transcutaneous Electrical Nerve Stimulation
TURP	Transurethral Resection Of The Prostate
UUT	Upper Urinary Tract
UPP	Urethral Pressure Profile
EMG	Urethral Sphincter Electromyography
UI	Urinary Incontinence
UTI	Urinary Tract Infection
VUR	Vesico-Ureteral Reflux
VUDS	Video-Urodynamics
VCUG	Voiding Cystourethrogram

14 Abstract.

14.1 Objectives.

The Urologic Egyptian Guidelines on Neuro-Urology aim to help and guide clinical practitioners to have knowledge of the incidence, standard definitions, diagnosis, therapy, and follow-up of NLUTD. This document integrates recent international guidelines with local experts' opinions based on Egyptian healthcare and socioeconomic circumstances.

14.2 Methods.

Databases searched included Medline, Cochrane Libraries, EAU guidelines, ICS recommendations, 6th ICI recommendations, AUA and NICE guidelines, from January 2018 and September 2020.

Review of several meta analyses, leading institutional protocols and relevant Egyptian publications were taken into consideration. All statements were graded according to strength of recommendation. Each statement was given a strength rating (strong or weak).

14.3 Results.

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

14.4 Conclusions.

Early diagnosis of NLUTD is fundamental before deciding any plan of management. Accordingly, tailoring and individualizing the plan of management follows, which ensures the best practice of clinical care offered to these patients. The role of these guidelines is to offer expert advice on how to manage these patients.

15 Introduction.

The lower urinary tract (LUT) is under the regulation of the nervous system, which acts at many levels; the cerebral cortex, pontine micturition center (PMC) and lastly the sacral spinal center. These centers relay their signals to the peripheral nerves in the pelvis to reach the end organs (bladder and sphincter). The two main functions of the LUT are the storage and voiding of urine.

Neurological diseases are vast, and they may have adverse consequences on the urinary system. The extent and site of the neurological insult will determine the type of neurogenic lower urinary tract disease (NLUTD).

The worst complication of NLUTD is upper urinary tract (UUT) deterioration, which is the leading cause of mortality in this subset of patients. UUT deterioration is more with spinal cord injury (SCI) and spina bifida (SB) patients. It is very crucial to stratify NLUTD patients into high and low risk groups, in order to individualize the plan of management and prevent further deterioration and complications. Therefore, early diagnosis, treatment and follow-up of these patients is crucial.

15.1 Aims and Objectives.

The Urologic Egyptian Guidelines on Neuro-Urology aim to help and guide clinical practitioners to have knowledge of the incidence, standard definitions, diagnosis, therapy, and follow-up of NLUTD. This document integrates recent international guidelines with local experts' opinions based on Egyptian healthcare and socioeconomic circumstances. It also reflects the opinions of experts in Neuro-Urology and represent state-of-the art references for all clinicians, as of the publication date.

The terminology used and the diagnostic procedures mentioned in this chapter follow the recommendations published by the International Continence Society (ICS).

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient. Every patient is a unique case by himself and the treating urologist should take an advice from the guidelines which may not be, in some situations, perfectly satisfying all the findings in a particular patient. Therefore, the guidelines should not be a final legal document but should help during investigation of a particular case.

15.2 Methodology.

The committee members were selected according to their expertise in the field of Neuro-urology. The committee members are all functional urologists from four different Egyptian Universities; Ain Shams, Alexandria, Zagazig and Menoufia Universities. All members have no conflict of interest.

Databases searched included Medline, Cochrane Libraries, European Association of Urology (EAU) guidelines, ICS recommendations, 6th International consultation on incontinence (ICI) recommendations, American Urological Association (AUA) and NICE guidelines, in the period from January 2018 and September 2020.

Review of several meta analyses, leading institutional protocols and relevant Egyptian publications were also taken into consideration. All statements were graded according to strength of recommendation. Each statement was given a strength rating (strong or weak).

16 Neurogenic bladder (NB)

16.1 Definition.

The term “neurogenic bladder” describes lower urinary tract dysfunction that has occurred likely as a result of a neurological injury or disease ⁽¹⁾ which may be in the central, autonomic or peripheral nervous systems.

The International Continence Society (ICS) defines “Adult neurogenic lower urinary tract dysfunction” (ANLUTD) as abnormal or difficult function of the bladder, urethra (and/ or prostate in men) in mature individuals in the context of clinically confirmed relevant neurologic disorder ⁽²⁾.

16.2 Causes, epidemiology and prevalence of Neuro-Urological Disorders.

These disorders are classified according to Panicker et al. into: ⁽³⁾.

16.2.1 Suprapontine and pontine lesions.

These patients suffer from storage symptoms, with neurogenic detrusor overactivity (NDO) due to loss of the inhibitory action of the pontine micturition center (PMC).

16.2.1.1 Cerebrovascular stroke (CVS):

57-83% of neuro-urological symptoms appear after 1 month of CVS and 71-80% show spontaneous recovery at 6 months ⁽⁴⁾. Persistence of urinary incontinence (UI) correlates with poor prognosis ⁽⁵⁾.

16.2.1.2 Dementias:

A group of diseases that occur in 6.4% of adults over 65 years old including Alzheimer’s disease (60–80%), Vascular disease (10–20%) and other diseases (10%) such as Lewy bodies, normal pressure hydrocephalus, fronto-temporal degeneration and Creutzfeldt-Jakob disease. Urinary incontinence incidence is 3 times more frequent than in non-demented patients ^(6, 7).

16.2.1.3 Parkinsonian syndrome (PS):

It includes idiopathic Parkinson’s disease (IPD) (75-80%), Non-IPD (18%) such as "Multiple system atrophy (MSA), progressive supranuclear palsy and secondary Parkinson’s (2%)". PS represents second most prevalent neurodegenerative disease after Alzheimer’s disease. Most of these patients present with nocturia (78%) and overactive bladder (OAB) (36–93%) ⁽⁸⁾. Patients with lower urinary tract symptoms (LUTS) at presentation fair worse disease progression ⁽⁹⁾.

16.2.1.4 MSA:

It is the most frequent non-IPD PS. Autonomic failure (postural hypotension and urinary dysfunction) is essential for diagnosis ⁽¹⁰⁾. OAB symptoms manifest early and detrusor

underactivity (DUA) appears with disease progression ⁽¹¹⁾. Impaired detrusor contractility with postvoid residual (PVR) > 150 mL is the urodynamic finding distinguishing MSA from IPD ⁽¹²⁻¹⁴⁾.

16.2.1.5 Traumatic brain injury:

Usually presents with 44% storage dysfunction, 38% voiding dysfunction and 60% have urodynamic abnormalities ⁽¹⁵⁾.

16.2.1.6 Cerebral palsy:

Its incidence is 3.1-3.6/1,000 in children aged 8 yrs. Urinary incontinence is the most frequent symptom (20–94%) and NDO is present in 9–97% ⁽¹⁶⁾.

16.2.1.7 Normal pressure hydrocephalus:

Presence of the classic triad of gait, cognitive disturbance and UI, which affects 98-100% of patients ⁽¹⁷⁾.

16.2.2 Spinal (Infrapontine and suprasacral) lesions.

These patients present with both storage (NDO) and voiding symptoms {NDO and detrusor sphincter dyssynergia (DSD)}

16.2.2.1 Spinal cord injury (SCI):

Prevalence of traumatic SCI in developed countries ranges from 280 to 906/million. Early after injury, it manifests with depressed spinal reflexes below the level of injury and areflexic acontractile bladder (spinal shock) which lasts for a variable amount of time (from days to months). Nearly 95% of cases present with NDO and DSD but DUA occurs in about 33% according to site of injury ^(18, 19).

16.2.2.2 Spina bifida (SB):

Lumbar and lumbosacral forms are the most common. Bladder function is impaired in up to 96% and half of patients are incontinent ⁽²⁰⁾.

16.2.2.3 Multiple sclerosis (MS):

Incidence is about 9.6/100,000/year and is more common in women. 10% of patients present with LUTS at disease onset, while 75% of patients will develop LUTS after 10 years. NDO occurs in 86%, DSD in 35% and DUA in about 25% of cases ^(21, 22).

16.2.2.4 Other causes: (spinal cord tumors, infections/para-infectious "transverse myelitis" and lesion following spinal anesthesia or spine surgery):

They present with storage and voiding symptoms, depending on lesion's level ⁽²³⁾.

16.2.3 Sacral and infrasacral lesions.

These patients present with voiding symptoms (detrusor acontractility)

16.2.3.1 Lumbar spine, degenerative diseases, disk prolapse, spinal canal stenosis and spinal tumours:

Disc prolapse is the most common lesion and is more common in females above 45 years. DUA is the most common finding (up to 83%)^(18, 24).

16.2.3.2 Iatrogenic pelvic nerve lesions:

(as in cases of radical pelvic surgeries). Voiding symptoms are more common than storage symptoms⁽²⁵⁾.

16.2.3.3 Peripheral neuropathy:

It is caused by diabetes mellitus (DM) (most common), alcohol abuse, genital herpes and Guillain Barré syndrome. They present initially with OAB symptoms then DUA at later phase (such as diabetic cystopathy)⁽²⁶⁾.

17 Classifications.

The current classification systems serve as a frame work, since it is not possible to map all lesions and its consequences in every patient in a single classification ⁽²⁷⁾. Most of these systems are of no use today such as: Lapedes (1970), Bors and Comarr (1971), Wein functional classification (1981), Hald and Bradley classification (1982), Krane and Siroky urodynamic classification (1984) and ICS system by Abrams et. al 2002 ⁽²⁸⁾.

More recently, three classification systems were described according to pattern of clinical urological and urodynamic manifestations and aimed to predict site of neurologic affection. These systems are:

17.1 Madersbacher system:

It presented eight main types of lower urinary tract dysfunction ⁽²⁷⁾

17.2 The system described by Panicker et al.:

It is a very simple system that can be used for every day practice ⁽³⁾

17.3 SALE classification

(Stratify by Anatomic Location and Etiology) that has seven categories based on the anatomic level of neurologic dysfunction. It also includes bowel dysfunction aspects and should describe a patient suffering from neurogenic bladder and simultaneously inform the most appropriate treatment, follow-up regime and long-term prognosis ⁽²⁹⁾.

18 Diagnosis.

18.1 History.

It includes onset, course and duration of various neurological, urinary, sexual and bowel manifestations.

Urologic history should include the following:

- **LUT assessment** using validated questionnaires like International prostate symptom score (IPSS), the Qualiveen questionnaire for MS patients ^(30, 31), the Quality life index-SCI ⁽³²⁾, the Neurogenic Bladder Symptom Score (NBSS) ^(33, 34) and Incontinence-Quality of Life (I-QoL) questionnaire ⁽³⁵⁾. It is worth mentioning that no evidence was found for which validated questionnaires are the most appropriate for use ⁽³⁶⁾.
- Exclusion of warning symptoms such as fever, loin pain, hematuria and dysuria which may be suggestive of urinary tract infection (UTI) ⁽³⁷⁾, because patients with SCI usually find it difficult to report UTI-related symptoms accurately ^(38, 39).
- A three-day frequency-volume chart bladder diary (FVC-BD) is important in diagnosis ⁽⁴⁰⁾; however, there is inadequate evidence or recommendations on its utility in neuro-urologic patients. It is recommended to be used before urodynamics (UDS) as it may help to ensure and evaluate whether the cystometry, especially cystometric capacity, is representative of the patient's typical situation ⁽⁴¹⁾.

Sexual history is crucial in NB patients. Men may have neurogenic erectile dysfunction (ED) and/or ejaculatory problems. Women may complain of dyspareunia, vaginal dryness, vaginal hyperaesthesia, arousal and/or orgasmic dysfunction ⁽⁴²⁾.

Bowel history includes defecation desire, pattern and frequency along with rectal sensation and presence or absence of fecal incontinence or constipation. The QoL scoring tool related to Bowel Management (QoL-BM) can be used to assess bowel dysfunction in MS and SCI patients ⁽⁴³⁾.

Present history of neurological and non-neurological diseases is important. Family history of neurological and urological diseases should be taken to exclude congenital, genetic and familial diseases. Moreover, history of pelvic or urological operations along with nature and time of brain or spinal trauma, if present, should not be missed in assessment. Lastly, special lifestyle habits such as smoking, alcohol intake and recreational drugs use should be evaluated ^(38, 39, 42, 44).

Autonomic dysreflexia (AD) is a sudden and exaggerated autonomic response to various noxious stimuli in patients with SCI or spinal dysfunction at or above level of T6. It is crucial to take into consideration the noxious stimuli which may elicit AD such as bladder or bowel distension, catheterization, cystoscopic manipulation, sexual intercourse, infected toe and pressure sores. AD

manifests with an increase in systolic blood pressure more than 20 mmHg from baseline and can lead to fatal complications if not discovered and treated promptly ^(45, 46).

18.2 Examination.

Vitals of the patient especially blood pressure are essential because patients with NB may suffer from either persistent or postural hypotension and/or episodes of uncontrolled hypertension ⁽⁴⁷⁾. General neurological examination especially for gait, motor power, sensations, mental health and spasticity should be done in the primary evaluation of these patients ⁽⁴⁸⁾.

Complete neuro-urological status should be described. The patient should lie in lithotomy position to have access to the lower sacral segments S3, S4 and S5. Pain (pin-prick), touch and pressure sensations and reflexes in the urogenital area must be tested (Figure 3) ⁽³⁾.

Most commonly tested reflexes in the lower spinal cord are the cremasteric reflex (L1-L2), the knee reflex (L2-L4), the ankle reflex (L5-S2), bulbocavernosus reflex (BCR) (S2-S4) and anal reflex (S4-S5) ⁽⁴⁹⁾. BCR and anal reflex are by far the most important reflexes ^(50, 51). In suprasacral SCI, a negative BCR indicates a defect in the sacral reflex arc either on the afferent or efferent sides of the pudendal nerve or in the spinal cord segments L5-S5. In contrast to other reflex activity, BCR returns within a few hours after SCI. Anal reflex usually parallels the findings of the BCR ⁽⁵²⁾.

Digital rectal examination (DRE) is a crucial step in examination. It should focus on the configuration of the anus (normal or patulous), the anal sphincter tone (normal, spastic, flaccid), rectal prolapse, stool impaction (if present) and prostate examination in males. Preserved ability for voluntary contraction and relaxation of the external anal sphincter is a good prognostic sign to achieve continence with bladder retraining programs. Finally, vaginal examination in females with assessment of pelvic organ prolapse should not be missed ⁽⁴⁹⁾.

18.3 Investigations.

Urine analysis is indicated in the presence of symptoms or signs of UTI such as fever, urinary incontinence, leakage around catheter, spasticity, malaise, lethargy, cloudy urine, malodorous urine, back pain, bladder pain, dysuria and AD (54). Moreover, it can be used to assess response to antibiotic treatment ⁽⁵⁵⁾.

Urine culture is done in case of significant pyuria. A cut off of 10³ cfu/ml is the minimum level of detection. Moreover, a cutoff 10⁵ cfu/ml with the absence of symptoms is compatible with a UTI. It is important to recognize that this cutoff is only a guideline recommendation and any colony count in a catheterized patient may potentially represent significant bacteriuria and should be interpreted along with the patients' clinical picture ^(40, 56).

Cystoscopy, either flexible or rigid, may be indicated in cases of recurrent UTI, abnormal imaging or recurrent catheter blockage which may be due to either bladder calculi or significant proteinaceous debris ⁽⁵⁷⁾.

Patients with NB have a higher risk of developing renal failure ⁽⁵⁸⁾. **Cystatin-C based glomerular filtration rate (GFR)** is more accurate than serum creatinine estimated GFR because body composition is usually disturbed with decreased muscle mass ⁽⁵⁹⁻⁶¹⁾.

Ultrasound is fundamental in NB patients in the initial assessment and during follow up for diagnosis of UUT dilatation and scarring, PVR and morphological abnormalities of the LUT (e.g. diverticulae, increased bladder wall thickness, presence of intravesical prostatic protrusion in men) as well ^(62, 63).

PVR measurement using a catheter or what is called “in–out catheterization” can be used, but it is more irritating to the patient and carries increased UTI risk ⁽⁶⁴⁾.

Voiding cystourethrogram (VCUG) is recommended in certain neuro-urological patients to assess the bladder capacity, detect vesico-ureteral reflux (VUR) if present and estimate PVR. Dimercaptosuccinic acid (DMSA) or mercaptoacetyl triglicine (MAG3) renal scan can be used for renal functions’ assessment in patients with risk factors of upper urinary tract (UUT) deterioration ⁽⁶⁵⁾.

Uroflowmetry should be used in primary assessment of LUTS, whenever feasible, before any invasive UDS in patients who can void ⁽⁶⁶⁾. It should be repeated at least two to three times, and patients should void volumes greater than 150 ml for proper interpretation of results ^(3, 67). It gives information about flow rate, flow pattern, flow time and voided volume.

UDS is the gold standard tool to evaluate LUT function in NB patients, especially when there is evidence or history of SCI ^(3, 68). Liquid-filled catheters and external transducers with the reference level of the upper edge of the symphysis pubis are recommended by the ICS ^(41, 69). Moreover, the rectal ampulla should be empty of stool before the start of the investigation ⁽⁷⁰⁾.

Continuous careful observation and assessment of collected signals along with in detail reporting of all findings according to the ICS technical recommendations and standards should be ensured. Moreover, FVC-BD, uroflowmetry and PVR results are recommended prior to invasive UDS. Also, patients should be actively engaged in the test ^(53, 66).

The fluid type and temperature, filling method and rate, catheter sizes, pressure recording technique, and patient position should all be patient tailored ⁽⁴¹⁾. In NB patients, body-warm saline using 6 Fr. double lumen urodynamic urethral or suprapubic catheter with filling rate starting at 10 ml/min is recommended. If there is no rise in the Pdet, this can be increased to 20 ml/min. However, if Pdet begins to rise, then filling should be stopped for 5-10 min until the pressure has settled, and then restarted at 10 ml/min ⁽⁷¹⁾. ICS also recommends that all UDS tests are performed in the patient's preferred or most usual position: comfortably seated and/ or standing, if physically possible ⁽⁴¹⁾. However, many NB patients will not be able to stand or even sit, so these patients have to lie down throughout filling and voiding. This is likely to give appropriate information ⁽³⁷⁾.

In patients at risk of AD, it is advisable to measure blood pressure (BP) during test because catheterization and bladder filling may be a noxious stimulus to the bladder ^(72, 73). Prophylactic

antibiotics reduce the risk of bacteriuria, but not of UTI after UDS (74). Thus, prophylactic antibiotics are not recommended before UDS testing (75). However, urinalysis for screening for infection or hematuria should be ordered before the test (76).

Filling cystometry has limited role as a solitary procedure. It is much more effective if combined with voiding phase or with **video-urodynamics (VUDS)**. The bladder should be empty at the start of filling (37).

High Pdet during UDS is a risk factor for UUT deterioration (77, 78). Cut-off values of Pdet are controversial (79, 80). It usually ranges from 40-75 cmH₂O in most studies (65). **Detrusor leak point pressure (DLPP)** has low sensitivity regarding prediction of UUT deterioration (79, 81).

McGuire et al. found that cut-off value of Pdet in patients with low bladder compliance secondary to myelomeningocele (MMC) is 40 cmH₂O. There is some evidence that a bladder capacity < 200 mL and detrusor pressures over 75 cmH₂O are independent risk factors for UUT damage in patients with SCI (65).

Urethral pressure profile (UPP) has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings in NB patients (82).

VUDS is the gold standard test for diagnosis of NLUTD. However, the physiological nature of VUDS is often questioned because of the use of radiological contrast (which has a different density than urine) and being instilled at a lower temperature. Furthermore, the bladder is retrogradely filled, often at a rate higher than physiological filling rates. The patient is placed in an artificial environment, which may also affect lower urinary tract dynamics (83).

Ambulatory urodynamics (AUDS) may theoretically be a more physiological test to evaluate LUT function as the bladder is filled through normal diuresis and it can be performed in the patient's own environment. Moreover, it can be conducted for a longer period of time allowing the patient to perform normal activities. However, the procedure is time-consuming, technically challenging and not widely available, making it more prone to artefacts (83).

Urethral sphincter electromyography (EMG) has a role in diagnosis of DSD in NLUTD but needs more studies to be popularized. The most common used electrodes are surface perineal electrodes (ICS standard), needle electrodes, vaginal or anal electrodes (41).

Table 8: Recommendations for investigations of NB.

Recommendations	Strength rating
1. Take extensive general history focusing on past and present symptoms, with special emphasis on four main domains: urinary, sexual, bowel and neurological functions	Strong

2. Quality of life assessment should be completed with validated QoL questionnaires for neuro-urolological patients	Strong
3. Drug, family, past and present history of neurologic and non-neurologic diseases along with history of external and iatrogenic trauma should be properly taken from patients with NLUTD	Strong
4. Special attention should be paid to warning signs such as fever, hematuria, dysuria, leaking around catheter and autonomic dysreflexia, which could alter/change diagnosis and thus affect the current management	Strong
5. Perineal and genital examination should be performed, including motor and sensory assessment beside specific lumbosacral reflexes	Strong
6. The anal sphincter activity and pelvic floor muscles should be tested	Strong
7. Urine analysis should be performed in the initial evaluation of NLUTD. It has a role in exclusion of UTI in NB patients. It also can be used for following up after antibiotic treatment	Strong
8. Assessment of renal functions is essential in diagnosis and follow-up. GFR can be best measured by Cystatin-C based GFR	Strong
9. Renal ultrasound should be done in all NB patients to assess UUT functions in primary assessment of NLUTD	Strong
10. Bladder ultrasound with PVR measurement is mandatory in the primary evaluation of NLUTD patients	Strong
11. VCUG is recommended in certain neuro-urolological patients to assess the bladder capacity, detect VUR if present and estimate PVR	Weak
12. Perform uroflowmetry in NLUTD patients who can void	Strong
13. Perform a urodynamic investigation to detect and specify LUTD, use same session repeat measurement	Strong
14. Body-warm saline using 6 Fr. double lumen urodynamic urethral catheter with filling rate starting at 10 ml/min is recommended. If there is no rise in the Pdet, this can be increased to 20 ml/min	Strong
15. Prophylactic antibiotics reduce the risk of bacteriuria, but not of UTI after UDS. It is not recommended before UDS testing	Strong
16. Use VUDS in neuro-urolological patients. if not, pressure-flow study should be used instead with VCUG when indicated	Strong
17. EMG, with surface perineal electrodes, could be used if DSD is suspected in NB patients	Weak

19 Treatment of NLUTD.

The main goals of management for NLUTD are satisfaction and avoidance of adverse outcomes which includes ^(84, 85):

- Protecting upper urinary tract from sustained high filling and voiding pressures (i.e., >40 cmH₂O).
- Achieving regular bladder emptying, avoiding stasis and bladder over distension and minimizing PVR to less than 100mls (ideally <50mls).
- Preventing and treating complications such as UTIs, stones, strictures and AD
- Achievement (or maintenance) of urinary continence (Social goal).
- Restoration of LUT function (Adequate storage and emptying at low intravesical pressure).
- Improvement of the patient's QoL.

Other factors should be considered when choosing therapy such as: disease prognosis (progressive or malignant), patient's disability, patient's compliance with treatments, desire to remain catheter free, desire to avoid surgery, sexual activity and possible complications ⁽⁸⁶⁾.

Treatment should always begin with the simplest, most reversible form(s) of therapy, and then proceed to the complex one ⁽⁸⁶⁾. The main goal in the management plan in patients with high Pdet during the filling phase (DO, low bladder compliance) is conversion of an overactive, high-pressure bladder into a low-pressure reservoir despite the increased PVR. Reduction of Pdet contributes to urinary continence, and consequently to social rehabilitation and QoL. It is also pivotal in preventing UTIs. However, it should be noted that complete continence cannot always be obtained.

Some specific situations require particular attention in NLUTD ⁽⁸⁷⁾:

AD: Various triggers of episodes of AD are recognized, including iatrogenic urological procedures. Routine blood pressure monitoring during investigation or invasive therapy is therefore appropriate.

Allergy to latex needs appropriate preventive and therapeutic arrangements to be in place in case of anaphylactic reaction.

Lines of treatment are divided into the following:

- Non-invasive treatment (conservative treatment)
- Minimally invasive
- Surgical treatment

19.1 Non-invasive treatment (Conservative treatment).

19.1.1 Assisted bladder emptying (Credé manoeuvre, Valsalva manoeuvre and triggered reflex voiding).

In males with tetraplegia and insufficient hand dexterity to perform CIC, drainage by reflex voiding with triggering manoeuvres such as suprapubic tapping, stroking inner thigh and use of an external urinary collection device is possible.

These methods could be used in cases of incomplete bladder emptying, but they carry dangerous risk factors for UTI, high intravesical pressure and incontinence^(53, 88). Such manoeuvres result in an increase in Pdet which is deleterious to the upper tract, therefore they could be recommended only for patients whose situation has proven to be urodynamically safe and stable, with absent or surgically reduced outlet resistance⁽⁸⁵⁾.

19.1.2 Containments.

External appliances that can be used for urine collection during incontinence include pads, condom catheters and penile clamps. Condom catheters with urine collection devices are practical in men⁽⁸⁵⁾. The penile clamp is absolutely contraindicated in case of NDO or low bladder compliance because of the risk of developing high intravesical pressure and pressure sores/necrosis in cases of altered/absent sensations.

19.1.3 Pelvic floor muscle training.

It is an option to be considered for people with NLUTD due to MS or other neurological conditions where the potential to voluntarily contract the pelvic floor is preserved. A variety of techniques that might improve the outcomes of pelvic floor muscle training have been described; these include electrical stimulation of the pelvic floor and biofeedback system⁽⁸⁹⁾.

19.1.4 Bladder rehabilitation.

Aims to re-establish bladder function in neuro-urological patients. Electrical stimulation aims at stimulation of the pudendal nerve afferents, thus inhibiting the micturition reflex and detrusor contraction⁽⁹⁰⁾. Tibial nerve stimulation and transcutaneous electrical nerve stimulation (TENS) might be effective and safe for treating NLUTD, but more well-designed randomized controlled trials are required to reach definitive conclusions⁽⁹¹⁻⁹³⁾.

19.1.5 Drug treatment.

To protect urinary tract and improve long-term outcomes, especially in patients with a suprasacral SCI or MS, a combination of different therapies (e.g. CIC and anti-muscarinic drugs) is advised⁽⁹⁴⁻⁹⁷⁾.

19.1.5.1 Anti-muscarinic drugs.

Are the first-line for treating NDO, increasing bladder capacity and reducing NDO incontinence episodes, by the inhibition of parasympathetic pathways ^(85, 98-104). Higher doses or a combination of anti-muscarinic agents may be an option to maximize outcomes in neurological patients ^(1, 99, 100, 105-107), but may result in higher incidence of adverse events.

Anti-muscarinic agents used are: Oxybutynin ^(85, 99), trospium chloride ⁽¹⁰³⁾, tolterodine ⁽¹⁰⁸⁾ and propiverine ⁽¹⁰³⁾. They are well-established, effective and well tolerated treatments even in long-term use ^(102, 103, 109, 110). Darifenacin ^(111, 112) and solifenacin ⁽¹¹³⁾ have been evaluated in NDO secondary to SCI, MS and PD ^(103, 111, 113), with results similar to other anti-muscarinic drugs. All these drugs are grade A recommendation.

Side effects include dry mouth, blurred vision, cognitive effects, dry eyes and constipation ⁽¹¹⁴⁾. Monitoring PVR in people who are not using intermittent or indwelling catheterization after starting anti-muscarinic treatment is essential ⁽⁸⁹⁾.

19.1.5.2 Beta-3-adrenergic receptor agonists (Mirabegron).

Its role in neuro-urological patients is still unclear. In MS and SCI patients, with very short follow up, mirabegron has not demonstrated any significant effect on urodynamic parameters (detrusor pressure or cystometric capacity) despite the reported improvement in LUTS ^(115, 116). A standard dosage of 50 mg has been found effective without affecting the cognitive function in patients with PD ⁽¹¹⁷⁾. Combination therapy of mirabegron and desmopressin in MS patients has shown promising results ⁽¹¹⁸⁾.

19.1.5.3 Phosphodiesterase type 5 inhibitors.

Male MS patients using daily tadalafil of 5mg to treat neurogenic ED ⁽¹¹⁹⁾ reported an improvement in their OAB symptoms.

19.1.5.4 Para-sympathomimetics (Pyridostigmine and bethanecol chloride).

Cholinergic drugs, have been considered to enhance detrusor contractility and promote bladder emptying ⁽¹²⁰⁾. However, their use in NLUTD hasn't been proven beneficial, and their use in NLUTD should not be offered.

19.1.5.5 Alpha-blockers.

They seem to be effective for decreasing bladder outlet resistance, PVR and AD ⁽¹²¹⁻¹²³⁾ e.g. tamsulosin, naftopidil and silodosin. However, 6th International consultation on incontinence (ICI) ⁽²⁰¹⁶⁾ suggested off-label use of α blockers in patients with DSD.

19.2 Minimally invasive treatment.

19.2.1 Catheterization.

Intermittent catheterization is the standard treatment for patients who cannot empty their bladders ⁽⁸⁵⁾. Whether sterile or clean IC, it is not established yet if the strategy used would affect the incidence of UTI, other complications or not ⁽¹²⁴⁾.

Factors responsible for contamination are inadequate patient education and the inherently high risk of UTI in neuro-uological patients ^(85, 125-129). The average catheterization times is four to six times per day and the catheter size most often used is between 12-16 Fr. Bladder volume should not exceed 400-500 mL at catheterization time.

Indwelling transurethral catheterization and suprapubic cystostomy are associated with wide range of complications as well as an enhanced risk for UTI ^(85, 130-135), therefore both procedures should be avoided, when possible.

Female patients with tetraplegia, due to greater difficulty with CIC and lack of a satisfactory external collecting device, generally use either a suprapubic or an indwelling urethral catheter due to difficulty in performing CIC. In addition, in males with tetraplegia, where there are concerns about long-term complications that may be associated with high intravesical pressures from unbalanced reflex voiding, suprapubic catheters are being recommended ⁽¹³⁶⁾.

Foley catheters should not be used because of the high incidence of latex allergy in the neuro-uological patient population, therefore silicone catheters are preferred as they are less susceptible to encrustations ⁽¹³⁷⁾.

19.2.2 Intravesical instillation.

Anti-muscarinics can also be installed intravesically to reduce NDO if the oral route cannot be tolerated ⁽¹³⁸⁻¹⁴¹⁾. A significant reduction in adverse events was observed for intravesical administration of oxybutynine compared to oral administration ⁽¹⁴²⁾.

19.2.3 Botulinum toxin injections in the bladder.

Botulinum toxin A causes reversible chemical denervation lasting for about nine months ^(143, 144). It has been proven effective in patients with neuro-uological disorders due to MS, SCI and PD in multiple randomized controlled trials (RCTs) and meta-analyses ⁽¹⁴⁵⁻¹⁴⁷⁾.

Neuro-uological patients with an indwelling catheter and concomitant bladder pain and/or catheter bypass leakage could benefit from botulinum toxin injections. The recommended dose is 200-300 IU injected in the detrusor muscle, in 30 sites in the bladder, with exclusion of the trigone, for theoretical prevention of VUR.

It is a valid food and drug administration (FDA-approved) option for patients with spinal cord diseases (SCI and MS) ⁽⁸⁹⁾. In patients with maximal filling detrusor pressure of > 40 cmH₂O, it is

necessary to perform UDS to monitor bladder pressure after its injection ⁽¹⁴⁸⁾. Repeated injections are possible even after initial low response rates without loss of efficacy ^(143, 149-152). The clinical efficacy of botulinum toxin A injection in patients with low morbidity after failure of augmentation enterocystoplasty has been shown ⁽¹⁵³⁾.

The most frequent side effects are UTIs, haematuria and urinary retention that may necessitate ⁽¹⁵⁴⁾ CIC especially in MS patients. However, a lower dose of botulinum toxin A (100 U) may reduce the rate of CIC in those patients ⁽¹⁵⁵⁾.

19.2.4 Bladder neck and urethral procedures.

19.2.4.1 Procedures to reduce of the bladder outlet resistance.

They aim at protection of the UUT. This can be achieved by chemical denervation of the sphincter using Botulinum Toxin A (100 IU injected in four spots 3,6,9,12 o'clock in the external sphincter) in cases of DSD (repeat injection is needed), or by surgical interventions (bladder neck or sphincter incision) which is indicated only for secondary changes (fibrosis) at the bladder neck. Sphincterotomy is irreversible and should be limited to men who are able to wear a condom catheter. The incision is at the twelve o'clock with cold knife or neodymium: YAG laser, and it needs to be repeated at regular intervals ^(156, 157).

Prosthetic sphincterotomy using a urethral endoprosthesis (or stent) is an alternative but is associated with significant complications. Men who wish to have children should be warned of the risk of ejaculatory duct obstruction ⁽⁸⁷⁾.

19.2.4.2 Procedures to increase bladder outlet resistance.

These procedures are reserved for those with sphincteric UI to improve the continence status. Despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with neuro-urological disorders ^(85, 158, 159).

19.3 Surgical treatment.

UDS should be offered before performing surgical treatments for NLUTD ⁽⁸⁹⁾.

19.3.1 Bladder neck and urethral procedures.

These procedures can be divided into those that increase outlet resistance for neuro urological patients with sphincteric UI and those procedures that decrease outlet resistance for patients with outlet obstruction.

19.3.1.1 Procedures to increase outlet resistance.

There is high risk of increased intravesical pressure, so it is suitable only when the detrusor activity can be controlled and when no significant reflux is present. A simultaneous bladder augmentation and CIC may be needed ⁽⁸⁵⁾.

19.3.1.1.1 Urethral sling.

The procedure is well established in women who can catheterise themselves ^(85, 160-163). The pubovaginal sling is considered the procedure of choice in this subgroup of patients, but recent reports suggest that both the transobturator (TOT) and the retropubic (TVT) approaches may also be considered but with a higher incidence of de novo urgency ^(164, 165). In men, both autologous and synthetic slings could be used ⁽¹⁶⁶⁻¹⁷⁰⁾.

19.3.1.1.2 Artificial urinary sphincter (AUS).

AUS insertion is a viable option, with acceptable long-term outcomes, but with higher complication and re-operation rates in neuro-urological patients; therefore, patients must be informed regarding the success rates as well as the complications that may occur following the procedure ^(171, 172). It is mainly reserved for males, however, could be used in female patients, but the cuff has to be inserted around the bladder neck.

19.3.1.1.3 Functional sphincter augmentation.

It entails transposing the gracilis muscle to the bladder neck ⁽¹⁷³⁾ or proximal urethra ⁽¹⁷⁴⁾, with the possible creation of a functional autologous sphincter by electrical stimulation ⁽¹⁷³⁻¹⁷⁵⁾.

19.3.1.1.4 Bladder neck and urethra reconstruction.

The classical Young-Dees-Leadbetter procedure ⁽¹⁷⁶⁾ for bladder neck reconstruction is an option to restore continence, provided that CIC is practiced and/or bladder augmentation is performed ^(85, 177).

19.3.1.2 Procedures to decrease anatomic outlet resistance.

19.3.1.2.1 Transurethral resection of the prostate (TURP).

Benign prostatic obstruction (BPO) is a common cause for bladder outflow obstruction in middle age and elderly men, and is often a contributory factor for NLUTD in PD. It was widely believed for several years that men with PD should not undergo prostate surgery because of the high risk of incontinence ⁽¹⁷⁸⁾. There is some evidence to support TURP in patients with PD. In a study on 23 patients with PD, TURP was successful in up to 70 %. The risk of de novo urinary incontinence after surgery was reported as minimal ⁽¹⁷⁹⁾.

19.3.1.2.2 Bladder neck incision/ resection.

It is done between the 3 or 9 o'clock position or full circle, and is indicated in those with high PVR and when a prominent obstruction of the sclerotic fibrotic ring in the bladder neck is identified during cystoscopy ⁽¹⁸⁰⁾.

19.3.2 Bladder covering by striated muscle.

Bladder contractility can be restored again by covering acontractile bladder with striated muscle, that can be stimulated electrically or can be contracted voluntarily. Latissimus dorsi ⁽¹⁸¹⁾ and rectus abdominis ⁽¹⁸²⁾ have been used successfully in patients with neuro-urological symptoms ^(183, 184).

19.3.3 Bladder augmentation.

Replacing or expanding the bladder by intestine improves bladder compliance and reduces NDO^(185, 186). It should be considered for:

- People with non-progressive neurological disorders
- Those with complications of impaired bladder storage (hydronephrosis, refractory NDO, hypo compliance or incontinence)
- Only after thorough clinical and urodynamic assessment and discussion with the patient and/or their family members and care givers about treatments to improve bladder storage⁽⁸⁹⁾.

Cautious use of such procedure is needed because of long-term complications that include bladder perforation (1.9%), mucus production (12.5%), metabolic abnormalities (3.35%), bowel dysfunction (15%), and urolithiasis (10%)⁽¹⁸⁷⁾. So, life-long follow-up should be offered to these patients.

Augmenting a bladder usually impairs its intrinsic ability to empty to completion, and CIC is usually needed⁽⁸⁹⁾. Patients performing CIC with augmentation cystoplasty had better urinary function and satisfaction with their urinary symptoms compared to patients performing CIC with or without botulinum toxin treatment⁽¹⁸⁸⁾.

Auto-augmentation (detrusor myectomy): This has been described with the adjunct of overlaying omentum or of a demucosalised intestinal patch in order to support the exposed bladder mucosa. The advantages include low surgical burden, low rate of long-term adverse effects, better patient QoL, and it does not interfere with further interventions^(84, 85, 189-192). However, it showed sub-optimal results in the long-term follow-up.

19.3.4 Urinary diversion.

Must be considered for the protection of the UUT when no other therapy is successful⁽⁸⁵⁾.

Continent diversion: It should be the first choice for urinary diversion for those with limited dexterity. Umbilicus is often used for the stoma site⁽¹⁹³⁻¹⁹⁷⁾. It is an effective treatment option in neuro-urological patients unable to perform CIC through the urethra.

Incontinent diversion: It is the last resort for patients with neurogenic bladder using ileal segment. It is considered in the event of a motor handicap with intractable incontinence and cannot catheterise themselves, in patients with LUT destruction, when the UUT is severely compromised, and in patients who refuse other therapies⁽⁸⁵⁾.

20 Management of UTIs in neuro-uological patients.

Patients with NLUTD are at increased risk of UTI as a result of a variety of factors which include incomplete bladder emptying, high storage and voiding bladder pressures, VUR and the use of catheters ⁽¹⁹⁸⁾.

The goal of reducing both the frequency and severity of UTIs can be achieved in some patients by general measures such as increasing fluid intake and attention to hygiene in relation to urinary tract management. Investigations may demonstrate treatable causes for repeated UTIs such as the presence of urinary tract stones or incomplete bladder emptying ⁽⁸⁹⁾.

Asymptomatic bacteriuria in patients with neuro-uological disorders should not be treated as it results in significantly more resistant bacterial strains without improving the outcome ⁽¹⁹⁹⁾. There is no consensus in the literature about the duration of treatment of symptomatic UTI as it depends on the severity of the UTI and the involvement of kidneys and the prostate. Generally, a five to seven-day course of antibiotic treatment is advised, which can be extended up to fourteen days according to the extent of the infection ⁽¹⁹⁹⁾. The choice of antibiotic therapy should be based on culture and sensitivity.

Recurrent UTI in patients with neuro-uological disorders may indicate suboptimal management of the underlying functional problem, e.g. high bladder pressure during storage and voiding, incomplete voiding or bladder stones.

In a meta-analysis, the use of hydrophilic catheters was associated with a lower rate of UTI ⁽⁵⁴⁾. Bladder irrigation has not been proven effective ⁽²⁰⁰⁾. Low-dose, long-term, antibiotic prophylaxis can reduce UTI frequency, but increases bacterial resistance and is therefore not recommended ⁽²⁰⁰⁾.

There is currently no preventive measure for recurrent UTI in patients with neuro-uological disorders that can be recommended without limitations. Prophylaxis in patients with neuro-uological disorders is important to pursue, but since there are no data favoring one approach over another, prophylaxis is essentially a trial and error approach.

21 Management of sexual dysfunction and infertility in patients with NLUTD.

21.1 Erectile dysfunction.

21.1.1 Phosphodiesterase type 5 inhibitors (PDE5Is).

They are recommended as first-line treatment in neurogenic ED ^(201, 202). In SCI patients, all currently available PDE5Is (tadalafil, vardenafil and sildenafil) improved retrograde ejaculation and improved erectile function and satisfaction on IIEF-15.

Long-term therapy for ED is necessary in most neuro-urological patients and due to this, some have a low compliance rate or stop therapy because of side effects ⁽²⁰³⁾, most commonly headache and flushing ⁽²⁰²⁾. It may induce relevant hypotension in patients with quadriplegia/high-level paraplegia and MSA ⁽²⁰³⁾. Many patients with SCI use on-demand nitrates for the treatment of AD, so they must be counselled that PDE5Is are contraindicated when using nitrate medication.

21.1.2 Mechanical devices.

Mechanical devices (vacuum tumescence devices and penile rings) are effective but are less popular ⁽²⁰⁴⁻²⁰⁸⁾. They should be used cautiously due to risks of penile necrosis from lost sensations.

21.1.3 Intracavernous injections and intraurethral application.

May be offered to those patients who are not responding to oral drugs. Intracavernous injections (alprostadil, papaverine and phentolamine) are effective in SCI, MS, and DM ⁽²⁰⁹⁻²¹⁵⁾. Complications include pain, priapism and corpora cavernosa fibrosis.

Intracavernous vasoactive drug injection is the first-line therapeutic option in patients taking nitrate medications, as well as those with concerns about drug interactions with PDE5Is, or in whom PDE5Is are ineffective.

21.1.4 Penile prostheses.

Penile prostheses may be considered for treatment of neurogenic ED when all conservative treatments have failed. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type ⁽²¹⁶⁻²¹⁸⁾.

21.2 Male fertility.

ED, ejaculation disorders, impaired sperm quality or various combinations of these disorders may deteriorate fertility in neuro urological patients. Other factors contributing to neurogenic infertility are pelvic and retroperitoneal surgery, diabetes mellitus, MS and SCI ⁽²¹⁹⁾.

Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck. These drugs include imipramine, ephedrine and pseudoephedrine ⁽²¹⁹⁾. Semen harvesting from the urine may be considered if antegrade ejaculation is not achieved ⁽²²⁰⁾.

Prostatic massage is safe and easy to use for obtaining semen in men with lesions above T10 ⁽²²¹⁾. In several patients, vibro-stimulation or trans rectal electro ejaculation are needed for sperm retrieval ^(219, 222, 223). In men with SCI, especially at or above T6, AD might occur during sexual activity and ejaculation ^(224, 225).

Surgical procedures, such as, microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE), may be used if vibro-stimulation and electro-ejaculation are not successful ^(226, 227).

21.3 Female sexuality.

The greatest physical barrier to sexual activity is UI. After SCI, about 65-80% of women continue to be sexually active, but to a much lesser extent than before the injury, and about 25% report a decreased satisfaction with their sexual life ⁽²²⁸⁻²³¹⁾. Reflex lubrication and orgasm are more prevalent in women with SCI who have preserved the sacral reflex arc (S2-S5). In SCI women with a complete lesion of the sacral reflex, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions ⁽²³²⁻²³⁴⁾. Problems with positioning and spasticity affect mainly quadriplegic patients ^(228, 235-237).

21.4 Female fertility.

There are limited numbers of studies on female fertility in neurological patients, therefore clinical management should be individualised to optimise both the mother's reproductive outcomes and medical condition.

Women with SCI are more likely to suffer complications during pregnancy, labour and delivery compared to able-bodied women. Regarding anaesthesia, epidural anaesthesia is chosen for most patients with AD during labour and delivery ^(238, 239).

22 Follow-up of NLUTD.

Patients with NLUTD are known to be at high risk of suffering from urinary tract symptoms and complications. For some conditions, such as SB and SCI, there is a risk of silent renal deterioration due to the development of hydronephrosis or the formation of renal stones. Furthermore, some patients with NLUTD will have progressive neurological conditions which will be expected to have an increasing adverse impact on LUT function. The effect of ageing on a damaged LUT will often be greater than its effect on the normally innervated LUT ⁽⁸⁹⁾. For all these reasons, there is an argument to be made for offering patients with NLUTD long-term monitoring of their urinary tract.

The time interval between initial investigations and control diagnostics should not exceed one to two years. In high-risk neuro-urological patients, this interval should be much shorter.

It should be in the form of:

- Urinalysis should be performed only in symptomatic patients (240).
- Lifelong ultrasonography of the UUT at regular intervals in high-risk patients (those with SCI or SB and those with adverse features on UDS such as impaired bladder compliance, DSD or VUR); about once every six months ^(3, 240).
- Physical examination and urine laboratory should take place every year ^(3, 240).
- UDS should be performed as a diagnostic baseline, and repeated during follow-up, more frequently in high-risk patients (SB and SCI) ^(3, 241). It is recommended yearly in this high-risk group, otherwise could be done every two years.
- Specialized, investigation should be warranted for any significant clinical change (e.g. DMSA scan), However, there is a lack of high level evidence ⁽²⁴²⁾.
- Increased prevalence of muscle invasive bladder cancer in NLUTD patients necessitates long-term follow-up ⁽²⁴³⁾. The exact frequency of cystoscopy with or without cytology remains unknown.
- Adolescent patients with neurological pathology are at risk of being lost to follow-up during the transition to adulthood ⁽²⁴⁴⁾.

Table 9: Recommendations for treatment of NB

Recommendations	Strength rating
1. Do not recommend assisted bladder emptying techniques (Crede, Valsalva or triggered reflex voiding) as they are hazardous to the upper tract EXCEPT in patients with absent or surgically removed outlet resistance	Strong

2. Do not offer penile clamps as they are absolutely contraindicated in cases of NDO or low bladder compliance because of the risk of developing high intravesical pressure and pressure sores/necrosis in cases of altered/absent sensations	Strong
3. Prescribe anticholinergics as the first-line medical therapy for NDO	Strong
4. Offer combination therapy of antimuscarinics and Beta 3 agonists to maximise outcomes for NDO	Strong
5. Monitor PVR in people who are not using intermittent or indwelling catheterisation after starting anticholinergics	Strong
6. Prescribe α -blockers to decrease bladder outlet resistance in NLUTD, putting into consideration their off-label use in patients with DSD	Strong
7. Do not offer cholinergics for underactive detrusor due to NLUTD	Strong
8. Use CIC as a standard treatment for patients who are unable to empty their bladder	Strong
9. The average catheterisation times is four to six times per day	Strong
10. The catheter size most often used is between 12-16 Fr	Strong
11. Bladder volume should not exceed 400-500 mL at catheterisation time	Strong
12. Do not use Foley catheters because of the high incidence of latex allergy in the neuro-urological patient population. Use silicone catheters instead	Weak
13. Avoid indwelling transurethral and suprapubic catheterisation whenever possible	Strong
14. Use intradetrusor botulinum toxin injection to reduce NDO when antimuscarinic therapy fails	Strong
15. The recommended dose of botulinum toxin is 200 IU, intradetrusor injection, in 30 sites in the bladder, with exclusion of the trigone, for theoretical prevention of VUR	Strong
16. Offer bladder neck incision in a fibrotic sclerotic bladder neck	Strong
17. Offer botulinum toxin A 100 IU intrasphincteric in cases of DSD	Weak
18. Offer pubovaginal sling as the procedure of choice in neuro-urological females with decreased outlet resistance who can do self-catheterization	Strong
19. Both TOT and the TVT may also be offered to neuro-urological females with decreased outlet resistance, but with a higher incidence of de novo urgency	Weak
20. Insert an AUS in male patients with neurogenic stress urinary incontinence (SUI)	Strong
21. Offer bladder augmentation as an alternative to treat refractory NDO and/or impaired bladder compliance	Strong
22. Consider urinary diversion when no other therapy is successful for NDO and/or impaired bladder compliance	Strong

23. Do not perform screening for asymptomatic bacteriuria nor treat it in NLUTD patients	Strong
24. Avoid the prescription of long-term antibiotics for recurrent UTIs	Strong
25. When changing catheters in patients with a long-term indwelling urinary catheter, do not offer antibiotic prophylaxis routinely	Strong
26. Consider antibiotic prophylaxis for patients who have a history of symptomatic UTI after catheter change or experience trauma during catheterisation	Strong
27. Prescribe oral PDE5I as first-line medical treatment in neurogenic ED	Strong
28. Perform intracavernous injections of vasoactive drugs as second-line medical treatment in neurogenic ED	Strong
29. Reserve penile prostheses for selected patients when all other treatments have failed	Strong
30. Perform vibrostimulation and transrectal electroejaculation for sperm retrieval in men with SCI	Strong
31. Do not offer medical therapy for the treatment of neurogenic sexual dysfunction in women	Strong
32. Assess the upper urinary tract every six months in high-risk patients by ultrasonography	Strong
33. Perform a physical examination and urine laboratory every year in high-risk patients	Strong
34. Perform UDS as a mandatory baseline diagnostic intervention. It is recommended yearly in high-risk group, otherwise could be done every two years	Strong

23 Conclusions.

Early diagnosis of NLUTD is fundamental before deciding any plan of management. Extensive history taking, thorough examination together with laboratory, radiological and urodynamic investigations should be done in every NLUTD patient. Accordingly, tailoring and individualizing the plan of management follows, which ensures the best practice of clinical care offered to these patients. The role of these guidelines is to offer you expert advice on how to manage these patients.

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Female Urology



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25 Abbreviations

ALPP	Abdominal Leak Point Pressure	MUI	Mixed Urinary Incontinence
ASC	Abdominal Sacrocolpopexy	MS	Multiple Sclerosis
AUA	American Urological Association	NLUTD	Neurogenic Lower Urinary Tract Dysfunction
SUI	Anti-Stress Urinary Incontinence	OAB	Overactive Bladder
BOO	Bladder Outlet Obstruction	PFME	Pelvic Floor Muscle Exercises
BPS	Bladder Pain Syndrome	PFMT	Pelvic Floor Muscle Training
BTX-A	Botulinum Toxin A	POP	Pelvic Organ Prolapse
CNS	Central Nervous System	PTNS	Percutaneous Tibial Nerve Stimulation
CIC	Clean Intermittent Catheterization	PGAD	Persistent genital arousal disorder
DHIC	Detrusor Hyperactivity with Impaired Contractility	PFME	Pessaries and Pelvic Floor Muscle Exercises
DO	Detrusor Overactivity	PVR	Post Void Residual
DSD	Detrusor Sphincter Dyssynergia	PFSAD	Psychological arousal disorder
DUA	Detrusor Underactivity	PVS	Pubovaginal Sling
DSM-5	Diagnostic and Statistical Manual for Mental Disorders	QoL	Quality of Life
ER	Extended Release	RVF	Rectovaginal fistula
FI	Fecal Incontinence	SNS	Sacral Neuromodulation
FOD	Female Orgasmic Disorders	SSRI	selective serotonin reuptake inhibitor
FSAD	Female sexual arousal disorders	SUI	Stress Urinary Incontinence
FSD	Female Sexual Dysfunctions	SCI	Suprasacral Spinal Cord Injuries
FSFI	Female Sexual Function Index	AUA	The American Urological Association
FM	Fibromyalgia	EUG	The Egyptian Urological Guidelines
GFSAD	Genital arousal disorder	ICSI	The Interstitial Cystitis Symptom Index
GU	Genitourinary	SUFU	The Society Of Urodynamics, Female Pelvic Medicine And Urogenital Reconstruction
GRA	Global Response Assessment	TENS	Transcutaneous Electrical Nerve Stimulation
GAG	Glycosaminoglycan	TCAs	Tricyclic Antidepressants
HSDD	Hypoactive sexual desire disorder	UD	Urethral Diverticulae (
IR	Immediate Release	UPP	Urethral Pressure Profilometry

ICI	International Consultation on Incontinence	UVF	Urethrovaginal fistula
ICS	International Continence Society	UUI	Urgency Urinary Incontinence
IUGA	International Uro-Gynecological Association	UI	Urinary incontinence
ISD	Intrinsic Sphincteric Deficiency	UTI	Urinary Tract Infection
ISD	Intrinsic Sphincteric Deficiency	UTIs	Urinary Tract Infections
LUTS	Lower Urinary Tract Symptoms	VVF	Vesicovaginal fistula
LUTS	Lower Urinary Tract Symptoms	VUDS	Videourodynamics
MRI	Magnetic Resonance Imaging	VAS	Visual Analogue Score
MUCP	Maximal Urethral Closure Pressure	VCUG	Voiding Cystourethrogram
MUS	Mid-Urethral Synthetic Slings		

26 Abstract.

26.1 Objectives

The Egyptian Urological Guidelines (EUG) on Female Urology aim to help and guide clinical practitioners to have knowledge of the incidence, standard definitions, diagnosis, therapy, and follow-up of females with urinary incontinence (UI), pelvic organ prolapse (POP), uro-gynecological fistulae, urethral injury, urethral diverticulae, geriatric urinary incontinence, bladder pain syndrome (BPS), bladder outlet obstruction (BOO) and female sexual dysfunctions (FSD). This chapter integrates recent international guidelines with local experts' opinions based on Egyptian healthcare and socioeconomic circumstances.

26.2 Methods

Databases searched included Medline, Cochrane Libraries, EAU guidelines, ICS recommendations, 6th ICI recommendations, AUA and NICE guidelines, from January 2018 to September 2020.

Review of several meta-analyses, leading institutional protocols and relevant Egyptian publications were taken into consideration. All statements were graded according to strength of recommendation. Each statement was given a strength rating (strong or weak).

26.3 Results

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

26.4 Conclusions

These guidelines provide practical evidence-based guidance on the clinical aspect of many uro-gynecological entities. The main target is entirely focused on assessment and treatment, reflecting the recommended clinical practice. This can provide the basis for thinking through patient's management and also for planning and designing clinical services.

Early diagnosis of the different female uro-gynecological problems is fundamental before deciding any plan of management. Accordingly, tailoring and individualizing the plan of management follows, which ensures the best practice of clinical care offered to these patients. The role of these guidelines is to offer expert advice on how to manage these patients.

27 Introduction.

Urinary incontinence (UI) is an extremely common complaint all over the globe. It causes great social distress and embarrassment, as well as significant costs, to individuals and societies. Estimates of prevalence vary according to the definition of incontinence and the population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost.

There are many types of UI, including stress urinary incontinence (SUI), urgency urinary incontinence (UUI) and mixed urinary incontinence (MUI). Uro-gynecological fistulae are common in Egypt and considered a cause of UI in females. Bladder pain syndrome (BPS), previously known as interstitial cystitis, has common symptoms with overactive bladder (OAB), thus needs to be diagnosed accurately to ensure the correct management.

Bladder outlet obstruction (BOO) in females is an under-reported and underdiagnosed problem. Diagnosis of this condition is crucial as the presenting lower urinary tract symptoms (LUTS) always intermingle. Another important topic is management of geriatric incontinence in females, and the considerations taken in the management of such patients. Female sexual dysfunction (FSD) is an entity always neglected in the urogynecology practice, with no definite guidelines or recommendations available.

27.1 Aims and Objectives.

The Egyptian Urological Guidelines on Female Urology aim to help and guide clinical practitioners to have knowledge of the incidence, standard definitions, diagnosis, therapy, and follow-up of females with urinary incontinence (UI), pelvic organ prolapse (POP), uro-gynecological fistulae, urethral injury, urethral diverticulae, geriatric incontinence, bladder pain syndrome (BPS), bladder outlet obstruction (BOO) and female sexual dysfunctions (FSD). This chapter integrates recent international guidelines with local experts' opinions based on Egyptian healthcare and socioeconomic circumstances. It also reflects the opinions of experts in Female Urology and represent state-of-the art references for all clinicians, as of the publication date.

The terminology used and the diagnostic procedures mentioned in this chapter follow the recommendations published by the International Continence Society (ICS). These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient. Every patient is a unique case by herself and the treating urologist should take some advice from the guidelines which may not be, in some situations, perfectly satisfying all the findings in a particular patient. Therefore, the guidelines should not be a final legal document but should help during investigation of a particular case.

27.2 Methodology.

The committee members were selected according to their expertise in the field of Female and Functional Urology. The committee members are all female and functional urologists from three different Egyptian Universities; Kasr Al-Ainy Medical School, Ain Shams and Alexandria Universities. All members have no conflict of interest.

Databases searched included Medline, Cochrane Libraries, European Association of Urology (EAU) guidelines, ICS recommendations, 6th International consultation on incontinence (ICI) recommendations, American Urological Association (AUA) and NICE guidelines, in the period from January 2018 and September 2020.

Review of several meta-analyses, leading institutional protocols and relevant Egyptian publications were also taken into consideration. All statements were graded according to strength of recommendation. Each statement was given a strength rating (strong or weak).

28 Urinary Incontinence (UI) in Females

- UI is defined as the involuntary passage of urine. There are many types of UI in the female:
 - **Stress urinary incontinence (SUI)**. It is involuntary urinary leakage due to increased abdominal pressure associated with sneezing, coughing, exercise, lifting heavy objects, and change of position ⁽¹⁾. Although the utility of urethral function assessment remains controversial, most of the urologists use abdominal leak point pressure (**ALPP**) and a minority still perform urethral pressure profilometry (**UPP**) ⁽²⁾.
 - **SUI** could be due to urethral hypermobility or intrinsic sphincteric deficiency (**ISD**). Urethral hypermobility is due to rotational descent of the bladder neck and the urethra, while ISD is defined as **ALPP** of less than 60 cmH₂O or a maximal urethral closure pressure (**MUCP**) of less than 20 cmH₂O. The urethra is usually fixed and immobile ⁽²⁾.
 - **SUI** can have a significant negative impact on the quality of life (**QoL**) of not only those who suffer from the condition, but also on those friends, family members and care givers whose lives and activities may also be limited ⁽³⁾.
 - **Urgency urinary incontinence (UII)** is the involuntary urinary leakage that is accompanied by or preceded by urgency ⁽³⁾.
 - Mixed urinary incontinence (**MUI**) refers to a combination of SUI and UII.
 - **Overflow urinary incontinence**: Its incidence is rare in females, and it is usually a consequence of bladder outlet obstruction (**BOO**) with increased post void residual (**PVR**) urine. It could result from high-stage pelvic organ prolapse (**POP**) or post anti-incontinence procedures.

28.1 Guidelines Statements on SUI.

- In females complaining of **SUI** and willing to undergo surgical intervention, their initial evaluation **should** include history taking, including assessment of the most bothersome complaint, pelvic examination, with objective demonstration of SUI with at least half-filled bladder, assessment of PVR urine and urinalysis (**LE 3**)
- In females undergoing surgical intervention for **SUI**, urologists should perform additional diagnostic procedures if there's any of the following conditions: (**LE 3**)
 - Inability to reach definitive diagnosis based on symptoms and initial evaluation
 - No clinically demonstrable **SUI**
 - Known or suspected neurogenic lower urinary tract dysfunction (**NLUTD**)
 - Abnormal urinalysis such as pyuria or hematuria

- Urgency-predominant **MUI**
- Raised **PVR** or obstructive urinary symptoms
- High-stage **POP** (stage 3 or higher) and SUI is not demonstrable clinically after **POP** reduction
- Failure of prior anti-incontinence surgery
- Prior **POP** repair surgery
- Urologists **may** omit performing urodynamic testing (**UDS**) for female patients with **SUI** desiring treatment when SUI is clearly demonstrated (**LE 2a**)
- Urologists may omit performing **UDS** for female patients with **SUI-predominant MUI** desiring treatment (**LE 2b**)
- In patients with SUI or stress-predominant **MUI** who wish to undergo treatment, urologists **should** counsel these patients regarding the availability of the following treatment options: (**LE 3**)
 - Observation
 - Pelvic floor muscle training with or without biofeedback
 - Other non-surgical options (e.g., continence pessary)
 - Surgical intervention
- Urologists **should** counsel patients on potential complications specific to each treatment option (**LE 1a**)
- In patients with **SUI** or stress-predominant **MUI**, physicians **may** offer non-surgical treatment options such as continence pessaries and pelvic floor muscle exercises (PFME) (**LE 3**)
- In female patients willing to undergo anti-SUI surgery, urologists may offer mid-urethral synthetic slings (**MUS**), pubovaginal sling (**PVS**), Burch colposuspension or bulking agents (**LE 1a**)
- Urologists must discuss the specific risks and benefits of **MUS** placement as well as the available alternative options (**LE 3**)
- Urologists may offer either the retropubic (**TVT**) or transobturator (**TOT**) **MUS** for female patients willing to perform **MUS** surgery (**LE 1a**)
- Urologists may consider retropubic (**TVT**) **MUS**, **PVS** or bulking agents for female patients with **ISD** and willing to perform **MUS** surgery (**LE 3**)
- Urologists **should not** place a synthetic **MUS** if the urethra is inadvertently injured at the time of planned **MUS** procedure (**LE 3**)

- Urologists **should not** place a synthetic **MUS** in patients undergoing concomitant urethral diverticulectomy, repair of urethrovaginal fistulae, or simultaneously during urethral mesh excision (**LE 3**)
- Synthetic **MUS** **should** be avoided in patients undergoing **SUI** surgery who have poor wound healing (e.g., irradiated patients, presence of significant scarring and fibrosis, poor tissue quality and immunocompromised patients) (**LE 3**)
- Urologists **may** offer patients with **SUI** and concomitant **NLUTD** surgical treatment of **SUI** after appropriate evaluation and dedicated counselling (**LE 3**)
- Urologists may offer synthetic **MUS** slings to female patients planning to get pregnant, diabetics, morbidly obese patients and geriatric females, after appropriate evaluation and dedicated counselling (**LE 3**)
- During the early postoperative period following anti-**SUI** procedures, patients **should** be examined for significant voiding problems, pain, occurrence of hematuria, any sign of mesh extrusion, wound healing or other unanticipated events (**LE 2a**)
- Patients should be seen and examined by their urologist within **six** months post-operatively of their anti-**SUI** procedure (**LE 2b**)
- The subjective outcome of anti-**SUI** surgery, as perceived by the patient, should be assessed and documented (**LE 1a**)
- Patients should be asked about **residual** incontinence, ease of voiding/force of stream, recent urinary tract infection (**UTI**), pain, sexual function and new onset or worsened **OAB** symptoms (**LE 1a**)
- A physical exam, including examination of all surgical incision sites, should be performed to evaluate healing, tenderness, mesh extrusion (in the case of synthetic **MUS**), and any other potential abnormalities. This should be coupled with **PVR** estimation (**LE 2a**)

28.2 Statement on the Use of Vaginal Mesh for the Surgical Treatment of SUI

- Synthetic **MUS** placement is the most common surgery currently performed for **SUI**. Extensive data exist to support the use of synthetic polypropylene **MUS** for the treatment of female **SUI**, with minimal morbidity. Advantages include shorter operative time, reduced postoperative pain, reduced hospitalization and reduced voiding dysfunction. Mesh-related complications can occur, but the rate of these complications is relatively low. Any restriction of the use of **MUS** would be a disservice to females who are willing to undergo surgical correction of **SUI**.
- Both the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) and the American Urological Association (AUA) recognize synthetic polypropylene monofilament **MUS** as a suitable treatment option for **SUI** in properly

selected patients who are appropriately counseled regarding this surgical procedure, by surgeons who are trained in the placement of such devices, as well as the recognition and management of potential complications associated with their use.

29 Diagnosis and Treatment of Overactive Bladder (OAB) in

Females.

- The International Uro-gynecological Association (**IUGA**) and International Continence Society (**ICS**) define **OAB** as the presence of "urinary urgency, usually accompanied by frequency and nocturia, with or without UII, in the absence of UTI or other obvious pathology."⁽⁴⁾ **OAB** is typically a clinical diagnosis.
- **Urgency** is the hallmark of OAB. It is defined as the "complaint of a sudden, compelling desire to pass urine which is difficult to defer."⁽⁴⁾
- **Urinary frequency** can be reliably measured with a voiding diary. Traditionally, up to seven micturition episodes during waking hours has been considered normal,⁽⁵⁾ however this number is highly variable based upon hours of sleep, fluid intake and comorbid medical conditions. It is the patient's perception that he/she voids too much as compared to their previous usual pattern.
- **Nocturia** is the complaint of interruption of sleep one or more times because of the need to void.⁽⁴⁾ Three or more episodes of nocturia constitute moderate or major bother.⁽⁶⁾ Nocturia is a multifactorial symptom which is often due to factors unrelated to OAB (e.g., excessive nighttime urine production, sleep apnea).

29.1 Epidemiology.

In population-based studies, OAB prevalence rates range from 9% to 43% in women.⁽⁷⁻¹⁴⁾ OAB symptom prevalence and severity tend to increase with age.^(11-12, 15) A proportion of OAB cases (37-39%) remits during a given year, but the majority of patients have symptoms for years.^(15, 16) Dry-OAB is more common in males, while wet-OAB is more prevalent in females.

29.2 Differential diagnosis.

- It includes nocturnal polyuria (defined as the production of greater than 20 to 33% of total 24-hour urine output during the period of sleep, which is age-dependent with 20% for younger individuals and 33% for elderly individuals)^(17,18), low nocturnal bladder capacity and diabetes insipidus.
- The clinical presentation of interstitial cystitis/ bladder pain syndrome (BPS) shares the symptoms of urinary frequency and urgency, with or without UII; however, bladder and/or

pelvic pain, including dyspareunia, is a crucial component of its presentation in contradistinction to OAB.

29.3 Guidelines statement on OAB.

- **Minimum** requirements for the diagnosis of **OAB** are careful history, physical examination and urinalysis (**LE 2b**)
- **UDS**, cystoscopy and imaging of the kidneys and bladder should not be used in the initial workup of the uncomplicated OAB patient (**LE 3**)
- **OAB** is not a disease; it is a symptom complex that generally is not a life-threatening condition (**LE 3**)
- Urologists **should** educate patients regarding normal lower urinary tract function, natural history of **OAB** and the available treatment options with their benefits/risks (**LE 3**)
- Acceptable symptom control **may** require trials of multiple therapeutic options before it is achieved (**LE 3**)
- Urologists **should** offer behavioral therapies (e.g., bladder training, bladder control strategies, PFME, fluid management) as first line therapy to all patients with OAB (**LE 1b**)
- Behavioral therapies **may be** combined with pharmacologic management in patients with OAB (**LE 2b**)
- Oral anti-muscarinics or oral β 3-adrenoceptor agonists **should** be offered as second-line therapy for OAB treatment (**LE 1a**)
- Extended release (**ER**) formulations of anti-muscarinics are preferred over immediate release (**IR**) formulations because of lower incidence of dry mouth (**LE 2a**)
- Dose modification of the same anti-muscarinic or a different anti-muscarinic medication or a β 3-adrenoceptor agonist **may be** tried if a patient experiences inadequate symptom control and/or intolerable adverse drug events with one anti-muscarinic medication (**LE 2b**)
- Urologists **may** consider combination therapy with an anti-muscarinic and β 3-adrenoceptor agonist for patients, who are refractory to monotherapy with either anti-muscarinics or β 3-adrenoceptor agonists (**LE 2a**)
- Anti-muscarinics **should** be used with extreme caution in patients with narrow-angle glaucoma, impaired gastric emptying or a history of urinary retention (**LE 3**)
- If an anti-muscarinic is effective in controlling **OAB** symptoms but with resultant occurrence of constipation or dry mouth as an adverse event, a trial to manage these side effects is **considered** before abandoning effective anti-muscarinic therapy. Management

may include bowel management, fluid management, dose modification or alternative anti-muscarinic. (LE 3)

- Urologists **should** be aware of the cumulative anticholinergic load in patients using other medications with anti-cholinergic properties. (LE 3)
- Urologists may offer intradetrusor onabotulinum toxin A (100U) as third-line treatment option in carefully selected and thoroughly counseled patients who has been refractory to first- and second line **OAB** treatments. (LE 2a)
- Patients willing to undergo intradetrusor onabotulinum toxin A injection must return for frequent **PVR** estimation and be able to perform clean intermittent catheterization (**CIC**) if necessary. (LE 2a)
- Urologists may offer percutaneous tibial nerve stimulation (**PTNS**) as third-line treatment in carefully selected patient population. (LE 2b)
- Sacral neuromodulation (**SNS**) may be offered as third-line treatment in refractory **OAB**. (LE 3)
- Augmentation cystoplasty or urinary diversion **may be** considered for severe, refractory **OAB** patients, not responding to any of the first, second or third-line treatment options, after careful and detailed counselling about the irreversible nature of the procedure, the possible complications and the need for **CIC** to empty their bladders. (LE 3)
- Indwelling urinary catheters (including transurethral and suprapubic catheters) are **not recommended** as a management option for **OAB** because of the adverse risks. They could be considered as a last resort in selected patients. (LE 3)

30 Pelvic Organ Prolapse (POP).

POP is a condition in which the urinary bladder, uterus, bowel or rectum protrudes into the vagina ^(19,20). Although various procedures have been tried to correct apical prolapse, until now, the most successful option has been abdominal sacrocolpopexy (**ASC**), whether open or laparoscopic, with success rates approaching 93–99% ⁽²¹⁾. It is considered an excellent choice, because it maximizes functional vaginal length and attains a near-normal vaginal axis.

POP usually co-exists with other urinary tract disorders, with **SUI** being the most socially unacceptable condition ^(19,20). About 40–50% of women with POP have concomitant **SUI** ⁽²⁰⁾. **SUI** can be manifest or occult (i.e., evident only upon reduction of the POP) and in some cases, can develop after surgical POP repair (denovo **SUI**). The relationship between POP and UI is complex, as both UI and POP probably share some of the same etiological mechanisms ^(22,23).

Surgical challenges exist for urogynecologists when they treat **POP** with or without concomitant **SUI**. One of the challenging scenarios is treating females with POP without **SUI**, whether to perform prophylactic anti-incontinence procedure or not in these continent women.

The other challenging scenario occurs when both **POP** and **SUI** are co-existing. Two strategies are present: a one-step strategy (combined prolapse and incontinence surgery) and a two-step strategy (correct the prolapse first and evaluate incontinence afterwards). Evidence supporting the value of combination surgery is still limited in these women ^(24,25). Nevertheless, many physicians combine incontinence surgery during POP repair and there are probably large regional differences in treatment ^(26,27,28).

30.1 Guidelines statements on POP.

- Take a **detailed history** to include symptoms of POP, urinary, bowel and sexual function in the initial assessment of **POP (LE 1a)**
- Perform a **complete pelvic examination** in the standing and supine position, to document presence of POP, the degree of prolapse of the anterior, central and posterior vaginal compartments of the pelvic floor, using the **POP-Q** (Pelvic Organ Prolapse Quantification) system (**LE 1a**)
- Do not routinely perform imaging to document the presence of vaginal prolapse if a prolapse is detected by physical examination (**LE 3**)
- Do not perform dynamic MRI in the initial assessment of POP (**LE 3**)
- Perform dynamic MRI of the pelvis to exclude presence of rectal intussusception or rectal prolapse. If not available, perform cystocolpodefecography (**LE 3**)
- Offer females with low grade POP non-surgical treatment options as losing weight if BMI >30, minimize lifting heavy objects and treating constipation (**LE 1a**)

- Consider topical vaginal estrogen for females with POP and signs of vulvovaginal atrophy (**LE 2a**)
- Consider **PFME** for at least **16 weeks** as a first option for females with symptomatic POP-Q stage 1 or stage 2 (**LE 2b**)
- Offer a vaginal pessary for females with symptomatic POP (**LE 2b**)
- When considering vaginal pessary for **POP**, advise patients about the effects of pessaries on sexual activity, risk of vaginitis and vaginal erosions, and the need for exchange every 3 months (**LE 2b**)
- Offer surgery for **POP** to females whose symptoms have not improved after non-surgical treatment (**LE 1b**)
- Patients willing to undergo surgery for **POP** should be advised about the risks and benefits of each procedure and the risk of recurrent prolapse (**LE 1a**)
- In patients who will undergo ASC for treatment of POP, they should be informed about the use of intra-abdominal synthetic mesh for fixation, and that risk of erosion is less than that with vaginally placed meshes (**LE 2b**)
- For female patients with apical uterine prolapse, offer surgical treatment in the form of ASC, vaginal sacrospinous fixation (SSF) or vaginal hysterectomy with or without vaginal SSF (**LE 2a**)
- Offer females with vault prolapse ASC or vaginal SSF (**LE 2a**)
- Consider **colpocleisis** for apical prolapse in sexually inactive elderly females who do not intend to have penetrative vaginal sex (**LE 3**)
- Offer anterior or posterior repair without mesh to females with anterior vaginal wall prolapse or posterior vaginal wall prolapse respectively (**LE 2b**)
- Offer females a follow-up visit six months after surgery for POP. Follow-up visit should include a vaginal examination and, if mesh was used, check for mesh exposure (**LE 1a**)
- When performing ASC for apical POP in females with concomitant SUI, it is advisable to perform ASC alone and evaluate SUI symptom after six months (**LE 3**)
- Perform cystourethroscopy in suspected vaginal erosion, urethral perforation, bladder perforation, uro-gynecological fistulae, stone on mesh (**LE 3**)
- Perform imaging of the pelvis (vaginal ultrasound or MRI) in suspected mesh exposure or perforation (**LE 3**)
- Discuss treatment with topical vaginal estrogen cream in females who have a single area of vaginal mesh exposure that is smaller than 1 cm² (**LE 2b**)

- Consider partial or complete surgical removal of the vaginal portion of mesh if the area of vaginal mesh exposure is 1 cm² or larger, or if there has been no response to non-surgical treatment after a period of 3 months, or in immunocompromised patients (**LE 2b**)
- Complete removal of the vaginal portion of mesh is associated with a greater risk of recurrent SUI than partial removal (**LE 3**)
- Partial removal of the mesh is associated with a higher rate of further mesh extrusion (**LE 2b**)
- Complete removal of the vaginal mesh is not always possible (**LE 3**)
- Perform sling release in females who have voiding difficulty after mesh sling surgery. If failed, sling incision is an alternative option (**LE 2a**)
- Refer females who are candidates for excision of mesh sling for persistent voiding dysfunction to a specialized tertiary center in the management of mesh-related complications (**LE 2b**)

Table 10: Recommendations for UI and POP.

Recommendations	Strength Rating
1. Use an appropriate validated questionnaire to assess the UI severity.	Strong
2. Ask patients with UI to complete a bladder diary, of at least three days, preferably not consecutive days.	Strong
3. Perform urinalysis in the initial assessment of patients with UI.	Strong
4. Do not routinely treat asymptomatic bacteriuria in geriatric population to improve or treat UI.	Strong
5. Measure PVR during the assessment of patients with complicated UI and in those with voiding problems, using ultrasound.	Strong
6. Monitor PVR in patients receiving treatments that may cause voiding dysfunction, including antimuscarinics, intradetrusor botulinum toxin injection and anti-SUI surgeries.	Strong
7. Adhere to the ‘Good urodynamic Practice’ standards described by ICS when performing UDS.	Strong

8. Do not perform UDS when offering treatment for uncomplicated SUI.	Strong
9. Perform UDS for patients with uncomplicated UI before surgical treatment.	Weak
10. Do not perform UPP in the assessment of SUI.	Strong
11. Do not use pad tests in the routine initial assessment of women with UI.	Strong
12. Do not routinely order imaging of the kidneys or the bladder or perform cystoscopy in the initial assessment of UI.	Strong
13. Obtain a drug history from all patients with UI.	Strong
14. Advise adults who suffer from UI and constipation about bowel management.	Strong
15. Offer incontinence pads and/or containment devices for management of UI in selected patients, only as a last resort of management.	Strong
16. Advise morbidly obese and overweight patients of BMI>30 with UI to lose weight to improve their UI or improve the outcome of anti-SUI procedures.	Strong
17. Advise patients with UI to decrease their caffeine intake to improve urgency and frequency episodes.	Strong
18. Advise females with UI to modify their fluid intake.	Weak
19. Offer bladder training as a first-line treatment option to adults with UUI or MUI, for at least six weeks.	Strong
20. Offer intensive PFME programs for at least three months, as a first-line therapy to females with SUI or MUI, after dedicated pelvic examination and ensuring compliance of the patients.	Strong
21. PFME should comprise at least 8 contractions performed 3 times per day.	Strong
22. Perform routine digital assessment of pelvic floor muscle contraction before the implementation of supervised PFME for the treatment of UI.	Strong

23. Bladder catheterization (intermittent or indwelling urethral or suprapubic) should be considered for females in whom persistent urinary retention is causing UI, symptomatic UTIs or renal impairment, and in whom this cannot otherwise be corrected.	Strong
24. Do not use intravaginal and intraurethral devices for the routine management of UI in women.	Weak
25. Do not offer electrical stimulation for treatment of SUI.	Strong
26. Do not offer magnetic stimulation for treatment of UUI.	Strong
27. Discuss with the females the benefit of non-surgical management and drugs for OAB before offering surgery if SUI is the predominant symptom in MUI.	Weak
28. Treat the most bothersome complaint first in patients with MUI.	Weak
29. Do not offer females with OAB flavoxate, propantheline or imipramine.	Strong
30. Offer antimuscarinics or B3 agonists for adults with UUI or urgency-predominant MUI who failed conservative treatment.	Strong
31. Consider dose modification or prescribing an alternative antimuscarinic, or mirabegron, or a combination if the efficacy of an antimuscarinic treatment was ineffective.	Strong
32. Prescribe extended release (ER) formulations of antimuscarinics whenever possible.	Strong
33. Do not offer immediate release (IR) of oxybutynin to geriatric females who may be at higher risk of a sudden deterioration in their physical or mental health.	Weak
34. Duloxetine may be offered in patients with mild SUI.	Weak
35. Offer long-term topical vaginal estrogen to post-menopausal women with UI and symptoms of genito-urinary syndrome of menopause (GSM).	Strong
36. Advise females with a history of breast cancer to consult their oncologist when prescribing long-term vaginal estrogen.	Weak
37. Do not prescribe systemic estrogen for females with UI.	Strong

38. Offer desmopressin to patients with nocturnal polyuria and nocturia.	Strong
39. Monitor plasma sodium levels in geriatric patients taking desmopressin.	Strong
40. Offer a synthetic MUS, colposuspension, PVS or bulking agents to females with uncomplicated SUI.	Strong
41. Explain in detail the specific complications associated with each procedure.	Strong
42. Inform women that any vaginal surgery may have an impact on sexual function, which is generally positive.	Weak
43. Advise females with SUI that synthetic MUS is a permanent implant and complete removal might not be possible.	Strong
44. Give the patient with SUI written information about the synthetic MUS implant, including its name, manufacturer, date of insertion, and the implanting surgeon's name and contact details.	Strong
45. Use type I macroporous, monofilament polypropylene, coloured MUS.	Strong
46. Inform female patients with MUI that synthetic MUS placement is not as successful as in females with SUI only.	Strong
47. Inform females with MUI that a single treatment option is less likely to cure their UI, and that it is prudent to treat other types of UI specially the most bothersome symptom.	Strong
48. Inform elderly females with SUI about the lower probability of success of MUS.	Weak
49. Do not offer females an artificial urinary sphincter (AUS) to treat SUI unless previous surgery has failed.	Weak
50. Advise females with SUI that bulking agents require repeat injections and long-term durability is not established.	Strong
51. Management of complicated SUI should only be offered in expert tertiary referral centers.	Weak
52. Consider performing UDS, imaging and/or cystoscopy in the evaluation of females with recurrent SUI.	Weak

53. Inform women with recurrent SUI that the outcomes of any surgical procedure used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications.	Weak
54. Perform UDS for females complaining of UI and POP	Weak
55. Offer simultaneous surgery for bothersome POP and symptomatic SUI.	Strong
56. Inform females with bothersome POP and symptomatic SUI of the increased risk of adverse events with combined surgery compared to POP surgery alone.	Strong
57. Inform females with bothersome POP but without symptomatic SUI that there is a risk of developing de novo SUI after POP repair surgery.	Strong
58. Warn women with bothersome POP but without symptomatic SUI of the increased risk of adverse events with combined surgery compared to POP surgery alone.	Strong
59. Do not offer prophylactic synthetic MUS placement in females with bothersome POP and without symptomatic SUI.	Strong
60. Offer intradetrusor onabotulinum toxin A (100 U) injections to patients with OAB as a second-line treatment.	Strong
61. Inform the patients of the limited duration of response of onabotulinum toxin A and warn them of the possible prolonged need of CIC.	Strong
62. Do not offer botulinum toxin B to females with OAB.	Strong
63. Offer PTNS as a third line treatment option for UUI in females.	Strong
64. Offer augmentation cystoplasty to patients with UUI who have failed all other treatment options.	Weak
65. Inform patients undergoing augmentation cystoplasty of the high risk of having to perform CIC.	Weak
66. Do not offer autoaugmentation (detrusor myectomy) as a treatment option for UI.	Weak
67. Only offer urinary diversion to patients who have failed all treatment options of UUI and who are not candidates for augmentation cystoplasty and not willing to do CIC.	Weak

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31 Female urethral diverticulae (UD)

31.1 Definition.

It is a peri-urethral cystic swelling connected to the urethra via an ostium ⁽¹⁾.

31.2 Etiology.

There is controversy regarding the exact origin. However, infection of the peri-urethral glands $\pm$ abscess formation $\pm$ gland rupture into the urethra is considered the most accepted theory 1. Mechanical trauma during vaginal delivery has been reported to be a cause of UD ⁽²⁾ Congenital urethral diverticulum is relatively uncommon; however, it has been reported. No accurate estimate of the prevalence but it is estimated to be 1-6% of adult females ⁽³⁾.

31.3 Evaluation and diagnosis.

31.3.1 Symptoms.

- Anterior vaginal mass
- Vaginal pain or urethral pain
- Dysuria
- Dyspareunia
- Urinary frequency, urgency and urinary incontinence (UI)
- Post-voiding dribbling
- Sense of incomplete emptying, double voiding and hesitancy
- Vaginal and urethral discharge ⁽³⁾

31.3.2 Signs.

- Recurrent urinary tract infections (UTIs) and hematuria
- Urine expression upon compression of the vaginal swelling, and if infected, pus may be expressed
- Anterior vaginal cystic swelling and vaginal tenderness
- Urinary retention
- Urethral discharge with stripping of anterior vaginal wall ⁽³⁾

Most UD are located posterolaterally over the middle and proximal portion of the urethra. During examination, evaluation for stress urinary incontinence (SUI) should be performed as well as the assessment for any concomitant pelvic organ prolapse (POP) ⁽⁴⁾

31.4 Investigations.

- Urine analysis/culture: Most common organism is E. coli. Proper treatment of infection is mandatory before any surgical intervention ⁽³⁾
- Voiding cystourethrogram (VCUG): It provides an excellent imaging of UD ⁽⁴⁾. However, it doesn't show the actual spatial configuration of the UD.
- Ultrasonography (transvaginal or trans-labial): UD appear as an anechoic or hypoechoic area. It is a noninvasive modality with no radiation that does not requires voiding. However, may not produce an image with precise anatomy ⁽⁵⁾.
- Magnetic resonance imaging (MRI) with postvoid films: Noninvasive, high resolution imaging appears as decreased signal intensity in T1 images with high signal intensity in T2 ⁽⁶⁾. This is considered the imaging modality of choice to show the number, the site and complexity of the UD.
- Urodynamic study in patient with significant voiding dysfunction: Can accurately differentiate SUI from post micturition dribbling, vaginal voiding and double micturition form a urine filled UD ⁽⁷⁾.
- Diagnostic urethroscopy is highly sensitivity however it is invasive ⁸ and may not show the ostium of the UD in most of the cases.

31.5 Differential diagnosis:

- Vaginal leiomyoma
- Skene gland abnormalities
- Gartner duct abnormalities
- Urethral mucosal prolapse
- Urethral carbuncle
- Bulking agent ⁽⁹⁾

31.6 Treatment.

31.6.1 Asymptomatic and/or poor medical condition and/or refusing surgical intervention:

Suppressive antimicrobial therapy, postvoiding stripping of the urethra and long-term surveillance.

31.6.2 In symptomatic patients:

- In absence of voiding dysfunction proceed for transvaginal repair.
- If associated with voiding dysfunction, UDS is recommended to evaluate the presence of SUI. If present, transvaginal repair of UD with anti-incontinence surgery, but avoid using synthetic tapes. Preoperative preparation includes treatment of UTI, topical estrogen cream for several weeks in case of postmenopausal atrophic vaginitis ^(3,10).
- Cystourethroscopy is performed to visualize the UD ostium as well as to evaluate for other causes of LUTS. UD excision and reconstruction are the preferred surgical technique.
- Transvaginal marsupialization may reduce operative time and blood loss with less recurrence; however, it may be associated with dyspareunia and should be reserved only for distal UD. Synthetic slings should not be placed concomitantly at the time of urethral diverticulectomy. A well vascularized vascular flap (e.g., Martius Flap) may reduce the risk of wound breakdown. A peri-catheter VCUG is done 2 to 3 weeks postoperatively before catheter removal ^(3,10,11).

Table 11: Recommendations for female urethral diverticulae.

Recommendations	Strength Rating
1. Although often highly symptomatic, not all urethral diverticula mandate surgical excision	Weak
2. Main modality of diagnosis is clinical examination and MRI with postvoid films	Strong
3. Sometimes UDS may be indicated if associated with SUI or significant LUTS	Weak
4. The corner stone of treatment is trans-vaginal excision and reconstruction in favorable conditions. Long term suppressive antibiotics may be helpful in unfavorable conditions	Strong

32 Female Urethral injury

32.1 Etiology.

Female urethral injuries are often associated with vaginal injuries. It is a common complication of obstructed labor in rural and slum areas. Iatrogenic injury usually occurs during insertion of a synthetic sub-urethral sling for the treatment of SUI. Also, pelvic fracture may be associated with urethral disruption ⁽¹²⁾.

32.2 Diagnostic evaluation.

- History of relevant trauma
- Examination
- Inability to void is usually a sign of a complete injury
- Incomplete injuries are associated with pain on urination, hematuria or blood present at the vaginal introitus in female patients with pelvic fractures and co-existing urethral injuries
- Cysto-urethroscopy is the preferred diagnostic modality in case of suspected female urethral injury
- VCUG may be needed in late diagnosis and to outline any associated urinary bladder, bladder neck injuries or uro-genital fistulae.

32.3 Surgical management.

32.3.1 Early diagnosis (Within 1st two weeks)

- In case of hemodynamic instability, provide urinary diversion by suprapubic catheterization or a single attempt of urethral catheterization.
- In case of pelvic fracture induced urethral injuries, early repair within seven days has the highest success rate and the lowest complication rate in comparison with delayed repair or early endoscopic re-alignment.
- In case of urethral injury during sling procedure, synthetic mesh should be removed and immediate urethral repair ⁽¹²⁾.

32.3.2 Late diagnosis (Two weeks' post trauma)

- It is preferred to do urinary diversion for three months then repair ⁽¹²⁾.

Table 12: Recommendations for female urethral injury.

Recommendations	Strength Rating
1. History of trauma and examination is the method of diagnosis with need of VCUG in certain indications	Weak
2. Cystourethroscopy is the preferred diagnostic modality	Strong
3. Treatment may be immediate reconstruction or urinary diversion depending on timing of diagnosis, hemodynamic status of the patient and available facilities ⁽¹²⁾	Strong

33 Uro-gynecological fistulae

33.1 Causes.

- In developed countries. Non-obstetric (surgical) fistula is considered the most common cause of uro-gynecological fistulae (e.g., post abdominal hysterectomy, POP repair surgery, anti-incontinent surgery)
- In the developing countries. Obstetric fistula is considered the most common cause due to prolonged obstructed labor ^(13,14)
- Risk factors for obstetric fistula include lack of prenatal care, young age of first marriage, low socio-economical class, short stature, poor nutrition, lack of proper surgical training for obstetrician ^(13,14)

33.2 Different types of uro-gynecological fistula.

- Vesicovaginal fistula (VVF)
- Urethrovaginal fistula (UVF)
- Rectovaginal fistula (RVF)
- Ureterovaginal fistula
- Vesicouterine fistula
- Sometimes more than one type of fistula may occur at the same time (Complex fistula)

33.3 Diagnosis.

Unfortunately, intraoperative diagnosis of a genitourinary (GU) is made in only about half of the cases that result in fistula. Clinical diagnosis of leakage of urine is the hallmark sign of a fistula. The leakage is usually painless, may be intermittent if its position is independent, or maybe constant ⁽¹⁵⁾.

The diagnosis of VVF usually requires clinical assessment often in combination with appropriate imaging or laboratory studies. Direct visual inspection, cystoscopy, retrograde bladder filling with a coloured fluid or placement of a tampon into the vagina to identify staining may facilitate the diagnosis of a VVF. A double-dye test is used to differentiate between ureterovaginal and VVF in some cases ⁽¹⁵⁾. Cyclic hematuria may be pathognomonic sign of vesico-uterine fistula.

Testing the creatinine level in either the extravasated fluid or the accumulated ascites and comparing this to the serum creatinine levels will confirm urinary leakage. Contrast-enhanced CT with late excretory phase reliably diagnoses urinary fistulae and provides information about ureteric integrity and the presence of associated urinoma ⁽¹⁶⁾.

33.4 Treatment.

33.4.1 Management of vesicovaginal fistula.

33.4.1.1 Conservative management.

It may tend to close spontaneously in small sized fistula before complete epithelialization of the fistulous tract, provided that the natural outflow is unobstructed or if urine is diverted. Hence, immediate management should be by urinary catheterization or diversion ^(17,18)

33.4.1.2 Surgical management.

The most important points to be considered in fistula repair are fistula location, fistula size and dimensions, number of fistulae, extent of vaginal scarring, surgical approach and technique used ⁽¹⁹⁾.

33.4.1.2.1 Timing of surgery.

Findings from uncontrolled case series suggest no difference in success rates for early versus delayed closure of VVF. Tailor the timing of fistula repair to the individual patient and surgeon requirements once any edema, inflammation, tissue necrosis, or infection are resolved ^(20,21).

33.4.1.2.2 Surgical principles.

The best chance for successful fistula closure is at the first operation and closure rates tend to diminish with each subsequent attempt at operative repair ⁽¹⁸⁾.

The ureters should be identified and protected to ensure they are not cut or ligated during the fistula repair ¹⁹. The fistula should be mobilized from the surrounding tissues at the time of repair. The fistula should be closed without tension at the site of repair. The repair must be watertight. To ensure this, a dye test is performed intra-operatively and, if there is still leakage, the repair is sutured again ⁽¹⁹⁾.

A single randomized controlled trial compared trimming of the fistula edge with no trimming showed no difference in success rates, but failed repairs in trimmed cases ended up with larger recurrences than untrimmed cases ⁽²²⁾.

A Martius flap in primary obstetric fistula repair is debatable with no clear evidence of its value and is usually reserved for recurrent cases, fistulae secondary to radiation or in case of associated urethral reconstruction ⁽¹⁹⁾.

One prospective randomized controlled trial compared the use of a Martius flap “as an interposition flap” to the use of a self-made fibrin glue. There was no statistical difference in outcome, but the authors stated that the use of fibrin glue allowed the fistula repair to be quicker ⁽²³⁾.

33.4.1.2.3 Surgical approaches.

33.4.1.2.3.1 Vaginal procedures.

There are two main types of closure techniques applied to the repair of urinary fistulae, the classical saucerisation/partial colpocleisis and the more commonly used dissection and repair in layers or 'flap- splitting' technique. There are no data comparing their outcomes ^(24,25).

33.4.1.2.3.2 Abdominal procedures.

Repair is indicated when high fistulae are fixed in the vault and are inaccessible through the vagina. A trans-vesical repair has the advantage of being entirely extraperitoneal. A simple transperitoneal repair is used less often although it is favoured by some surgeons using the laparoscopic approach. A combined transperitoneal and transvesical procedure is favoured by many urologists and is particularly useful for fistula repair following Caesarean section.

There are no randomised studies comparing abdominal and vaginal approaches. When concurrent ureteric re-implantation or augmentation cystoplasty are required, the abdominal approach is necessary.

33.4.1.2.4 Post-operative management.

Catheter drainage for at least 10 days and longer periods in radiation associate fistulae (up to 3 weeks). No sexual intercourse for one month. Surgical treatment of postoperative SUI should only be considered six months after the fistula repair.

33.4.2 Management of radiation fistula.

Successful repair of irradiated fistulae requires prior urinary diversion and the use of non-irradiated tissues to ensure successful repair ⁽²⁶⁾.

33.4.3 Management of ureteric fistula.

33.4.3.1 Endoscopic management.

Is often possible ⁽¹⁶⁾ by retrograde stenting, percutaneous nephrostomy and antegrade stenting if there is pelvicalyceal dilatation, or by ureteroscopy ⁽¹⁷⁾.

33.4.3.2 Surgical management.

33.4.3.2.1 Timing of repair.

If early discovery within two weeks, immediate repair of any injury should be performed observing the principles of debridement, adequate blood supply and tension free anastomosis with internal drainage using stents ⁽²⁷⁾.

In case of delayed presentation of upper tract injury, conservative management is still possible with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< 3 months) or delayed (> 6 months) surgical repair when required ⁽¹⁴⁾.

If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is the standard and requires re-implantation into the bladder with or without psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration (28,29).

Functional and anatomical imaging should be used to follow up patients after repair to guard against late upper tract deterioration (14).

33.4.4 Management of vesicouterine fistula.

Surgical repair through abdominal approach whether by open or laparoscopic techniques, which can be preceded by cystoscopy and gauging of the fistulous tract using ureteric catheter. Hysterectomy may be considered in multiparous women (30,31).

33.4.5 Management of urethro-vaginal fistula.

Principles of reconstruction include identifying the fistula, creation of a plane between vaginal wall and urethra, watertight closure of urethral wall, eventual interposition of tissue, and closure of the vaginal wall (32).

Table 13: Recommendations for uro-gynecological fistulae.

Recommendations	Strength Ratings
1. Uro-gynecological fistulae can be diagnosed mainly by clinical examination which can be complemented by some radiological investigation as VCUG, or CT urography in some types of fistula and cystoscopy	Strong
2. The commonest of uro-gynecological fistulae is VVF, which is managed mainly by surgical repair whether through vaginal or abdominal approaches	Strong
3. Small VVF less 5 mm may close spontaneously by urinary catheterization or diversion provided that natural outflow is unobstructed	Weak
4. Timing of repair has no difference in the success of surgery	Weak
5. Tailor the timing of fistula repair to the individual patient and surgeon requirements once any oedema, inflammation, tissue necrosis, or infection, are resolved	Weak

6. There is no high-quality evidence of differing success rates for repair of vesicovaginal fistulae by vaginal, abdominal, trans-vesical or transperitoneal approaches	Weak
7. Trimming of the edges of VVF has no difference in success rates but failed repairs in trimmed cases ended up with larger recurrences than untrimmed cases	Strong
8. A Martius flap in primary obstetric fistula repair is debatable with no clear evidence of its value and usually reserved for recurrent cases, fistulae secondary to radiation or in case of associated urethral reconstruction	Weak
9. Endoscopic management is the cornerstone in treatment of uretro-vaginal fistula. Otherwise, open or laparoscopic ureteric re-implantation may be performed	Weak
10. Vesico-uterine fistula repair is mainly through abdominal approach, whether by open or laparoscopic techniques	Strong
11. Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to, and following, fistula repair	Weak
12. Successful repair of irradiated fistulae requires prior urinary diversion and the use of non-irradiated tissues to ensure successful repair	Weak
13. There is no high-level evidence to support any particular practice in post-operative management, but most reported series used catheter drainage for at least ten days and longer periods in radiation-associated fistulae up to three weeks	Weak

33.5 References.

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34 Bladder Pain Syndrome (BPS).

34.1 Definition.

- It is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and daytime and/or night-time urinary frequency with no proven infection or other obvious local pathology for a period more than six weeks. ⁽¹⁾
- Pain characteristics include pain, pressure or discomfort perceived to be related to the bladder, increasing with increasing bladder volume. It is located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum. It is relieved by voiding but soon returns ^(2,3). It could be aggravated by food or drink. ⁽³⁾
- Bladder pain syndrome is often associated with negative cognitive, behavioral, sexual or emotional consequence. BPS is believed to represent a heterogeneous spectrum of disorders. Localization of the pain can be difficult by examination. Cystoscopy with hydrodistension and biopsy may be indicated to define phenotypes. Recently, ESSIC has suggested a standardized scheme of sub-classifications ⁽⁴⁾ to acknowledge differences and make it easier to compare various studies. Other terms that have been used include “interstitial cystitis”, “painful bladder syndrome”, and “PBS/IC” or “BPS/IC”. These terms are no longer recommended.
- Prevalence varies largely, along with the diagnostic criteria and populations studied. Recent reports range from 0.06% to 30% ⁽⁵⁻¹⁴⁾. There is a female preponderance of about

10:1⁽⁹⁾ but no difference in race or ethnicity^(15,16). The relative proportions of classic and non-lesion disease are unclear and their incidence in studies has ranged from 5 to 50%⁽¹⁶⁻²⁰⁾. Children under the age of eighteen may be affected as well, although prevalence figures are low⁽²¹⁾.

34.2 Risk factors.

- The cause of BPS is proposed to be an unidentified insult to the bladder, leading to urothelial damage, neurogenic inflammation and pain. BPS might be a local manifestation of a systemic disorder. No infection has been incriminated in the pathogenesis of BBS⁽¹⁾.
- Pancystitis, with associated perineural inflammatory infiltrates, and mastocytosis is an essential part of BPS type 3 C⁽²²⁾, but is scant in non-lesion BPS^(23,24). Cystoscopic and biopsy findings in both lesion and non-lesion BPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer which might expose submucosal structures to noxious urine components⁽²⁵⁻³¹⁾ and a consequent cytotoxic effect^(32,33). Autonomic dysfunction with sympathetic predominance may be implicated in BPS^(34,35).
- An association has been reported between BPS and non-bladder syndromes such as fibromyalgia (FM), inflammatory bowel syndrome, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma and systemic lupus erythematosus⁽³⁶⁻⁴⁰⁾. Risk of BPS correlates with a number of non-bladder syndromes in each patient⁽⁴¹⁾. Recent research showing non-lesion BPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than BPS type 3C patients, emphasizes the need for subtyping⁽⁴²⁾.

34.3 Diagnosis.

- This is mainly a disease of exclusion. The clinical examination often serves to confirm what we have gained from the history taking. Besides the local examination, a general musculoskeletal and neurological examination should be considered an integral part of the assessment. There is no specific diagnostic test for BPS, therefore, procedures are directed towards identification and exclusion of specific diseases associated with pelvic pain, and for phenotypic description.
- Ultrasound on the abdomen and pelvis is done to exclude gross pelvic pathology, but with limited value to diagnose PBS. Urine dipstick and urine culture (including culture for tuberculosis if sterile pyuria) are recommended in all patients suspected of having BPS. Urine cytology is also recommended to exclude malignancy⁽¹⁾.
- Symptom scores may help to assess the patient and act as outcome measures. The O'Leary-Sant Symptom Index, also known as the Interstitial Cystitis Symptom Index (ICSI) was validated for use⁽⁴³⁾.

- Objective findings from cystoscopy are important for diagnosis, prognosis and ruling out other treatable conditions ⁽⁴⁴⁾. Endoscopically, BPS type 3 displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit - the Hunner ulcer ⁽²⁾. The scar ruptures with increasing bladder distension, producing a characteristic waterfall type of bleeding. There is a strong association between BPS type 3 and reduced bladder capacity under anaesthesia. Non-lesion disease displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign although they can be observed without BPS. Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease ^(26,44-47). Important differential diagnoses to exclude, by histological examination, are carcinoma in situ and tuberculous cystitis.

34.4 Management.

- Treatment is usually multimodal ⁽¹⁾. It includes lifestyle interventions such as fluid intake modifications, smoking cessation, exercise and no wearing of tight clothes. Another aspect is pain education and education about the causes of pain. Dietary restrictions alone do not produce significant symptomatic relief and scientific data are limited, however, consider the involvement of a dietician.
- The physiotherapist is part of the pain management team, together with the pain doctor and the psychologist. Physiotherapists can either specifically treat the pathology of the pelvic floor muscles, or more generally treat myofascial pain if it is part of the pelvic pain syndrome ⁽⁴⁸⁾. Efficacy and safety of pelvic floor myofascial physical therapy has been compared with global therapeutic massage in women with BPS; global response assessment (GRA) rate was 59% and 26%, respectively. Pain, urgency and frequency ratings, and symptoms decreased in both groups during follow-up, and did not differ significantly between the groups. This suggests that myofascial physical therapy is beneficial in women with BPS ⁽⁴⁹⁾.
- Psychological interventions are directed at pain itself or at adjustment to pain in terms of function and mood. Ideally, treatment follows general principles and practice in the field of chronic pain ⁽⁴⁹⁾. Two systematic reviews and meta-analyses of the few heterogeneous trials of psychologically based treatment for pelvic pain ^(50,51) found some short-term benefits for pain, of around 50%, comparable to that from pharmacotherapy, but this was not sustained at follow-up.
- Medical therapy includes many option modalities. Histamine receptor antagonists have been used to block the H1 and H2 receptor subtypes ⁽⁵²⁾, with unsatisfactory results ⁽⁵³⁾. Amitriptyline is a tricyclic antidepressant. Several reports have indicated improvement of BPS symptoms after oral amitriptyline ^(54,55). Drowsiness is a side effect of amitriptyline. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported

with use of Pentosane polysulphate ^(56,57). It has a more favorable effect in BPS type 3C than in non-lesion disease ⁽⁵⁸⁾. Immunosuppressants have been tried. Azathioprine and cyclosporin A ^(59,60) treatment have resulted in disappearance of pain and urinary frequency. Corticosteroids are not recommended in the management of patients with BPS because of lack of evidence.

- Intravesical route is an appealing mode of delivery in PBS. Intravesical drugs are administered due to poor oral bioavailability, establishing high drug concentrations within the bladder, with few systemic side-effects. Disadvantages include the need for intermittent catheterization which can be painful in BPS patients, cost and risk of infection ⁽⁶¹⁾. Several drugs have been tried. There are sporadic reports of successful treatment of BPS with intravesical lidocaine ^(62,63). Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after two weeks in 80% ⁽⁶⁴⁾. Intravesical instillation of alkalized lidocaine for five consecutive days resulted in significantly sustained symptom relief for up to one month ⁽⁶⁵⁾. Hyaluronic acid and chondroitin sulphate are described to repair defects in the GAG layer ⁽⁶⁶⁾. Most of the studies are uncontrolled and with a small number of patients and most studies are non-randomized and with few numbers ⁽⁶⁷⁾. Symptomatic improvement was reported in 80% of BPS patients with intravesical heparin ^(67,68).
- There are treatments which are of limited value in BPS. These include cimetidine, with limited data to suggest that cimetidine improves symptoms of BPS in the short-term. These treatments also include misoprostol, which is a prostaglandin, oral L-arginine, intravesical oxybutynin and duloxetine ⁽⁶⁹⁻⁷⁴⁾. None of these drugs have proven to be recommended for treatment of BPS.

34.5 Neuromodulation.

- The role of neuromodulation in the management of chronic pelvic pain (CPP) should only be considered by specialists in pelvic pain management. These techniques are used as part of a broader management plan and require regular follow-up. These are expensive interventional tools for patients who are refractory to other therapies. There has been growing evidence, but more detailed, high quality research is required ⁽⁷⁵⁾. Two recent systematic reviews have evaluated neuromodulation techniques for CPP ^(76,77). Both studies concluded that neuromodulation may be effective in reducing pain and improving QoL in patients with CPP, however studies were of a low quality and long-term results were needed.
- Transcutaneous Electrical Nerve Stimulation (TENS) is a non-invasive technique used in many pain conditions. All RCTs demonstrated a significant reduction in pain following twelve weeks of treatment for pain conditions including CPP. There was conflicting data with regard to improvement of quality of life (QoL) following TENS; where validated

questionnaires were used. TENS could offer an effective non- invasive treatment option for patients with CPP.

- Percutaneous Tibial Nerve Stimulation (PTNS) is a minimally invasive technique that can be use in an outpatient setting. Two trials have shown that PTNS is effective in reducing pain in patients with CPP ^(76,77). Adverse events were rare and minor including temporary slight pain at application site and haematoma.
- Sacral nerve stimulation ⁽⁷⁷⁾ is an invasive technique requiring sedation or general anaesthesia for implantation of a device following trial stimulation. All studies reported an improvement in pain and QoL. There was a large variation in adverse events reported ranging from 0-50%.
- Re-operation rate ranged between 11-50% for complications including lead migration, systemic infection, intrathecal implantation, loss of efficacy and erosion.
- Although bladder hydrodistension is a common treatment for BPS, the scientific justification is scarce. It can be part of the diagnostic evaluation but has limited therapeutic role. Diagnostic hydrodistention is done under general anesthesia for 2 minutes and with height of fluid above the bladder of 81cmH₂O. Therapeutic hydrodistension is done under same circumstances but for 8 minutes ⁽⁷⁸⁾. Treatment with hydrodistension and hydrodistension plus intravesical botulinum toxin A (BTX-A) has been compared ⁽⁷⁹⁾. There was symptomatic improvement in all patients. However, in the hydrodistension-only group, 70% returned to their previous symptoms after one month, while in the BTX-A-treated patients, visual analogue score (VAS) score and functional and cystometric bladder capacity improved at three months. BTX-A trigonal-only injection seems effective and long-lasting as 87% of patients reported improvement after three months' follow-up ⁽⁸⁰⁾. Over 50% reported continued benefit nine months after the first treatment. When re-treatment was needed, similar results were obtained. Adverse effects of BTX-A administration for IC/BPS were significantly less than for overactive bladder syndrome ⁽⁸¹⁾. The American Urological Association (AUA) guidelines panel has upgraded BTX-A treatment from fifth to a fourth line treatment ⁽⁸²⁾.
- Endourological destruction of bladder tissue aims to eliminate urothelial lesions, mostly Hunner ulcer. Resection and fulguration have been reported to achieve symptom relief, often for more than three years ^(83,84). Prolonged amelioration of pain and urgency has been described for transurethral laser ablation as well ⁽⁸⁵⁾. Laser fulguration is preferred due to chronicity of the disease and need for refulguration, with possible bladder fibrosis and shrinkage.
- There is no evidence that open surgery for PBS relieves pain. Surgery for refractory BPS is only appropriate as a last resort for patients with refractory end-stage disease. Urinary diversion without cystectomy ⁽⁸⁶⁾ is performed to minimise the duration and complexity of surgery, but complications related to the retained bladder commonly occur. Supratrigonal

cystectomy with bladder augmentation represents the most favoured continence preserving surgical technique particularly in younger patients ⁽⁸⁷⁾. Subtrigonal or simple cystectomy refers to removal of the entire bladder at the level of the bladder neck. This approach has the benefit of removing the trigone as a possible disease site, but at the cost of requiring ureteric re-implantation. Trigonal disease is reported in 50% of patients and surgical failure has been blamed on the trigone being left in place ⁽⁸⁸⁾, especially in patients with non-ulcer type disease ^(89,90).

Table 14: Recommendations for bladder pain syndrome (BPS).

Recommendations	Strength Rating
1. Basic assessment should include history taking, physical examination, and laboratory examination to rule in symptoms that characterize BPS and exclude other confusable disorders	Strong
2. Patients should be educated about normal bladder function, what is known and not known about IC/ BPS, the benefits versus risks/burdens of the available treatment alternatives, the fact that no single treatment has been found effective for the majority of patients, and the fact that acceptable symptom control may require trials of multiple therapeutic options	Strong
3. Multiple, simultaneous treatments may be considered if it is in the best interests of the patient	Weak
4. Perform general anaesthetic rigid cystoscopy in patients with bladder pain to subtype and rule out confusable disease	Strong
5. Cystoscopy under anesthesia with short-duration, low-pressure hydrodistension may be undertaken if first- and second-line treatments have not provided acceptable symptom control and quality of life	Strong
6. Always consider offering multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments of BPS	Strong
7. Offer dietary advice	Weak
8. Amitriptyline, cimetidine or hydroxyzine may be administered as first-line oral medications	Strong
9. Administer amitriptyline 25mg-50mg for treatment of BPS	Strong
10. Intravesical heparin, lidocaine, hyaluronic acid or chondroitin sulfate may be administered as second line intravesical treatments	Weak
11. Offer intravesical hyaluronic acid or chondroitin sulphate before more invasive measures	Weak
12. Offer intravesical lidocaine plus sodium bicarbonate plus heparin prior to more invasive methods	Weak

13. Offer intravesical heparin before more invasive measures alone or in combination treatment	Weak
14. If Hunner's lesions are present, then laser fulguration and/or injection of triamcinolone should be performed. This should be performed in BPS type 3 C only	Strong
15. Offer submucosal bladder wall and trigonal injection of BTX-A plus hydrodistension if intravesical instillation therapies have failed	Strong
16. Do not recommend oral corticosteroids for long-term treatment	Strong

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35 Female Bladder Outlet Obstruction (BOO).

35.1 Definition and Background.

- BOO in females is an under-reported and underdiagnosed problem worldwide due to paucity of clinical studies and lack of well-defined diagnostic criteria. ⁽¹⁾ Prevalence of BOO among females undergoing urodynamics (UDS) for lower urinary tract symptoms (LUTS) range from 2.7% to 29%. ⁽²⁻⁵⁾ This is attributed to many definitions used to diagnose BOO in these studies. Different nomograms based on urodynamic parameters have been reproduced, but none was approved worldwide for use. ^(2,6,7)
- Symptoms of female BOO are mostly non-specific and the classic voiding LUTS of impaired urine flow, hesitancy, intermittent stream, straining and even retention may be less apparent, making diagnosis difficult. ^(1,8) Other presenting symptoms, e.g. irritative voiding complaints, may be secondary to BOO. Urethral pain and recurrent urinary tract infections (UTIs) are other presenting symptoms as well. Bending forward to void or having to change positions to empty effectively usually indicates an element of obstruction in post anti-stress urinary incontinence (SUI) operations ⁽⁸⁾. This raises the importance of high level of suspicion for BOO in women. Finally, this problem is often not suspected in women, and so its management is typically delayed. ⁽¹⁾
- Female BOO can be caused by anatomical or functional causes. Furthermore, anatomical causes include extrinsic and intrinsic (luminal) factors. ⁽⁹⁾ Extrinsic causes include pelvic organ prolapse (POP), iatrogenic post anti-incontinence procedure and skene gland abscess or cyst, while intrinsic causes include urethral stricture or fibrosis, urethral diverticulum, excessive bulking agent, urethral tumour, condyloma accuminata, urethral stone, urethral caruncle or urethral prolapse. Functional causes include primary bladder neck obstruction, pseudo-dyssynergia known as Hinman's syndrome and detrusor sphincter dyssynergia (DSD). ^(1,8)
- Detrusor failure or acontractility should be excluded, and pressure-flow study could be of help in the diagnosis. However, there are currently no nomograms that accurately assesses detrusor underactivity (DUA) in women. ^(1,9)
- In a study by Greenwell et al ⁽¹⁾, 192 females with BOO were diagnosed. Anatomical obstruction was found in 64% and functional obstruction was present in 36%. The most common anatomical cause of BOO was previous anti-SUI surgery (21%), followed by urethral stricture (20%).

35.2 Diagnosis.

- Urine analysis is an important initial tool to exclude infections. Urine culture and sensitivity is recommended specially in the context of recurrent UTIs. Renal function tests

could be elevated if condition is severe or chronic with elevated postvoid residual (PVR). Bladder scan is indicated to estimate PVR. Imaging is indicated when renal function is impaired or when organic cause is suspected. Role of cystourethroscopy is crucial, especially if associated with difficult catheterization or previous anti-incontinence procedures. ^(1,8)

- Many nomograms have been utilized, with different prevalence rates. Ferrar et al. diagnosed BOO based only on Qmax of <15 mL/s with prevalence of BOO of 6.7%. ⁽³⁾ Massey and Abrams diagnosed BOO in only 2.7% of 5948 females based on 2 or more of the following criteria: Qmax <12 mL/s, pdet @Qmax >50 cmH2O, urethral resistance (pdet @Qmax/ 2Qmax) >0.2, and significant PVR. ⁽⁴⁾ Lemack and Zimmern used cut-off values of Qmax ≤15 mL/s and pdet@ Qmax>20 cmH2O, diagnosing BOO in 20% of the patients. ⁽⁷⁾ Blaivas and Groutz created a nomogram to diagnose BOO and classify its severity based on pressure–flow criteria of a free Qmax ≤12 mL/s and a Pdet @Qmax ≥20 cmH2O, in association with radiographic evidence of obstruction, and reported a prevalence of 8.3%. ⁽²⁾
- Elmissiry et al. categorized females with BOO into three different subtypes based on urodynamic patterns (early, compensated and late obstruction). They recommended that UDS should be combined with the clinical presentation and estimation of PVR for an accurate diagnosis of BOO. ⁽¹⁰⁾
- The role of pressure flow studies alone to diagnose female BOO is questioned because voiding dynamics in females are different from those in males, and most of the females void predominantly by pelvic floor relaxation or abdominal straining with low detrusor pressures. Nitti et al. introduced the role of videourodynamics (VUDS), combined with clinical suspicion of BOO, with an overall prevalence of 29%. ^(11,12)

35.3 Treatment.

- Treatment usually depends on treatment of the cause. ⁽⁸⁾ Prolapse correction in cases of POP. ^(12,14) In cases of iatrogenic post-tape obstruction, CIC could be tried for the first week. Tape release could be tried initially within the first 10 days. If failed, tape incision could be done in the first two months ⁽¹⁵⁾, with urethrolisis being a last resort in some refractory cases. ^(16,17)
- Most urethral strictures or fibrosis in women are iatrogenic and can result from previous urethral or periurethral surgery, or in some cases from previous urethral dilatation. Many females experience urethral strictures from previous obstructed labors. Options include urethral dilatations, better under brief anesthesia, cystourethroscopy, or in resistant recurrent cases, urethroplasty with vaginal flap or buccal mucosal grafts is indicated but in highly specialized referral centers. ^(8,18,19)

- Primary bladder neck obstruction is caused by lack of relaxation of the smooth muscle of the bladder neck during voiding, and it responds well to alpha blockers. CIC could be an option if medications fail. Transurethral incision of the bladder neck is definitive, but with increased risks of postoperative incontinence. Neuromodulation is of help in these cases. (20-24)
- Pseudo-dyssynergia or Hinman's syndrome results from an external sphincter that does not relax during voiding in an otherwise neurologically intact woman. First-line treatment consists of pelvic floor relaxation. Skeletal muscle relaxants such as diazepam can be used as well, but the side-effects limit their applicability. Intrasphincter botulinum injection is successful in many cases, but this is off-label use. Finally, sacral neuromodulation has been used successfully.
- DSD occurs when the external sphincter contracts during a detrusor contraction in a neurologically impaired individual. It is common in patients with suprasacral spinal cord injuries (SCI) and multiple sclerosis (MS). Introduction of botulinum toxin injections into the external sphincter of these patients is successful. (8,25)

Table 15: Recommendations for female bladder outlet obstruction (BOO).

Recommendations	Strength Rating
1.Role of VUDS, combined with the clinical symptoms of BOO, is more accurate in diagnosing BOO and determining the site of obstruction	Strong
2.Pressure-flow study is of low yield in diagnosing female BOO	Weak
3.Suspect BOO in females who underwent slings recently if they experience deNovo storage symptoms, or if they report change in position when they void (lean forward or squat)	Weak
4.Estimation of PVR in patients suspected with BOO is mandatory	Strong
5.Perform cystourethroscopy in female patients suspected with BOO	Weak
6.Offer alpha blockers initially in cases diagnosed with primary bladder neck obstruction	Strong
7.Urethral dilatations, better under general anesthesia, is of help in cases of urethral strictures or fibrosis in women	Strong
8.Transurethral incision or resection of the bladder neck is definitive in primary bladder neck obstruction, but with increased risks of postoperative incontinence	Weak
9.Offer initially pelvic floor muscle exercises in patients suspected with Hinman's syndrome	Strong

10. Offer skeletal muscle relaxants such as diazepam in patients diagnosed with Hinman's syndrome, but the side effects limit their applicability	Weak
11. Offer intrasphincter botulinum injection in cases of Hinman's syndrome, pseudodyssynergia and DSD, with better results in DSD patients	Weak

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36 Geriatric urinary incontinence.

- Urinary incontinence (UI) can be considered both a specific diagnosis and a geriatric syndrome. This is particularly of significance in frail elderly population, with multiple chronic morbid conditions. ⁽¹⁾
- Geriatric syndromes are defined as common conditions seen in the elderly, that are complex in nature, are usually multifactorial, and can have clinical or other negative health outcomes for affected patients. ⁽²⁾
- The incidence and prevalence of UI increase in the elderly population. However, incontinence should not be considered a normal or inevitable aging event. This is a common myth among both health care providers and patients. ⁽³⁾
- UI is accompanied with social isolation, stigmatization, depression, aversion from sexual life and embarrassment. Skin irritation and cracking from urine, development of pressure ulcers, recurrent urinary tract infections (UTIs), falls and fractures are all substantial physical problems. ⁽⁴⁾ UI has a stronger negative influence on overall levels of happiness than diabetes, hypertension, arthritis, and osteoporosis. ⁽⁵⁾
- Economic data has shown an estimated national cost of evaluation and care for wet-overactive bladder (OAB) of \$65.9 billions in 2007, with estimated increase to \$76.2 billions in 2015 and \$82.6 billions in 2020. ⁽⁶⁾ The degree of incontinence in the elderly as measured by severity appears to be more influential on health-related quality of life (QoL) outcomes than type of UI. ⁽⁷⁾

36.1 Transient urinary incontinence.

- Up to 30% of UI in community-dwelling older adults and 50% of UI in elderly patients admitted to acute care hospitals may be caused by transient conditions. ⁽⁸⁾ Treatment of underlying causative conditions could result in improvement or cure of UI. ⁽⁹⁾
- A wide variety of conditions can lead to associated transient UI. UTI can cause urinary frequency and in some cases UI. This should be considered symptomatic and should be evaluated and treated appropriately. True asymptomatic bacteriuria does not by itself cause UI and does not require antibiotic therapy. Atrophic vaginitis or urethritis is common in elderly females and may be associated with dysuria or a burning sensation with voiding. Treatment with vaginal estrogens can help ameliorate symptoms of this condition and may help improve UI and decrease incidence of UTIs. ⁽¹⁰⁾
- Fecal impaction is frequently caused by slow transit time through the gut or increased water reuptake in the colon. Fecal incontinence (FI) and diarrhea may be presenting symptoms because liquid stool proximal to the impaction moves around the impacted stool bolus. Disimpaction often results in resolution of both urinary and fecal symptoms. Chronic

constipation is a common problem in older adults. Treatment and prevention with a bowel regimen can help. ⁽¹¹⁾

- Different medications can cause transient incontinence the elderly including psychotropics, diuretics, benzodiazepines, calcium channel blockers, tricyclic antidepressants (TCAs), α -blockers, and narcotic analgesics. Diuretics increase urinary output leading to urinary urgency, frequency, and UUI. Opioids and narcotic analgesics tend to decrease detrusor contractility and can cause urinary retention with associated incontinence. TCAs have pronounced anticholinergic effect and decrease detrusor contractility, leading to difficulty voiding or urinary retention. Alcohol and other substance abuse are also causing UI. ^(12,13)
- Other causes of transient incontinence include depression, anxiety, delirium, dementia, Alzheimer's disease, mobility impairment, excess urinary output and polyuria. ⁽³⁾

36.2 Established Urinary Incontinence.

- Chronic UI is an extremely common problem in geriatric patients. Of all people, over 65 years of age, 43.8% report a history of any urinary leakage. Among community-dwelling elderly women, 12% report severe or very severe UI. ⁽¹⁴⁾
- Urgency urinary incontinence (UUI) is the most common form of established incontinence among elderly people. ⁽¹⁵⁾ The term precipitancy has been used to describe the symptom that occurs with detrusor overactivity (DO) in older adults. In patients with no sensation of warning, precipitant leakage may be experienced as an unconscious or reflex episode of incontinence. ⁽¹⁶⁾
- One form of bladder dysfunction that is unique in the geriatric population is detrusor hyperactivity with impaired contractility (DHIC). Patients experience DO with bladder filling, which is associated with the typical symptoms of urinary urgency, frequency, and UUI. However, during voiding the bladder does not contract efficiently to completely empty. Successful treatment often requires multimodal therapy including behavioral interventions and medications to inhibit DO and clean intermittent catheterization (CIC) to empty the bladder. ⁽¹⁷⁾
- Stress urinary incontinence (SUI) is common in the elderly, and urethral atrophy associated with decreased tissue estrogenization and other age-related factors can exacerbate sphincteric competency, leading to intrinsic sphincteric deficiency (ISD). ⁽³⁾ Detrusor underactivity (DUA), sometimes called underactive bladder, can be caused by a wide variety of conditions. Often the cause is idiopathic. Pelvic atherosclerosis is associated with diminished arterial blood flow to the bladder, which could cause ischemic changes. ⁽¹⁸⁾
- Targeted protocols to treat UI in long-term care settings have proven quite successful. Prompted toileting can be used in patients with adequate mobility and cognitive function to use toilet facilities independently. Patients are prompted by caregivers or staff to use the toilet on a regular schedule. Timing is adjusted based on specific individual needs. In those

older adults with mobility and/or cognitive impairment, assisted toileting procedures may be necessary. The use of assistive toileting devices such as handheld urinals or bedside commodes may be necessary depending on functional status. ^(19,20)

- Evaluation should be individually tailored to the clinical needs and goals of the patient and his or her caregivers. It includes detailed history taking, review of medical records, identifying the most bothersome component of UI. Physical examination, including pelvic examination in women, is essential. ⁽³⁾ Many elderlies do not completely empty the bladder with voiding. Elevated PVR is common in the elderly, however, no specific volume is considered pathologic and there is a great deal of controversy surrounding the importance of elevated PVR volume in older adult patients. ⁽²¹⁾ Urinalysis and urine cultures should be obtained when clinically indicated and can help to identify underlying comorbidity. ⁽²²⁾
- Urodynamic studies can be useful in the evaluation of select elderly patients with UI and other forms of voiding dysfunction. Indications for urodynamic studies, in the elderly, include failed prior therapy and underlying neurologic or other comorbid conditions. Pressure-flow urodynamic testing can be particularly helpful to differentiate between functional obstruction and poor contractility. ^(23,24)

36.3 Treatment.

- Behavioral therapies are considered the mainstay of therapy for treatment of UI in older adults. They offer the advantage of good clinical efficacy while avoiding potential side effects often associated with medications or surgery. Limiting fluid intake in an attempt to reduce UUI or urinary urgency or frequency episodes is advocated. Avoidance of foods or beverages that tend to trigger urinary urgency and frequency symptoms like caffeine, carbonated beverages, alcohol, and spicy or acidic foods is tried. ⁽²⁵⁻²⁷⁾
- Timed or scheduled toileting can be quite useful in some patients with urgency and frequency. Many older adults have worse symptoms near full bladder capacity. Voiding on a more regular schedule before reaching capacity may help. Bladder retraining to increase the intervoiding interval, can be useful in select cases. ⁽²⁸⁾
- Most older adults require specific pelvic floor muscle training (PFMT). Cognitive impairment may limit practicality of this therapy in some patients. It requires a motivated patient who is willing to do the exercises and is able to follow guided instruction. PFMT is often used in combination with other forms of behavioral or pharmacologic therapies. ^(29,30)
- Medications are widely used in treatment of UI. Duloxetine, a balanced serotonin and noradrenaline reuptake inhibitor, also has α -adrenergic properties and has been considered as a possible treatment option for SUI. ⁽³¹⁾
- Anticholinergics are the main stay of pharmacological treatment in OAB. Adverse effects on the central nervous system (CNS) include cognitive impairment, acceleration of neurodegenerative processes, appearance of psychotic or confusional symptoms and

functionality disturbances. On the other hand, adverse effects on the PNS include dry mouth, urinary retention, constipation and paralytic ileus, increased heart rate and blurred vision. ⁽³²⁾

- Improved selectivity of muscarinic receptor binding is another focus in drug development. The goal is to target the bladder (M2 and M3) but avoid the salivary gland and bowel (both M3), which may help reduce the risk of dry mouth and constipation. ⁽³³⁻³⁴⁾ Some experts suggest that there is little evidence regarding the reversibility of anticholinergic cognitive effect through discontinuation and question the safety of this measure. Different studies have proposed conflicting hypotheses regarding the reversibility of cognitive effects after discontinuation. Abrupt discontinuation is not recommended due to the risk of a cholinergic rebound, i.e., symptoms of agitation, diarrhea, vomiting, lacrimation, tachycardia, insomnia and movement
- disorders after withdrawal. ⁽³⁵⁾ Tolterodine and oxybutynin are the UI drugs with the highest anticholinergic load. ⁽³⁶⁾ Oxybutynin has the highest blood-brain barrier permeability and trospium chloride the lowest.
- Mirabegron is a B3 agonist with no side effects of the anticholinergics. This acts on detrusor smooth muscle to decrease contractility and reduce symptoms associated with overactivity. In the PILLAR study ⁽³⁷⁾, efficacy of mirabegron in the elderly for the treatment of wet-OAB in patients aged > 65 years was tested. Results revealed good clinical efficacy, relatively few side effects and tolerability consistent with the known safety profile of the drug over 12 weeks.
- A number of different forms of surgical therapy is used for treatment of UI in older adults. These include surgical procedures for both SUI and UUI. Many older adults want to avoid surgery as a possible treatment option for UI. Age alone is rarely a significant risk factor for postoperative outcomes. ⁽³⁸⁾
- A number of published studies have examined safety and efficacy of sling procedures for treatment of SUI in geriatric patients. These have shown good outcomes in general, with no significant difference in complication rates compared with younger patients. ⁽³⁹⁾
- Use of indwelling catheters is usually avoided in older adults because of the associated risks of UTI, catheter colonization, urinary tract stones, or tissue erosion. Catheters should be removed as soon as feasible to help prevent negative outcomes. Cystoscopy is recommended on at least an annual basis, particularly after the first several years of use, to evaluate for any mucosal changes such as squamous metaplasia or development of stones. If patients have problems with urinary leakage around the catheter or from the urethra, treatment should be focused on reducing bladder contractions with antimuscarinics. It is strongly recommended that providers don't increase the caliber of the tube. Increasing the diameter of the catheter will not solve the underlying cause of the urinary leakage and will serve only to dilate the suprapubic tract or urethra. This can lead to severe problems with

erosion and catheter extrusion. Catheters of 16 or 18 Fr are typically adequate for use as a suprapubic tube. ⁽⁴⁰⁻⁴²⁾

- Urine containment and absorbent products are also valid options to help manage urinary leakage. Although these should not be considered a curative treatment option, they can be quite useful for management of symptomatic urine loss. Absorbent pads come in many designs and range from small pads to extra absorbent briefs and can be used for both light and heavier volumes of urinary leakage. ⁽⁴³⁾ Gel-based products may offer better odor control and have good overall absorbency, although they may not be able to control large volume leakage. Pads and absorbent products are used in UI management scheme of nursing home residents. ⁽³⁾

Table 16: Recommendations for geriatric urinary incontinence.

Recommendations	Strength Rating
1. Treatment of underlying causative conditions could result in improvement or cure of UI	Strong
2. Don't treat asymptomatic bacteriuria to treat UI	Strong
3. Elevated PVR is common in the elderly, however, no specific volume is considered pathologic and there is a great deal of controversy surrounding the importance of elevated PVR volume in older adult patients	Weak
4. Urodynamic studies can be useful in the evaluation of select elderly patients with UI and voiding dysfunctions. Indications for urodynamic studies, in the elderly, include failed prior therapy and underlying neurologic or other comorbid conditions	Strong
5. Treatment of atrophic vaginitis or urethritis with vaginal estrogens can help ameliorate symptoms of this condition and may help improve UI and decrease incidence of UTIs	Strong
6. DHIC requires multimodal treatment with behavioral interventions and medications to inhibit DO and CIC to empty the bladder	Weak
7. Use prompted toileting in patients with adequate mobility and cognitive function	Strong
8. Use assistive toileting devices such as handheld urinals or bedside commodes in elderlies with mobility and/or cognitive impairment	Strong
9. Urinalysis and urine cultures should be obtained when clinically indicated	Strong
10. Offer PFME in a motivated patient who is willing to do the exercises and is able to follow guided instruction. It is often used in combination with other forms of behavioral or pharmacologic therapies	Strong

11. Offer behavioral therapies as the mainstay of therapy for treatment of UI in older adults	Strong
12. Anticholinergics should be offered as the main stay of pharmacological treatment in OAB, putting into consideration the PNS and CNS side effects	Strong
13. Do not offer Oxybutynin to the elderly population as it has the highest blood-brain barrier permeability	Strong
14. Abrupt discontinuation of anticholinergics is not recommended due to the risk of a cholinergic rebound	Weak
15. Don't use indwelling catheters in older adults	Strong
16. Prescribe antimuscarinics if urinary leakage occurs around the catheter or from the urethra	Strong
17. Don't increase the diameter of the catheter as it will not solve the underlying cause of the urinary leakage and will serve only to dilate the suprapubic tract or urethra	Strong
18. Use catheters of 16 or 18 Fr for use as a suprapubic tube	Strong
19. Urine containment and absorbent products are also valid options to help manage urinary leakage. They should not be offered as a curative line of management	Weak

36.4 References.

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37 Female Sexual Dysfunctions (FSD).

37.1 Definition.

- FSD is an umbrella term that entails distressing situations which interfere with a woman's ability to enjoy a satisfying sexual life. It is defined as persistent or recurrent inability to engage in satisfying sexual activity leading to marked distress or interpersonal difficulty after excluding general medical conditions, psychiatric issues, substance abuse and medications. Duration of at least 6 months is required to apply a diagnosis except in the case of medication-induced sexual dysfunction ⁽¹⁾.
- Prevalence of sexual problems in the general female population is unknown ⁽²⁾ due to selection bias, limited data collection, and variation/disagreement about what constitutes a sexual problem. Prevalence in the general population varies widely from 23% to 82% ⁽³⁻⁸⁾.
- FSD has been linked to increasing age ^(9,10), menopausal symptoms ⁽¹⁰⁻¹²⁾, absence of partner ⁽¹²⁾, age of partner ⁽¹⁰⁾, partner sexual dysfunction ^(9,13), urinary incontinence (UI) ^(14,15), depression ^(14,16), tobacco use ⁽¹¹⁾, sedentary lifestyle ⁽¹⁷⁾, hypothyroidism ⁽¹⁸⁾, diabetes ⁽¹⁹⁾ and poor general health ^(9,12).

37.2 Evaluation of sexual health in women.

- Sexuality and sexual health are sensitive topics that many patients are hesitant to discuss with their health care providers. In a study by Nusbaum et al in 2000 ⁽²⁰⁾, 98% of females seeking routine gynecological care had sexual concerns, yet, both physicians and patients are reluctant to ask. Physicians' questioning increases patients' reporting of sexual dysfunction, where 14% of females report spontaneously, and 55% of patients reports FSD after direct questioning. Approximately 43% of American women have sexual complaints.
- FSD is more difficult to diagnose and manage, and even more challenging than male sexual dysfunction. Inquiry about sexual health can be incorporated into a general urologic clinic visit. Normalizing statements (e.g., "Many patients have questions about their sexual life") may help the patient to feel at ease discussing their sexual complaints ⁽²¹⁾. A simple, open-ended question (e.g., "What concerns do you have about sexuality?") is recommended as an initial screen ⁽²²⁾. Yes/no questions (e.g., "Are there any problems with your sexual life that you wish to discuss with me?" "Are you satisfied with your sexual life?") may be a more practical way to screen for sexual problems.
- Evaluation of the partner is another pivotal issue. Sexual distress is linked to incompatibility with the partner ⁽²³⁾ and therefore involvement of the sexual partner is mandatory in the management of any sexuality problem. Education of the partner may be of particular importance given the generally low knowledge of female sexual response in the community ⁽²⁴⁾.

- A general physical examination is required. The patient should be assessed for evidence of endocrinopathy, nerve injury, diabetes, or obesity ^(24,25). Evaluation of the genitals should start with careful inspection of the external genitalia including mons pubis, labia majora, labia minora, clitoris, and the vulva. This superficial examination may show genital lesions, erythema that may predispose to sexual pain disorders, redundancy of the labia, or atrophy of the external genitalia ^(24,25). Vulvar skin conditions are common and can lead to a variety of sexual concerns. Examples include eczema, contact dermatitis, fungal infections, aphthous ulcers, and drug reactions.
- Testing for genital neuropathy may be accomplished by application of heat/cold stimuli, vibration, and/or application of a toothpick. A simple assessment for stress urinary incontinence (SUI) as performing cough test is mandatory. Urinary symptoms are associated with sexual problems and are within the scope of practice for urologists to manage. Bimanual examination of the vagina is performed to assess for pelvic organ prolapse (POP) and ovarian pathology ⁽²⁴⁾. Assessment of the levator ani muscles should be included as part of the bimanual examination ⁽²⁶⁾. A speculum examination should be considered. Assessment of vaginal pH is a simple and inexpensive test. High pH signifies disruption of the normal vaginal microbiome; this may have relevance to recurrent infection and vulvovaginal atrophy collectively known as genitourinary syndrome of menopause ⁽²⁷⁾.
- The role of laboratory studies in evaluation of FSD is controversial ^(24,25). Serum lipids, and glycosylated hemoglobin should be assayed, as these are low-risk tests for common problems relevant to female sexual function. Assessment of sex steroids particularly, serum estradiol and testosterone (T), should be considered ^(28,29). Most widely available assays for T are not precise in women ⁽³⁰⁾. The timing of assay with respect to menstrual cycle should be clearly defined. T should be assayed in the morning between days 8 and 14 of a 28-day menstrual cycle ⁽³¹⁾. The decision to measure serum T should only be made after consultation with the patient about the unknowns and with a clear sense of what will be done with the data if the test result is concerning for androgen insufficiency ^(32,33). Elevated prolactin is associated with decreased sexual desire and suppression of serum T levels ⁽¹⁸⁾.
- Many questionnaires are developed to diagnose FSD. The most widely used and cited research in urologic sexual medicine is the Female Sexual Function Index (FSFI) ⁽³⁴⁾. The FSFI is a 19-item questionnaire that assesses 6 domains of female sexual experience (desire, arousal, lubrication, orgasm, satisfaction, and pain). In most studies, a total FSFI score of less than 26.55 has been used as a marker for a higher risk of FSD. The FSFI has been shown to be more reliable in predicting treatment success in studies of sexual dysfunctions. An abbreviated six-item version of the FSFI has been reported ⁽³⁵⁾.

37.3 Classification of FSD.

- FSD is classified in the fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) into ⁽³⁶⁾:
 1. Female sexual interest/arousal disorder which includes desire and arousal disorders.
 2. Female orgasmic disorder.
 3. Genito-pelvic pain/penetration disorder” which includes dyspareunia and vaginismus.

37.3.1 Female sexual interest/arousal disorders.

They include.

37.3.1.1 Hypoactive sexual desire disorder (HSDD).

- It is the most common disorder, and it is defined as diminished feelings of sexual interest or desire, absence of sexual thoughts, and/or lack of receptivity to sexual activity.
- Common precipitating factors include hormonal changes, medication use, changes in relationship status, or life stressors ⁽³⁷⁾. It is very common for women to experience a reactive decline in sexual desire in the presence of other impediments to sexual activity.
- Hypoestrogenism has been clearly linked to decreased sexual desire in women, primarily in association with menopause ⁽³⁸⁾. Androgen deficiency has also been linked to decreased sexual interest in women ⁽³⁹⁾. Psychosocial stressors have a marked effect on sexual interest in women. Depression is prevalent and includes a well-known association with HSDD ⁽⁴⁰⁾. Aging is associated with declines in sexual desire ⁽³⁸⁾. The use of medications, particularly antidepressants of the SSRI class, is associated with HSDD ⁽⁴⁰⁾.
- There is no approved pharmacotherapy for HSDD in women. Stress reduction strategies, maintenance of general health, and addressing relationship issues are generally regarded as positive interventions. Psychosexual therapy encompasses numerous mental health approaches to addressing HSDD in women. The general goals of therapy include education on sexual physiology and response, determination of type and frequency of sexual activity that is personally desired and developing interpersonal communication skills ⁽²²⁾. If it is selective serotonin reuptake inhibitor (SSRI)-related medication, cessation of the drug or modulation of the dose would be beneficial ⁽⁴¹⁾. A meta-analysis of adjunctive treatments for SSRI-induced sexual dysfunction confirmed that twice-daily dosing with bupropion 150 mg improved sexual function outcomes ⁽⁴²⁾. On-demand use of sildenafil enhances orgasmic function in women taking SSRIs for depression ⁽⁴³⁾.
- Correction of estrogen deficiency has been associated with improvement in female sexual function, including desire ⁽⁴⁴⁾. Supplementation with T increases sexual desire in women with low libido and low serum androgen levels ⁽⁴⁵⁾. Currently there is no approved androgen-based treatment for sexual-interest disorders in women in the United States.

Other drugs increase androgens such as tibolone which is a synthetic hormone that is metabolized to several forms with estrogenic activity ⁽⁴⁶⁾. Flibanserin is an agonist against the 5HT1A receptor and antagonist against the 5HT2A receptor. It exerts dopaminergic and noradrenergic actions. These CNS effects may enhance sexual interest. High doses of flibanserin (100 mg/day) are consistently associated with statistically significant positive changes in sexuality (particularly desire) ⁽⁴⁷⁾. However adverse events include somnolence, headache, vertigo, and nausea.

37.3.1.2 Female sexual arousal disorders (FSAD) ⁽²⁵⁾

37.3.1.2.1 Genital arousal disorder (GFSAD).

Impaired genital arousal with minimal vulvar swellings and vaginal lubrication from genital stimulation.

37.3.1.2.2 Psychological arousal disorder (PFSAD).

Absent or markedly diminished feelings of excitement or pleasure in response to sexual stimulation.

37.3.1.2.3 Mixed arousal disorder.

It includes GFSAD and PFSAD.

37.3.1.2.4 Persistent genital arousal disorder (PGAD).

Persistent, recurrent, intrusive, and/or distressing sensations of genital arousal not related to sexual stimulation that do not resolve after orgasm. It may last for hours to days.

37.3.1.3 Pathogenesis.

Vascular or neurologic disease may contribute to GFSAD ⁽⁴⁸⁾. Pelvic surgery (gynecologic, urologic, or colorectal) may also disrupt genital innervations (particularly the autonomic innervation of the pelvic nerve) and vascular supply ⁽⁴⁹⁾. Smoking is associated with impairment of genital response due to effect of nicotine ⁽⁵⁰⁾. Diabetes represents a special risk factor for FSD, as it may be associated with neurologic, vascular, and/or hormonal defects ⁽¹⁹⁾. Antidepressants may also impair genital arousal responses. Although depression itself is a risk factor for FSD, some women may experience improvement in sexual satisfaction when treated with antidepressant drugs ⁽⁵¹⁾. Endocrinopathy is an important cause of GFSAD. Perturbation of genital response (thinning of vagina and dryness) is often related to hypoestrogenism from menopause ⁽²⁷⁾. PFSAD typically originates from psychological causes. Common examples include dissatisfaction with a sexual partner and depression ⁽²⁵⁾.

37.3.1.4 Treatment.

Psychosocial therapy entails attention to psychosocial factors mediating FSAD. Eros Clitoral Therapy Device ⁽⁵²⁾ is a battery-powered vacuum-driven suction device designed to be applied to the clitoris. It was shown to enhance sensation, arousal, and orgasmic potential in women. Phosphodiesterase 5 inhibitors (PDE5I) ⁽⁵³⁾ have been of great

interest in treating FSAD because of the similarities in the mechanisms of vascular engorgement between men and women. PDE5I are not approved for use in women and hence any use of these drugs in women is off label. Use of sexual lubricants is one of the simplest approaches to treat GFASD ⁽⁵⁴⁾. There are innumerable formulations of sexual lubricants which vary in terms of lubricity, additives, durability, and cost. Transdermal prostaglandin E1 (PGE1) applied to the vulva and/or clitoris has been reported as a therapy for GFSAD. One gram of ointment containing 0.2% PGE1 applied to the external genitalia produced a pronounced genital response when compared to placebo ointment ⁽⁵⁵⁾. Estrogens and tibolone may prove efficacious in treating FSAD ⁽⁴⁶⁾.

37.3.1.5 Persistent genital arousal disorder (PGAD).

Genital sensations associated with PGAD include throbbing, lubrication, pelvic congestion, sense of imminent orgasm without climax, and unprovoked orgasm ⁽⁵⁶⁾. PGAD has been associated with a dysfunction of sexual beliefs ⁽⁵⁷⁾ and restless legs syndrome ⁽⁵⁶⁾. PGAD has also been associated with anxiety and obsessive-compulsive symptoms ⁽⁵⁸⁾, withdrawal of SSRI medications ⁽⁵⁹⁾, and pelvic arteriovenous malformations ⁽⁶⁰⁾. The largest series of women with confirmed PGAD revealed high (55%) prevalence of pelvic varices ⁽⁶¹⁾. Clinical examination of these women demonstrated that two thirds of them had restless legs syndrome and/or overactive bladder ⁽⁵⁶⁾. Many women also reported exacerbation of PGAD symptoms with stress. PGAD may be a manifestation of nonsexual “hyperexcitability” of the genitals.

Benzodiazepine drug, clonazepam (0.5 to 1.5 mg/day) is effective in reducing PGAD symptoms in 56% of treated subjects ⁽⁶¹⁾. Benefit was also reported in some women from treatment with tramadol 50 mg ⁽⁵⁶⁾. Cognitive/behavioral treatments have been proposed, including training to direct attention away from genital sensations and the reduction of overall anxiety ⁽⁵⁸⁾. Women with this poorly understood disorder have very positive responses to empathy and support from their providers ⁽⁵⁶⁾.

37.3.2 Female orgasmic disorders (FOD).

It is defined as lack of experience of orgasm or diminished orgasm intensity despite high sexual arousal after a period of sufficient sexual stimulation and arousal.

Primary orgasmic disorders are typically the result of sexual inexperience and are treated using cognitive behavioral therapy, directed masturbation ⁽⁶²⁾, and sex education. Permission giving by the physician regarding sexual exploration and masturbation is hugely helpful to women with anorgasmia.

Secondary anorgasmia, or acquired anorgasmia, is often the result of antidepressant medications. This can be treated by stopping the offending medication. There are no approved pharmacotherapies for FOD. PDE5I enhance orgasmic response in women with decreased sexual desire related to the use of SSRI drugs ⁽⁴³⁾ and in postmenopausal women with orgasmic dysfunction. Use of these drugs in women is off label.

37.3.3 Genito-pelvic pain/penetration disorders.

9.3.3.1. Dyspareunia is defined as persistent/recurrent pain with attempted/complete vaginal entry with a penis, finger, or another object. It could be superficial or deep. Introital or superficial type could be caused by vaginitis, decreased lubrication and superficial vestibulodynia. Deep dyspareunia could be due to endometriosis and pelvic inflammatory diseases.

Treatment of dyspareunia includes pelvic floor physical therapy with biofeedback and pelvic floor electrical stimulation. Vaginal dilators have all been used with reported clinical benefit but without scientific evidence. Postmenopausal women with pain secondary to atrophic vaginitis should be treated with topical estrogen, whereas women with vulvovaginitis should be treated with oral or transvaginal antifungal and/or antibacterial agents.

9.3.3.2. Vaginismus is defined as vaginal spasm or pain in response to penetration with a penis, finger, or other object despite a desire for penetration to occur. Treatment includes topical lidocaine, gabapentin, botulinum toxin injection in the vagina, biofeedback and cognitive behavior.

Table 17: Recommendations for female sexual dysfunctions (FSD).

Recommendations	Strength Rating
1. Inquiry about sexual health can be incorporated into a general urologic clinic visit	Strong
2. Duration of sexual dysfunction for at least 6 months is required to apply a diagnosis	Weak
3. Use normalizing statements (e.g., “Many patients have questions about their sexual life”). This may help patients feel comfortable during discussing their sexual complaints	Strong
4. Ask simple, open-ended questions (e.g., “What concerns do you have about sexuality?”) as an initial screening	Strong
5. Yes/No questions (e.g., “Are you satisfied with your sexual life?”) could be used to screen for sexual problems	Strong
6. A complete history (medical, sexual, partner, etc.) and thorough physical examination (particularly of the genitals) is fundamental for the evaluation of sexual wellness in women	Strong
7. Evaluate the male partner in cases of female sexual dysfunctions	Strong
8. Education of the male partner may be of particular importance given the generally low knowledge of normal female sexual function	Strong
9. Use validated FSFI in the initial assessment of FSD	Strong
10. Psychosocial support is critical in the management of any sexual concern	Strong

11. There are few approved pharmacotherapies for FSD; there are a number of treatments, but many of these are off label	Weak
12. Twice daily-dosing of Bupropion 150 mg in SSRI-induced sexual dysfunction is associated with improved sexual function outcomes	Strong
13. On-demand use of sildenafil enhances orgasmic function in women taking SSRIs for depression	Strong
14. High doses of flibanserin (100 mg/day) are consistently associated with statistically significant positive changes in sexuality (particularly desire) but be aware of the side effects associated	Weak
15. PDE5I could be used in treating FSAD, however they are not approved for use and they are considered off-label drugs	Weak
16. Use of sexual lubricants is one of the simplest approaches to treat GFASD	Strong
17. Benzodiazepines (clonazepam 0.5 to 1.5 mg/day) is effective in reducing PGAD symptoms in 56% of patients. Benefit was also reported with tramadol 50 mg	Weak
18. Postmenopausal women with pain secondary to atrophic vaginitis should be treated with topical estrogen	Strong
19. Women with vulvovaginitis should be treated with oral or transvaginal antifungal and/or antibacterial agents	Strong
20. Treatment of vaginismus includes topical lidocaine, gabapentin, botulinum toxin injection in the vagina, biofeedback and cognitive behavior	Weak

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38 Conclusions.

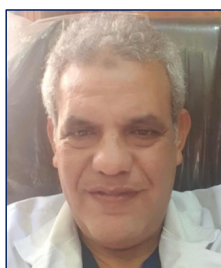
- These guidelines provide practical evidence-based guidance on the clinical aspect of many uro-gynecological entities. The main target is entirely focused on assessment and treatment, reflecting the recommended clinical practice. This can provide the basis for thinking through patient's management and also for planning and designing clinical services.
- Early diagnosis of the different female urogynecological problems is fundamental before deciding any plan of management. Accordingly, tailoring and individualizing the plan of management follows, which ensures the best practice of clinical care offered to these patients. The role of these guidelines is to offer expert advice on how to manage these patients.

Committee IV

Renal Tumors



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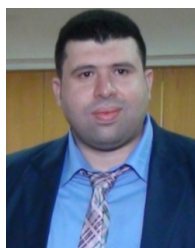
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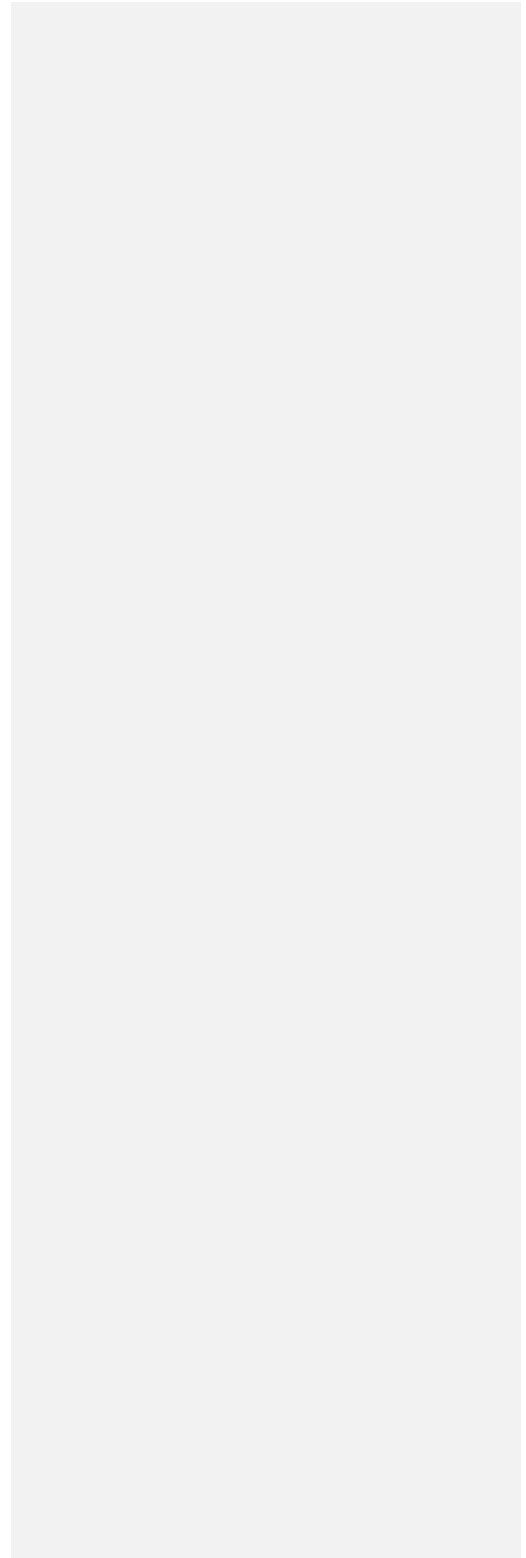


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39 Abbreviations

CT	Computed Tomography
CN	Cytoreductive nephrectomy
HNPCC	Hereditary Non-Polyposis Colorectal Carcinoma
KSS	Kidney Sparing Surgery
LN	Lymph Nodes
PN	Partial Nephrectomy
PS	Performance Status
RN	Radical Nephrectomy
RCC	Renal Cell Carcinoma
RMB	Renal Mass Biopsy
SCC	Squamous cell carcinoma
TS	Tuberous Sclerosis
US	Ultrasound
UTUCs	Upper Urothelial Tract Tumors

40 Introduction

We have been trying to merge updated international guidelines of renal tumors, taking in account the social and financial limitation. It is a step for more development of pure Egyptian guidelines, by also putting solutions for many problems facing us like data registry, multicenter cooperation, and financial limitation.

40.1 Methodology

Data resources included the following:

1. 4 guidelines with their recent updates: National Institute for Health and Care Excellence, European Urological Association, American Urological Association and National Comprehensive Cancer Network.
2. Associated Egyptian publications

The Strength Rating of grading depends on 2 parameters:

Strength Rating of clinical practice recommendation, graded as strong or weak. This is the consensus of the Egyptian guidelines committee for renal tumors, relying on international guidelines recommendations, taking in accounts the socio-economic factors and the Egyptian environment.

40.2 2.2 Results

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

40.3 Conclusions.

These guidelines provide practical evidence-based guidance on the clinical aspect of Renal tumors. The main target is entirely focused on assessment and treatment, reflecting the recommended clinical practice. This can provide the basis for thinking through patient's management and also for planning and designing clinical services.

41 Renal Cell Carcinoma (RCC):

41.1 Epidemiology of Renal Cell Carcinoma (RCC):

Renal cell carcinoma represents around 3% of all cancers worldwide, with the highest incidence occurring in Western countries. Generally, during the last two decades, there has been an annual increase of about 2% in the RCC incidence worldwide. ⁽¹⁾

Based on the results published from the National Cancer Registry Program (NCRP) in 2014, the crude rate for renal cancer was 1.8 while the age-standardized incidence rate was 2.7 for a relative percentage of 1.53% of cancers at all sites in males; while in females it was 0.97%. ⁽²⁾

20% of Small renal mass less than 4 cm are benign tumors. Oncocytoma is a benign tumor that originates from intercalated collecting duct cells like chromophobe RCC. It is characterized by Y chromosomal anomalies and associated incidence of RCC. It is a well-circumscribed tumor with central stellate scar. On microscopic examination it shows eosinophilic cells with negative Hale stain. As it is difficult to diagnose it clinically, it is diagnosed pathologically post-surgery. ⁽³⁾

AML (angiomyolipoma) is a benign mesenchyme tumor. It is either sporadic or familial like tuberous sclerosis (TS). It is diagnosed clinically by CT by the presence of fat except in poor fat AML. Venous thrombosis is a rare complication especially in the epithelioid pattern. Familial AML and large size AML have a higher risk for bleeding. ⁽³⁾

Table 18: Recommendations of Epidemiology of RCC

Recommendation	Strength Rating
1. Treat AML either with NSS or angioembolization: a) Tumor > 4cm b) Female in childbearing period. c) Patient away from medical service.	Weak
2. Offer systemic therapy with mTOR Inhibitors for patient not fit for surgery or embolization.	Weak

41.2 Etiology of RCC

Factors that have been identified as risk factors in the etiology of RCC include smoking, obesity, and hypertension. Increasing physical activity, eliminating cigarette smoking and in obese patients reducing weight are therefore potential preventative measures to decrease the risk of RCC. ⁽¹⁾

Table 19: TNM staging :

T - Primary tumor ⁽³⁾
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour

T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney		
T1a	Tumour ≤ 4 cm or less		
T1b	Tumour > 4 cm but ≤ 7 cm		
T2	Tumour > 7 cm in greatest dimension limited to the kidney		
T2a	Tumour > 7 cm but ≤ 10 cm		
T2b	Tumour > 10 cm, limited to the kidney		
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adreal gland and not beyond Gerota fascia		
T3a	Tumour grossly extends into the renal vein or its segmental (muscle- containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia		
T3b	Tumour grossly extends into the vena cava below diaphragm		
T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumour invades beyond Gerota fascia (including congiguous extension into the ipsilateral adrenal gland)		
N - Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension		
M - Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
pTNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1,T2,T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

41.3 Evaluation of Renal masses

41.3.1 Diagnosis and staging:

41.3.1.1 Symptoms:

Renal masses remain asymptomatic until the late stages. More than 60% of RCCs are detected incidentally with abdominal ultrasound (US) or computed tomography (CT) performed for other reasons). The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare today, and correlates with advanced disease and subtypes associated with poor prognosis.

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs. A few patients present with symptoms caused by mRCC, such as bone pain, deterioration of performance status (PS), or persistent cough.⁽⁶⁾

41.3.1.2 Imaging:

For a solid or complex cystic renal mass, high quality, multiphase, cross-sectional abdominal imaging should be performed to optimally characterize and clinically stage the renal mass. Characterization of the renal mass should include assessment of tumor complexity, degree of contrast enhancement (where applicable), and presence or absence of fat.⁽⁷⁾ With solid RMs, the most important criterion for differentiating malignant lesions is the presence of contrast enhancement or restriction. CT and MRI cannot reliably distinguish oncocytoma and fat-free angiomyolipoma from malignant renal neoplasms⁽⁶⁾.

In patients with RCC, chest CT is the most accurate investigation to diagnose lung metastases or enlarged mediastinal lymph nodes (LNs). Since most bone and brain metastases are symptomatic at diagnosis, bone or brain imaging is performed on indication⁽⁶⁾.

In the case of a renal cystic mass, the Bosniak classification distinguishes five categories based on CT presentation, can predict the risk of malignancy, and provides guidance for management⁽⁶⁾.

41.3.1.3 Laboratory investigations:

In patients with suspected renal malignancy, physicians should obtain comprehensive metabolic panel, complete blood count, and urine analysis. For patients with a solid or complex cystic renal mass, physicians should assign CKD stage based on GFR and degree of proteinuria.⁽⁷⁾

41.3.1.4 Renal mass biopsy (RMB):

Renal mass biopsy should be considered when a mass is suspected to be hematologic, metastatic, inflammatory, or infectious.⁽⁷⁾ Percutaneous renal mass biopsies are increasingly used for histological diagnosis to avoid unnecessary surgery in the event of a benign lesion, to select patients for surveillance, and to obtain histology before ablative treatment. Tumor biopsies are also used in mRCC for the selection of medical and surgical treatment⁽⁶⁾.

When considering the utility of RMB, patients should be counseled regarding rationale, positive and negative predictive values, potential risks and non-diagnostic rates of RMB. In the setting of a solid renal mass, RMB is not required for: 1) young or healthy patients who are unwilling to accept the uncertainties associated with RMB; or 2) older or frail patients who will be managed conservatively independent of RMB findings⁽⁷⁾. Core biopsies are preferable to fine needle aspiration for solid RMs and are not recommended for cystic RMs due to their low diagnostic yield, unless areas with a solid pattern are present⁽⁶⁾.

A core biopsy should be performed with 18G needle and a coaxial technique to minimize the risk of seeding. At least two quality cores (non-fragmented, >10 mm in length) should be obtained,

and necrotic areas should be avoided to maximize diagnostic accuracy. Peripheral biopsies are preferable for larger masses, to avoid central necrosis ⁽⁶⁾.

In experienced centers, percutaneous core biopsies have low morbidity, a high diagnostic yield, and accuracy for the diagnosis of malignancy and RCC type. However, they are non-diagnostic in 2.5–22% of cases. If a biopsy is non-diagnostic, a second biopsy or surgical exploration should be considered ⁽⁶⁾.

41.3.1.5 Counseling:

In patients with a solid or Bosniak 3/4 complex cystic renal mass, a urologist should lead the counseling process and should consider all management strategies. A multidisciplinary team should be included when necessary. Physicians should provide counseling that includes current perspectives about tumor biology and a patient-specific risk assessment inclusive of sex, tumor size/complexity, histology (when obtained), and imaging characteristics.⁽⁷⁾

During counseling of patients with a solid or Bosniak 3/4 complex cystic renal mass, physicians must review the most common and serious urologic and non-urologic morbidities of each treatment pathway and the importance of patient age, comorbidities/frailty, and life expectancy.⁽⁷⁾

Physicians should review the importance of renal functional recovery related to renal mass management, including the risk of progressive CKD, potential short- or long-term need for renal replacement therapy, and long-term overall survival considerations. Physicians should consider referral to nephrology in patients with a high risk of CKD progression. Such patients may include those with eGFR less than 45 ml/min/1.73m², confirmed proteinuria, diabetics with preexisting CKD, or whenever eGFR is expected to be less than 30 ml/min/1.73m² after intervention. ⁽⁷⁾.

Physicians should recommend genetic counseling for all patients ≤ 46 years of age with renal malignancy and consider genetic counseling for patients with multifocal or bilateral renal masses, or if personal or family history suggests a familial renal neoplastic syndrome ⁽⁷⁾.

Table 20: Recommendations of Diagnostic Evaluation of Renal Tumours

Recommendations	Strength
1. Multiphasic contrast enhanced computed tomography of abdomen and chest is mandatory for diagnosis and staging	Strong
2. Bone scan and PET CT is routinely used for staging	Weak
3. Performing renal biopsy is indicated before ablative or systemic therapy with coaxial core biopsy technique	Strong
4. In cystic renal mass biopsy, should be avoided	Strong
5. Bosniak type 4 should be considered a malignant RCC	Strong

41.4 Treatment of localised RCC and local treatment of mRCC

Surgical treatment Surgery is the only curative treatment for localised RCC. Based on oncological and functional outcomes, localised T1a-b tumours are best managed by partial nephrectomy (PN) rather than by radical nephrectomy (RN), irrespective of the surgical approach. In clinically localised RCCs of ≤ 4 cm, compared with RN, PN was associated with equal or better survival, whereas serious adverse event rates, CSS, and time to recurrence were similar for both groups⁽⁸⁾

The decision process is necessarily influenced by surgeon's factors (own surgical expertise and prior outcomes, as well as comfort with various surgical procedures. Also complexity according to RENAL score is important factor.⁽⁹⁾ RN is preferred when all of the following criteria are met: (a) there is high tumor complexity and PN would be challenging, even in experienced hands; (b) there is no preexisting CKD or proteinuria; and (c) the contralateral kidney is normal and the new baseline estimated glomerular filtration rate will likely be greater than 45 mL/min/1.73 m².⁽⁷⁾

Partial nephrectomy should be considered for patients with solid or Bosniak 3/4 complex cystic renal masses who are young, and have multifocal masses or comorbidities that are likely to impact renal function in the future, such as moderate to severe hypertension, diabetes mellitus, recurrent urolithiasis or morbid obesity.⁽⁷⁾

Negative surgical margins should be a priority. The extent of normal parenchyma removed should be determined by surgeon discretion considering the clinical situation, tumor characteristics including growth pattern and interface with normal tissue. Tumor enucleation should be considered in patients with familial RCC, multifocal disease or severe CKD to optimize parenchymal mass preservation.⁽⁷⁾

Table 21: Recommendations of Treatment of RCC

Recommendations	Strength
1. Partial nephrectomy is indicated in T1 tumors (open/laparoscopy)	Strong
2. Laparoscopic / open radical nephrectomy for T2 Tumors and localized tumors difficult to be treated with partial nephrectomy.	Strong
3. Minimal invasive approach should be avoided if it will comprise the functional or the oncological outcome.	Strong
4. Ipsilateral adrenalectomy is indicated if there is clinical invasion for adrenal gland	Strong
5. Offer active surveillance or ablative therapy for comorbid patients with small renal mass	Weak
6. Offer embolization as palliative treatment (inoperable cases) in cases of hematuria or flank pain	Weak

7. Lymphadenectomy can be done to radiologically positive lymph nodes for staging and therapeutics benefits	Weak
8. In non-metastatic locally advanced RCC with venous thrombus. Removal of the tumor with the thrombus is necessary.	Strong
9. Don't offer adjuvant therapy for non-metastatic RCC	Strong

41.4.1 Cytoreductive nephrectomy (CN):

It is curative only if all tumor deposits can be resected. In patients with multiple metastases it is only palliative and systemic treatment are necessary. IMDC(the metastatic renal cancer database consortium) or MSKCC(Memorial Sloan Kettering Cancer Center) for classifying metastatic patients.⁽¹⁾

Table 22: Recommendation on Treatment of mRCC

Recommendations	Strength
1. CN is not indicated for poor risk MSKCC metastatic patients	Strong
2. Start systemic therapy 1st for intermediate risk MSKCC patients whom have no complaint from 1ry tumor.	Weak
3. Perform immediate CN in good performance patients whom do not require systemic therapy or in patients with resectable oligometastasis.	Weak
4. Offer local treatment for symptoms palliation like metastatectomy or streostatic radiotherapy for brain and bone metastasis	Weak

41.4.2 Systemic therapy for advanced disease:

41.4.2.1 Clear cell RCC

41.4.2.1.1 Recommendations for first line treatment:

1- Limited disease burden in asymptomatic patient:

Active surveillance

2- IMDC favorable risk:

Pembrolizumab/axitinib

Sunitinib

Pazopanib

3- IMDC intermediate/poor risk:

A- Immune checkpoint inhibitors available:

Pembrolizumab/axitinib

Ipilimumab/Nivolumab

B- Immune checkpoint inhibitors unavailable:

Sunitinib or Pazopanib

41.4.2.1.2 Recommendations for second line treatment:

1- Prior TKI:

Nivolumab:

Immunotherapy unavailable: Axitinib

2- Prior immune checkpoint inhibitor

Sunitinib or

Pazopanib

41.4.2.1.3 Non-clear cell RCC:

Sunitinib (preferred)

Everolimus

Surveillance protocol post-RN:

The aim of surveillance mainly is to detect recurrences and many classifications system is used to stratify risk of recurrence like university of California system. Also surveillance is used for monitor post-operative complications and functional outcomes. ⁽¹⁾

Table 23: Surveillance protocol post-RN :

Risk Profile	Surveillance				
	6 mo	1y	2y	3y	3y
Low	US	CT	US	CT	CT once every 2 years; Counsel about recurrence risk of 10%
Intermediate/ High	CT	CT	CT	CT	CT Once every 2 years

42 Upper urothelial tract tumors (UTUCs)

42.1 Epidemiology:

UTUCs are not common and represent about 5-10% of urothelial carcinoma. Pelvicalyceal tumors are more common than ureteral tumor, 60% of UTUCs are invasive. Concurrent bladder cancer occurs in 17% of cases while up to 47% of cases show bladder recurrence. Familial/hereditary UTUCs are linked to hereditary non-polyposis colorectal carcinoma (HNPCC).⁽¹⁰⁾

42.2 Risk factors:

Exposure to tobacco or aromatic amines are risk factors to develop UTUCs. Aristolochic acid contained in Aristolochia fangchi and Aristolochia clematis is linked to P53 mutation which increased risk of UTUCs as in Balkan nephropathy.⁽¹⁰⁾

42.3 Histologic Variants:

Urothelial carcinoma is the most common variant. Squamous cell carcinoma accounts for 10% only. SCC usually associated with chronic inflammation and infection.⁽¹⁰⁾

Table 24: TNM staging

T - Primary tumor ⁽¹¹⁾
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Non-invasive papillary carcinoma
Tis Carcinoma in situ
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscle
T3 (Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter)
T4 Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension
or multiple lymph nodes, none more than 5 cm in greatest dimension
N3 Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis
M0 No distant metastasis
M1 Distant metastasis

Use the WHO 1973 and 2004 grading systems for the histological classification of UTUC

Table 25: Recommendations for Diagnosis of UTUCs:

Recommendation ⁽¹⁰⁾	Strength Rating
1. CT urography and urinary cytology is essential for diagnosis	Strong
2. Cystoscopy is indicated to diagnose associated bladder tumors.	Strong
3. Diagnostic ureteroscopy, biopsy and retrograde ureteropyelogram is indicated when additional information will impact treatment strategy.	Weak

Table 26: Risk stratifications of UTUCs:

Low risk (all factors should present)	High risk (any factor present) ⁽¹⁰⁾
• Unifocal disease • Tumour size < 2 cm • Low-grade cytology • Low-grade URS biopsy • No invasive aspect on CTU-urography	• Hydronephrosis • Tumour size > 1 cm • High-grade cytology • High-grade URS biopsy • Multifocal disease • Previous radical cystectomy for bladder cancer

Table 27: Recommendations for Disease management of localized tumors:

Recommendation ⁽¹⁰⁾	Strength Rating
1. Kidney sparing surgery (KSS) should be offered for low-risk disease	Strong
2. KSS is offered for distal ureteral tumor or in patient with solitary kidney or poor renal function, but thus should not affect oncological outcomes.	Weak
3. Radical nephroureterectomy with removal of bladder cuff is indicated in high-risk patient.	Strong
4. Lymphadenectomy is performed in high-risk patients	Weak
5. Offer intravesical chemotherapy to lower bladder recurrence.	Strong

The instillations of BCG post KSS still have not been confirmed to be beneficial. ⁽¹⁰⁾

Laparoscopic radical nephroureterectomy should avoided in cT3/4 or N positive tumors ⁽¹⁰⁾

Metastatic disease:

Radical nephroureterectomy has no role in metastatic disease. It may be offered as palliative treatment. Platinum based chemotherapy should be offered but still data is insufficient.

Radiotherapy has no role. ⁽¹⁰⁾

42.3.1 After Radical Nephroureterectomy:

- low risk
 - Perform cystoscopy at 3month and 12 month then yearly for 5 years.
- high risk
 - Cystoscopy and cytology every 3months for 2years then every 6 months till 5 years then yearly CT urography and CT chest every 6 months for 2 years then every year.

42.3.2 After kidney Sparing Surgery

- low risk
 - Perform cystoscopy and CT urogram at 3month and 6 month then yearly for 5 years.
 - Perform ureteroscopy at 3 months
- high risk
 - Cystoscopy and cytology and CT urograpy and CT chest at 3and 6 month then yearly
 - Ureterscopy and cytology in situ at 3month and 6 month.

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43 WILMS' TUMOUR “Nephroblastoma”

43.1 Epidemiology

It is the 5th most common tumor, the 2nd common abdominal tumor and the 1st common renal tumor in children. It represents 5% of pediatric tumors. Bilateral wilms occur in 5-7% of patients. More than 80% occur before 5yrs of age with highest incidence among blacks & lowest among Asians

43.2 Pathology:

43.2.1 Microscopic:

1) “Classic” Wilms’

It is composed of blastemal cells, epithelial cells, & stromal cells, If mostly blastemal (highly aggressive tumours) will responds to chemotherapy. However, if mostly epithelial will be less aggressive but not will respond to chemotherapy. Kids less than 1yr of age diagnosed with Wilms’ tumor with Nephrogenic Rests are associated with increased risk of developing contralateral disease

2) Anaplastic Wilms’

It is characterized by 3 histologic abnormalities, nuclear enlargement (3-4x adjacent cells), hyperchromasia of enlarged nuclei and abnormal mitotic figures. Presence of diffuse anaplasia associated with resistance to chemotherapy with worst prognosis.

43.3 Staging

COG Staging system used for Wilms’ tumour: (Children’s Oncology Group)

- Based on surgical & histopathologic findings

Table 28: Staging system for Wilm’s Tumour

Stage		Capsule	Surgical margin	Tumour	Hilar structure
I	Limited to kidney	intact renal capsule	-ve completely excised	no rupture	
II	not limited to kidney	beyond renal capsule	-ve completely excised	Focal spillage	+/-extrarenal vessel thrombus

III	Residual tumour confined to abdomen		+ve Incomplete excision	Previous Biopsy Diffuse spillage /rupture peritoneal implant	+ve LNs
IV	Hematogenous metastasis				
V	BILATERAL				

43.4 Diagnosis:

Abdominal mass, gross hematuria is common presentation. The child seems well unlike neuroblastoma. Ultrasound determines solid and cystic renal mass. Doppler ultrasound can detect renal vein thrombosis. Cross sectional imaging on abdomen and chest should be used for Wilms tumor staging.

Table 29: Recommendations for Diagnosis of Wilms Tumour:

Recommendation	Strength Rating
1. Cross sectional imaging on abdomen and chest for Wilms tumor staging	Weak
2. Bone scan and skeletal survey for bone metastasis	Weak
3. Histopathological examination should be combined with chromosomal evaluation to set the management plan	Weak

43.5 Treatment

43.5.1 Principles of Surgical Management:

- Radical Nephrectomy with sampling of suspicious LNs
 - Trans peritoneal approach assess entire abdomen liver, LN for Mets.
 - No role for exploration of contralateral kidney if good pre-op CT/MRI
 - Complete excision without contamination is essential
- 6-fold higher relapse rate with tumor spillage
 - Lower complication rate if Nephrectomy done after neoadjuvant chemotherapy
- Partial Nephrectomy
 - CONTROVERSIAL
 - Local recurrence rate is 8%
 - Intra-abdominal relapse associated with markedly decreased survival (40%) after pre-op CHEMO, partial Nephrectomy possible in 10-15%

- Should be reserved for select cases
 - 1) Bilateral tumours (stage 5)
 - 2) Tumours in solitary kidney
 - 3) Tumours in kids with renal insufficiency
 - 4) Kids with syndromes associated with renal failure (Denys-Drash, WAGR).

43.5.2 Principles of Chemotherapy:

Everyone should get pulse intensive Chemotherapy

- Differing schools: neoadjuvant VS adjuvant
- Preferred protocol
 - Neoadjuvant Chemotherapy:
 - Our standard in Egypt
 - Biopsy performed before initiation of chemotherapy
 - Advantage
 - Majority of shrinkage in first 4 weeks
 - Decrease incidence of tumor rupture
 - Disadvantage
 - Difficult histology and staging
 - No effect on survival
 - It is indicated in
 - I. Stage 5 (bilateral tumors ... including NRs)
 - II. Solitary kidney
 - III. Inoperable tumor at time of diagnosis. should not be based on pre-op imaging as local tumor extension can be overestimated
 - IV. Tumor extension into IVC above hepatic veins

43.5.3 Principles of Radiotherapy:

NO radiation therapy if Stage 1 Wilms' (FH and anaplasia), given if :

- High-risk of relapse
 - high stage (3-4)
 - presence of anaplasia in stage 2-4

- Option for local recurrence if nephrectomy cannot be done

43.5.4 Localized Disease:

Preoperative actinomycin D and vincristine for patients newly diagnosed with Wilms tumor aged ≥ 6 months,

The SIOP–RTSG accounts for the risk of misdiagnosis of Wilms tumor by recommending direct surgery instead of preoperative chemotherapy for children < 6 months old, and the consideration of fine-needle biopsy for patients who have unusual clinical presentations or unusual findings on imaging.

To avoid treatment delay, routine histological assessment before treatment is not advocated. This approach has been shown to be safe and identifies the vast majority of patients with non-Wilms tumors who are at risk of being unnecessarily treated with preoperative chemotherapy

Furthermore, preoperative chemotherapy enables personalized assessment of tumor chemosensitivity, including identification of the high-risk, blastemal-type Wilms tumors.

Patients registered in the UMBRELLA protocol will continue to be stratified for postoperative treatment according to tumor stage and histological risk group, as was the protocol in SIOP–2001

The new standard management regimen for most patients in the UMBRELLA protocol with stage II–III intermediate-risk Wilms tumors. This regimen consists of 27 weeks of vincristine and actinomycin D without doxorubicin.

Thus, the inclusion of doxorubicin in postoperative treatment of patients with large-volume (≥ 500 ml) stage II–III nonstromal, nonepithelial tumours is recommended in the UMBRELLA protocol.

blastemal-type tumors in which treatment was intensified by changing to the high-risk tumor treatment schedule for patients with blastemal-type Wilms tumor, EFS increased from 67% to 80% (log rank $P = 0.006$) avoiding intensive treatment for relapse in a considerable number of patients

43.5.5 Metastatic Disease (Stage IV)

Overall, ~17% of patients with Wilms tumors present with stage IV disease at diagnosis, which is defined as hematogenous metastases to the lungs, liver, or other sites, or extra-abdominal lymph node metastases.

Patients with CT-only nodules, included in the definition of lung nodules and treated as metastases in the UMBRELLA protocol if they have a transverse diameter of at least 3 mm, who were treated with vincristine and actinomycin D plus doxorubicin had superior EFS to those who received vincristine and actinomycin D only, but overall survival was similar in both groups

Preoperative treatment for metastatic (stage IV) disease includes a combined vincristine, actinomycin D, and doxorubicin regimen for 6 weeks, followed by reassessment imaging of local tumors (using MRI) and metastatic sites (using CT and/or MRI) before surgery (61–67% of patients have complete metastatic response before surgery)

43.5.6 Management of Bilateral Wilms' Tumour (Stage 5):

- 1) Initial Biopsy before pre-op Chemotherapy (moving towards NOT doing pre-op Biopsy now).
 - Confirm Wilms' & define histology
 - Chemotherapy
 - Nephrectomy can be avoided in ~50% of patients that undergo this strategy
- 2) Repeat imaging after 6 weeks of chemotherapy
 - Assess feasibility of partial Nephrectomy
 - If no response, perform or repeat an open biopsy
 - o if blastemal-predominant or anaplastic Wilms' on repeated Biopsy. 12 more weeks of different chemotherapy regime are needed.
- 3) Reassess to see if partial Nephrectomy possible on either or both kidneys
- 4) Bilateral Radical Nephrectomy if tumors fail to respond to chemo & radio therapy
- 5) Long-term close follow up is essential, late relapses can occur (>4yrs later)
 - if ESRD develops despite partial Nephrectomy. Remove remaining renal mass is needed before Treatment

43.5.7 Bilateral Disease (Stage V)

Synchronous bilateral Wilms tumor (stage V) accounts for ~5–8% of instances of Wilms tumor and long-term overall survival is currently ~80%

Functional renal outcome was considerably better after bilateral nephron sparing surgery (NSS) than when other types of surgery were used.

Avoiding total nephrectomy at initial surgery is advised for bilateral tumors in the UMBRELLA protocol.

Patients with bilateral disease received preoperative chemotherapy including vincristine and actinomycin D until NSS was deemed feasible, with response evaluations performed every 4 weeks.

Prolonged preoperative chemotherapy is often ineffective (especially as many bilateral tumors are the chemotherapy-insensitive stromal subtype)

So, Limits preoperative chemotherapy to a maximum of 12 weeks, with time intervals for evaluation fixed to 6 weeks

In instances of tumor non-responsiveness or inoperability switching to treatment with etoposide and carboplatin is recommended, to avoid use of anthracyclines, and biopsy can be considered to determine histology.

43.5.8 Relapsed Wilms Tumour

Thus, patients with relapsed tumors will be prospectively classified into three groups in the UMBRELLA protocol, group AA, group BB, and group CC, based on these factors.

Treatment of a relapsed Wilms tumors, defined as patients with initial stage I–II low-risk or intermediate-risk tumors, who received only vincristine and/or actinomycin D (no radiotherapy) in their first-line treatment, will include four drugs (combinations of doxorubicin and/or cyclophosphamide and carboplatin and/or etoposide).

Patients without initial diffuse anaplasia or blastemal-type histology, who have already received doxorubicin in their initial treatment, will receive an intensive reinduction drug regimen (including the combination of etoposide and carboplatin with either ifosfamide or cyclophosphamide), followed by either high-dose melphalan and autologous stem cell rescue (ASCR) or two further reinduction courses, at the discretion of the local physician. Patients with initial diffuse anaplasia or blastemal-type tumors. advises trying camptothecins (irinotecan or topotecan) or novel compounds.

These Guidelines:

- Include considering resection after proven reduction of relapsed disease after chemotherapy, independently of histological subtype or risk group,
- When radical surgery seems possible or
- When it is useful to evaluate histological tumor response.

Applying radiotherapy to initially nonirradiated sites is uniformly accepted, but developing standard recommendations for the approach to previously irradiated sites is difficult

43.6 Infant Wilms Tumors:

Infants, defined as patients younger than 6 months (182 days), considered for primary surgery unless tumors are judged not amenable to immediate nephrectomy in a multidisciplinary team consensus. The reason for upfront nephrectomy is that, compared with older children, a higher proportion of renal tumors in infants are congenital mesoblastic nephroma or malignant rhabdoid tumors that either need surgery alone (congenital mesoblastic nephroma) or alternative chemotherapy at the outset (more intensive chemotherapy than actinomycin D and vincristine)

Percutaneous cutting needle biopsy is recommended in instances of stage IV disease or when immediate surgery is deemed difficult.

Postoperative chemotherapy for Wilms tumor is similar in infants to that in older children who underwent direct nephrectomy, with adjustment of drug doses according to age and body weight

43.7 Adult Wilms Tumors:

Adult Wilms tumor is often diagnosed unexpectedly after nephrectomy for a suspected renal cell carcinoma. In rare instances in which the diagnosis of Wilms tumor is histologically proven before surgery, preoperative chemotherapy is recommended, like treatment strategies for Wilms tumor diagnosed in childhood.

The treatment regimen for pediatric stage I disease of actinomycin D and vincristine is only advised for a selected group of adult stage I patients without anaplasia.

All other adult patients will receive more intensive treatment, either consisting of vincristine and actinomycin D plus doxorubicin for patients with non-anaplastic subtypes, or four drugs (carboplatin, cyclophosphamide, etoposide, and doxorubicin) for anaplastic tumors of any stage.

Table 30: Recommendations for management of Wilms' tumours (Umbrella protocol)

Recommendation	Strength
1. Neoadjuvant chemotherapy is better to be followed. Pre-chemotherapy biopsy is preferred	Weak
2. Radical nephrectomy with suspicious lymph node sampling is indicated	Strong
3. Adjuvant radiotherapy / chemotherapy for residual mass	Strong
4. Treatment should be tailored depending on tumor and patient factors.	Strong
5. NSS is now acceptable for non-syndromic unilateral Wilms tumors under certain conditions, specified in the UMBRELLA protocol, that include small tumor volume (<300 ml) and the expectation of a substantial remnant kidney function in patients with tumors <300 ml who never had lymph node involvement	Strong
6. For bilateral Wilms tumors, assess the feasibility of NSS and minimize the risk of upstaging by incomplete resection of the tumor.	Strong
7. Minimally invasive or laparoscopic surgery are acceptable in selected circumstances, including small, central tumors with a rim of nonmalignant renal tissue, which still enable lymph node sampling. (should not be done in patients in whom NSS can be safely performed).	Strong

43.8 Radiotherapy Recommendations

No locoregional control or survival benefit was observed with the boost dose to the area of lymph node involvement for stage III intermediate-risk tumors.

The dosage of whole-lung irradiation was decreased from 15 Gy to 12 Gy in the UMBRELLA protocol with high relapse-free and overall survival (72% and 78% respectively) for favourable-histology tumours after treatment with doxorubicin, actinomycin-D, vincristine, and 12 Gy to the lungs

Whole-abdominal radiotherapy is indicated for intermediate-risk or high-risk histology tumours with major (visible on imaging or during surgery) preoperative or intraoperative tumour rupture, or macroscopic peritoneal deposits.

Pulmonary radiotherapy is administered for lung metastases lacking complete response by postoperative week 10.

Patients achieving a complete response after induction chemotherapy with or without surgery do not need radiotherapy to the lungs, as they have excellent survival even without radiotherapy

Patients with viable metastases at surgery or high-risk histology, both of which are associated with poor survival of <40%, are the exception and receive radiotherapy to the lungs

Whole-lung irradiation is recommended for patients who did not receive lung irradiation during first-line treatment, irrespective of histology

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Committee V

Bladder Cancer



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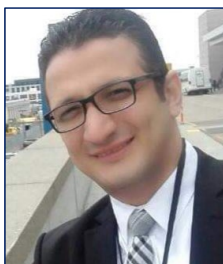
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44 Abbreviations:

BCG	Bacillus Calmette-Guérin
BC	Bladder cancer
CIS	Carcinoma in Situ
CT	Computed tomography
CT-IVU	Computed Tomography-Intravenous Urography
FGFR	Fibroblast Growth Factor Receptor
G-CSF	Granulocyte Colony-Stimulating Factor
HD	High-Dose
HG	High-Grade
IVU	Intravenous Urography
LG	Low-Grade
MRI	Magnetic Resonance Imaging
MVAC	Methotrexate, Vinblastine, Adriamycin plus Cisplatin
MMT	Multimodality Treatments
MIBC	Muscle invasive bladder cancer
NAC	Neoadjuvant Chemotherapy
NMIBC	Non-muscle invasive bladder cancer
NMP	Nuclear Matrix Protein
PUNLMP	Papillary Urothelial Neoplasm of Low Malignant Potential
QoL	Quality of Life
RC	Radical Cystectomy
RT	Radiotherapy
SREs	Skeletal-Related Events
TERT	Telomerase Reverse Transcriptase
US	Ultrasound
UUT	Upper Urinary Tract
ZA	Zoledronic Acid

45 Introduction:

This overview represents the updated recommendations for bladder cancer diagnosis and management. The aim is to provide practical advice on the clinical work-up and treatment of different patterns of bladder cancer presentation (Non muscle invasive, muscle invasive and metastatic).

It must be emphasized that guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions and considering the personal values and preferences/individual circumstances of patients into account.

45.1 Methods:

A comprehensive scoping effort covering all guidelines (American, European and Canadian) and panels (National Comprehensive Cancer Network and International Bladder Cancer Database Consortium) as regard to different patterns of bladder cancer was performed.

For each recommendation and advice in this overview, all of the following elements were highly considered:

- Quality of evidence for this recommendation.
- Impact of this practice on patient and oncological outcomes.
- The balance between this practice and the different aspects of health service in our locality.

45.2 Results

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

45.3 Conclusions.

These guidelines provide practical evidence-based guidance on the clinical aspect of Urinary bladder cancer. The main target is entirely focused on assessment and treatment, reflecting the recommended clinical practice. This can provide the basis for thinking through patient's management and also for planning and designing clinical services.

46 Epidemiology, Etiology and Pathology:

46.1 Epidemiology

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered. In Egypt, it is the most commonly diagnosed cancer in males ⁽¹⁾.

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1) ⁽²⁾.

46.2 Etiology

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases ⁽³⁾. Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted. Occupational exposure to aromatic amines and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases ⁽⁴⁾. This type of occupational exposure occurs mainly in industrial plants, which process paint, dye, metal and petroleum products ⁽⁵⁾.

Schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, is also a cause of BC. Exposure to ionizing radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone ⁽⁶⁾. The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol and triglycerides) is uncertain ⁽⁷⁾.

46.3 Pathology

46.3.1 Staging:

TNM classification is the standard tool for staging of BC ⁽⁸⁾ (Table 1).

Table 31: TNM classification of bladder cancer

T- Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : 'flat tumor'
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopically

T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumor invades pelvic wall or abdominal wall
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastases

46.3.2 Histological grading:

Histological grading of BC should be done using the available two systems of grading (WHO 1973 and WHO/ISUP 2004) ⁽⁹⁾ (Table 2).

Table 32: Grading systems of bladder cancer

1973 WHO grading	
Grade 1: well differentiated	
Grade 2: moderately differentiated	
Grade 3: poorly differentiated	
2004 WHO/ISUP grading system (papillary lesions)	
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	
Low-grade (LG) papillary urothelial carcinoma	
High-grade (HG) papillary urothelial carcinoma	

46.3.3 Carcinoma *in situ* and its classification

Carcinoma *in situ* (CIS) is a flat, high-grade, non-invasive urothelial carcinoma. Carcinoma *in situ* is often multifocal and can occur in the bladder, but also in the upper urinary tract (UUT), prostatic ducts, and prostatic urethra ⁽¹⁰⁾.

46.3.3.1 Classification of CIS according to clinical type:

- Primary: isolated CIS with no previous or concurrent papillary tumors and no previous CIS.

- Secondary: CIS detected during follow-up of patients with a previous tumor that was not CIS.
- Concurrent: CIS in the presence of any other urothelial tumor in the bladder.

46.3.4 Variants of urothelial carcinoma and lymphovascular invasion

Currently the following differentiations are used ⁽¹¹⁾:

1. Urothelial carcinoma (more than 90% of all cases)
2. Urothelial carcinomas with partial squamous and/or glandular or trophoblastic differentiation
3. Micropapillary urothelial carcinoma
4. Nested variant (including large nested variant) and microcystic urothelial carcinoma
5. Plasmocytoid, giant cell, signet ring, diffuse, undifferentiated
6. Lymphoepithelioma-like
7. Small-cell carcinomas
8. Sarcomatoid urothelial carcinoma

In these pathological variants, the decision of optimal treatment is individualized. Early cystectomy with or without neo-adjuvant or adjuvant therapy is considered according to the decision of multidisciplinary team agreement.

The presence of an element of these variants together with TCC tumors is considered as nonurothelial and should be treated as tumor cell variant.

Revision of the histopathology may be needed by another expert to support the diagnosis

47 Non-muscle invasive bladder cancer (NMIBC)

47.1 Diagnosis

47.1.1 Patient history

A focused patient history is mandatory.

47.1.1.1 Signs and symptoms

Hematuria is the most common finding in NMIBC. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding. Sometimes, the bladder lesion is detected during routine sonographic survey especially those located in the **bladder** dome and anterior wall.

47.1.1.2 Physical examination

A focused urological examination is mandatory although it does not reveal NMIBC.

47.1.1.3 Imaging

47.1.1.3.1 Ultrasound

Ultrasound (US) may be performed as an adjunct to physical examination as it has moderate sensitivity to a wide range of abnormalities in the upper and lower urinary tract⁽¹²⁾.

It permits characterization of associated pathology, detection of hydronephrosis, and visualization of intraluminal masses in the bladder.

47.1.1.3.2 Computed tomography urography and intravenous urography

Computed tomography (CT) urography is used to detect papillary tumors in the urinary tract, indicated by filling defects and/or hydronephrosis⁽¹³⁾.

Intravenous urography (IVU) is an alternative if CT is not available but particularly in muscle-invasive tumors of the bladder and in UTUCs, CT urography provides more information (including status of lymph nodes and surrounding organs)⁽¹⁴⁾.

The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumors located in the trigone. The risk of UTUC during follow up increases in patients with multiple- and high-risk tumors⁽¹⁵⁾.

CTU or magnetic resonance imaging are an essential tool in the diagnosis, staging and Management

47.2 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in G3 and high-grade tumors (84%), but low sensitivity in G1/LG tumors (16%). The sensitivity in CIS detection is 28-100%⁽¹⁶⁾.

Positive voided urinary cytology can indicate an urothelial carcinoma anywhere in the urinary tract; negative cytology, however, does not exclude its presence⁽¹⁷⁾.

Cytological interpretation is user-dependent. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations; however, in experienced hands specificity exceeds 90% ⁽¹⁸⁾.

47.3 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests have been developed. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines ⁽¹⁹⁾.

The following conclusions can be drawn regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity, compared to urine cytology.
- Benign conditions and previous BCG instillations may influence the results of many urinary marker tests.
- The wide range in performance of the markers and low reproducibility may be explained by patient selection and complicated laboratory methods required.
- Positive results of cytology, UroVysion (FISH), Nuclear Matrix Protein (NMP)22R, *Fibroblast Growth Factor Receptor (FGFR)3/Telomerase Reverse Transcriptase (TERT)* and microsatellite analysis in patients with negative cystoscopy and upper tract work-up, may identify patients more likely to experience disease recurrence and possibly progression.
- If main aim is to avoid unnecessary cystoscopies, rather than looking for markers with a high sensitivity and specificity.

Table 33: Recommendations for bladder cancer classification

Recommendations	Strength rating
1. Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
2. Do not use the term “superficial bladder cancer”.	Strong

47.4 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue by either cold-cup biopsy or resection ⁽²⁰⁾.

Carcinoma *in situ* is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies ⁽²¹⁾.

Cystoscopy is initially performed as an outpatient procedure. A flexible instrument with topical intraurethral anesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men ⁽²²⁾.

When flexible cystoscopy is not available, provided that the imaging is positive for bladder lesion; formal cystoscopy is required under anesthesia ⁽²³⁾. The urologist should be ready to carry out resection or at least biopsy.

47.5 Transurethral resection of TaT1 bladder tumors

47.5.1 Strategy of the procedure

Transurethral resection of the bladder should be performed systematically in individual steps.

The operative steps necessary to achieve a successful TURB include identifying the factors required to determine the disease risk (number of tumors, size, multifocality, characteristics, concern for the presence of CIS, recurrent vs. primary tumor), clinical stage (bimanual examination under anesthesia, assignment of clinical tumor stage), adequacy of the resection (visually complete resection, visualization of muscle at the resection base), and presence of complications (assessment for perforation) ⁽²⁴⁾.

47.5.2 Surgical and technical aspects of tumor resection

A complete resection, performed by either fractioned or *en-bloc* technique, is essential to achieve a good prognosis.

- Piecemeal resection in fractions (separate resection of the exophytic part of the tumor, the underlying bladder wall and the edges of the resection area) provides good information about the vertical and horizontal extent of the tumor ⁽²⁴⁾.
- *En-bloc* resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser is feasible in selected exophytic tumors. It provides high quality resected specimens with the presence of detrusor muscle in 96-100% of cases ⁽²⁵⁾.

The technique selected is dependent on the size and location of the tumor, experience of the surgeon and the availability of the facilities as well.

47.5.3 Evaluation of resection quality

The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence and tumor understaging. The presence of detrusor muscle in the specimen is considered as the surrogate criterion of the resection quality and is required (except in TaG1/LG tumors) ⁽²⁶⁾.

The resected tissues should be identified in specific well labelled containers (tumor, base, random biopsies) ⁽²⁷⁾.

47.5.3.1 Bladder biopsies

Carcinoma *in situ* can present as a velvet-like, reddish area, indistinguishable from inflammation, or it may not be visible at all. For this reason biopsies from suspicious urothelium should be taken. However, in patients with positive urine cytology, or with a history of HG/G3 NMIBC

and in tumors with non-papillary appearance, mapping biopsies from normal-looking mucosa is recommended ⁽²⁷⁾.

47.5.3.2 Prostatic urethral biopsies

The risk of prostatic urethra or duct involvement is higher if the tumor is located at the trigone or bladder neck, in the presence of bladder CIS and multiple tumors ⁽²⁸⁾. Based on this observation, a biopsy from the prostatic urethra is necessary in some cases.

It is preferable to obtain biopsy from the prostatic urethra if the patient would receive orthotopic diversion ⁽²⁹⁾.

47.5.3.2.1 Second resection

A second TURB can increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information ⁽³⁰⁾. It is recommended in selected cases two-six weeks after initial resection.

Second TURB is indicated in the following situations ⁽³¹⁾:

- After incomplete initial TURB, or in case of doubt about completeness of a TURB)
- If there is no muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumors and primary CIS
- In T1 tumors

47.6 Predicting disease recurrence and progression

Treatment of NMIBC should be based on a patient's prognosis ⁽³²⁾. In order to predict, both the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group has developed a scoring system and risk tables ⁽³³⁾.

The scoring system is based on the six most significant clinical and pathological factors which are shown in Table-4. It also illustrates the weights applied to various factors for calculating the total scores for recurrence and progression.

Table 34: Calculation of NMIBC recurrence and progression scores

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumor diameter		
< 3 cm	0	0
≥ 3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year		

	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	0-17	0-23

47.6.1 Prognosis of Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease. There are no reliable prognostic factors, some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumors compared to primary CIS multifocal disease and in CIS in the prostatic urethra ⁽³⁴⁾.

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC. Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders ⁽³⁵⁾.

47.6.2 Patient stratification into risk groups

Three major risk groups are considered which takes into account the EORTC risk tables' probabilities of recurrence and, especially, progression ⁽³⁶⁾ (Table 5).

Table 35: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumors	Primary, solitary, TaG1 (PUNLMP, LG), < 3 cm, no CIS.
Intermediate-risk tumors	All tumors not defined in the two adjacent categories (between the category of low- and high risk).
High-risk tumors	Any of the following: • T1 tumor • G3 (HG) tumor • carcinoma <i>in situ</i> (CIS) • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumors (all features must be present)

. Table 36: Recommendations for primary Management of non-muscle invasive bladder cancer

Recommendations	Strength Rating
1. Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
2. Use renal and bladder ultrasound and/or computed tomography (CT)-intravenous urography during the initial work-up in patients with haematuria.	Strong
3. Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
4. Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended when cytology is positive, in case of a history of HG/G3 tumours and in tumours with non-papillary appearance.	Strong
5. Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma <i>in situ</i> is present or suspected, if there is positive cytology without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	Strong
6. The TURB protocol must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
7. In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
8. Perform a 2nd TURB in the following situations:	Strong
9. After incomplete initial TURB, or in case of doubt about completeness of a TURB)	Strong
10. If there is no muscle in the specimen after initial resection, with the exception of TaG1 tumours and primary CIS;	Strong
11. In T1 tumours.	Strong
12. If indicated, perform a 2nd TURB within two to six weeks after initial resection. This 2nd TURB should include resection of the primary tumour site.	Strong
13. Stratify patients into three risk groups	Strong
14. Apply the EORTC risk tables and calculator for the prediction of the risk of tumour recurrence and progression in different intervals after transurethral resection of the bladder, in individual patients.	Strong

48 Disease management

48.1 Adjuvant treatment

Although TURB by itself can eradicate a TaT1 tumor completely, these tumors commonly recur and can progress to MIBC. It is therefore necessary to consider adjuvant therapy in all patients.

48.1.1 Intravesical chemotherapy

48.1.1.1 A single, immediate, post-operative intravesical instillation of chemotherapy

Immediate single instillation has been shown to act by destroying circulating tumor cells after TURB, and by an ablative effect on residual tumor cells at the resection site and on small overlooked tumors ⁽³⁷⁾. Some reports did not demonstrate the efficacy of immediate single instillation in intermediate and high risk patients ⁽³⁸⁾.

48.1.1.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients, a single instillation reduces the risk of recurrence and is considered to be the standard and complete treatment ⁽³⁹⁾.

Additional adjuvant chemotherapy instillation is indicated in intermediate risk patients with no history of allergy to the utilized agent. The most widely utilized chemotherapeutic agents are mitomycin C, pararubicin and doxorubicin ⁽⁴⁰⁾. The length and frequency of repeat chemotherapy instillations is still controversial; however, Initial induction regimen (six weekly instillations) followed by maintenance regimen (monthly instillation for at least one year) is advocated ⁽³⁹⁾.

48.1.1.3 Intravesical bacillus Calmette-Guérin (BCG) immunotherapy

BCG therapy delays and potentially lowers the risk of tumor progression, most studies showed a reduction in the risk of progression in high- and intermediate-risk tumors ⁽⁴¹⁾.

Induction BCG instillations are given according to the empirical 6-weekly schedule. For optimal efficacy, BCG must be given in a maintenance schedule. Many different maintenance schedules have been used, ranging from a total of ten instillations given in eighteen weeks to 27 over three years ⁽⁴²⁾.

BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy ⁽⁴³⁾. However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases ⁽⁴⁴⁾. The patient should be counseled about the possible adverse events of BCG instillations up to severe form of contracted bladder which may obligate cystectomy and urinary diversion.

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumors ⁽⁴⁵⁾.

Table 37: Treatment recommendations in TaT1 tumours and carcinoma in situ according to risk stratification

Risk category	Criteria	Treatment Recommendation
Low-risk tumors	Primary, solitary, TaG1 (PUNLMP, Low Grade), < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB
Intermediate risk tumors	All tumors not defined in the two adjacent categories (between the category of low and high risk).	In patients, with previous low recurrence rate ($\leq$ one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intra-vesical chemotherapy after TURB. In all patients; either 1-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumours	Any of the following: • T1 tumours; • G3 (High Grade) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1G2/Low Grade tumours (all features must be present).	Intravesical full-dose BCG instillations for one to three years or radical cystectomy (in highest-risk tumours in selected patients)

Table 38: Recommendation for intravesical therapy:

Recommendation	Strength Rating
1. Intravesical therapy after TURBT should be based on the risk groups	Strong
2. In patients with tumors presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate one immediate chemotherapy instillation is recommended.	Strong
3. In patients with intermediate-risk tumours one-year full-dose bacillus Calmette- Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months)	Strong
4. In patients with high-risk tumors, full-dose intravesical BCG for one to three years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side-effects and problems connected with BCG shortages.	Strong
5. Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra. Weak Discuss immediate radical cystectomy (RC) with patients at highest risk of tumor progression.	Strong
6. If given, administer a single immediate instillation of chemotherapy within 24 hours	Weak
7. Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

48.1.2 Treatment of carcinoma in situ

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumors, in this case further treatment according to the risk categorization and previous treatment is mandatory. Carcinoma in situ cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or radical cystectomy ⁽⁴⁶⁾.

48.1.3 Treatment of failure of intravesical therapy

48.1.3.1 Failure of intravesical chemotherapy

Patients with NMIBC recurrence after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation ⁽⁴⁷⁾.

48.1.3.2 Recurrence and failure after intravesical BCG immunotherapy

Several categories of BCG failures, broadly defined as any disease occurrence following therapy, have been proposed.

Non-muscle-invasive BC presenting after BCG can be categorized into BCG refractory, BCG unresponsive and BCG relapse ⁽⁴⁸⁾.

48.1.3.3 Treatment of BCG failure

Patients with BCG unresponsive disease are unlikely to respond to further BCG therapy; radical cystectomy is therefore the preferred option. Additionally, several bladder preservation strategies are under different stages of investigation such as cytotoxic intravesical therapies, device assisted instillations, intravesical immunotherapy, systemic immunotherapy or gene therapy ⁽⁴⁸⁾.

48.1.3.4 Radical cystectomy for non-muscle-invasive bladder cancer

Early radical cystectomy (RC) is strongly recommended in patients with BCG unresponsive tumors, as mentioned above. A delay in RC may lead to decreased disease-specific survival ⁽⁴⁹⁾.

Table 39: Recommendations for Treatment of BCG Failure

	Treatment options	Strength Rating
BCG unresponsive	Radical cystectomy (RC).	Weak
	Bladder-preserving strategies in patients unsuitable or Refusing RC.	Weak
Late BCG relapsing: T1Ta/High Grade Recurrence > 6 months or CIS > 12 months of last BCG exposure	Radical cystectomy or repeat BCG course according to individual Situation.	Weak
	Bladder-preserving strategies.	Weak
Low Grade recurrence after BCG for primary intermediate risk tumour	Repeat BCG or Intravesical Chemotherapy.	Weak
	Radical cystectomy.	Weak

48.2 Critical consideration in management of NMIBC

External beam radiation therapy and / or systemic chemotherapy are not useful modalities in patients with NMIBC

48.3 Follow up of patients with NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need surveillance, following therapy. However, the frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk ⁽⁵⁰⁾.

Patients with low-risk Ta tumors should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years ⁽⁵¹⁾. Patients with high-risk tumors should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly ⁽⁵²⁾. Patients with intermediate-risk Ta tumors should have an in-between (individualized) follow-up scheme

using cystoscopy. Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumors.

Endoscopy under anesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.

Table 40: Recommendations for Follow Up of Patients with NMIBC

Recommendation	Strength Rating
1. Base follow-up of TaT1 tumours and carcinoma <i>in situ</i> (CIS) on regular Cystoscopy.	Strong
2. Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.	Weak
3. Patients with high-risk tumours should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
4. Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy. Weak	Weak
5. Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumours.	Weak
6. During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping-biopsies. Investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong

49 Muscle invasive bladder cancer (MIBC)

49.1 Diagnosis

49.1.1 Symptoms

Painless hematuria is the most common presenting complaint. Other clinical signs include urgency, dysuria, increased frequency, and in more advanced tumors, pelvic pain and symptoms related to urinary tract obstruction ⁽⁵³⁾. One third of patients underwent repeat TURBT might progress to muscle invasive disease and should be picked up early ⁽⁵⁴⁾.

49.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumors. In addition, bimanual examination under anesthesia should be carried out before and after TUR of the bladder (TURB), to assess whether there is a palpable mass or if the tumor is fixed to the pelvic wall ⁽⁵³⁾.

49.1.3 Bladder imaging

Patients with a bladder mass identified by any diagnostic imaging technique should undergo cystoscopy, biopsy and/or resection for histopathological diagnosis and staging. Staging cross sectional imaging should be carried out prior to cystoscopy biopsy or TURB to avoid overstating of the disease ⁽⁵⁵⁾.

49.1.4 Cystoscopy

Ultimately, the diagnosis of BC is made by cystoscopy and histological evaluation of resected tissue. If a bladder tumor has been visualized unequivocally by imaging studies such as computed tomography (CT), or magnetic resonance imaging (MRI), diagnostic cystoscopy may be omitted, and the patient can proceed directly to TURB for histological diagnosis and resection ⁽⁵⁵⁾.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumors, as well as a description of any mucosal abnormalities. The use of a bladder diagram is recommended ⁽⁵⁶⁾.

Biopsy from the prostatic urethra (or bladder neck in female) is required especially when orthotopic diversion is planned ⁽⁵⁷⁾.

49.1.5 Transurethral resection of invasive bladder tumors

The goal of TURB is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection specimen ⁽⁵⁸⁾.

At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable them to make a correct diagnosis. In cases in which radiation therapy is considered, CIS is to be excluded ⁽⁵⁸⁾.

If the plan of treatment is to utilize definitive/palliative chemo-radiotherapy, safe maximum resection should be tried during the first look biopsy to avoid further need to re-anesthesia.

49.1.6 Imaging for staging of MIBC

The treatment and prognosis of MIBC is determined by tumor stage and grade. In clinical practice, CT with contrast and MRI are the imaging

techniques used ⁽⁵⁹⁾. The purpose of using imaging for staging MIBC is to determine:

- Extent of local tumor invasion
- Involvement of LNs
- Tumor spread to the upper tract and other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands)

Timing of radiological staging is preferred either before TURB or at least two weeks after resection biopsy to avoid radiological overstating ⁽⁵⁹⁾.

49.1.7 Evaluation of comorbidity

Evaluation of comorbidity helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC ⁽⁶⁰⁾.

Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumor was the strongest predictor for decreased cancer specific survival. Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help selecting patients most likely to benefit from radical surgery and to optimize treatment outcomes ⁽⁶¹⁾.

49.2 Disease management

49.2.1 Neoadjuvant therapy (NAC)

The standard treatment for patients with urothelial MIBC and MIBC with variant histologies is radical cystectomy. However, radical cystectomy only provides 5-year survival in about 50% of patients ⁽⁶²⁾.

There are theoretical advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with resectable muscle-invasive urothelial carcinoma of the bladder and cN0M0 disease ⁽⁶²⁾:

- Chemotherapy is delivered at the earliest time-point, when the burden of micro metastatic disease is expected to be low.
- Potential reflection of *in-vivo* chemo sensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients might respond to NAC and reveal a favorable pathological status, determined mainly by achieving pT0, pN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy, although published studies on the negative effect of delayed cystectomy only include chemo-naïve patients ⁽⁶³⁾.

Diabetes, hypertension, pulmonary and cardiac diseases are prevalent in this age group, preoperative medical assessment and correction are a must, and the operation should be performed in well-equipped hospital

49.2.2 Pre-operative radiotherapy

Pre-operative radiotherapy (RT) should not be offered for operable MIBC since it will only result in down-staging, but will not improve survival ⁽⁶⁴⁾.

49.2.3 Post-operative radiotherapy

Data on adjuvant RT after RC are very limited and old. However, advances in targeting and reducing the damage to surrounding tissue, may yield better results in the future. It is not recommended in routine daily practice ⁽⁶⁴⁾.

Table 41: Recommendations for Neoadjuvant Chemotherapy for MIBC

Recommendation	Strength Rating
1. Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
2. Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
3. Do not offer pre-operative radiotherapy (RT) for operable MIBC since it will only result in down-staging, but will not improve survival.	Strong
4. Do not offer pre-operative RT when subsequent radical cystectomy with urinary diversion is planned.	Strong

49.3 Intravesical instillation treatment in MIBC

Any kind of intravesical instillation of chemo-or immunotherapy has no place at all in this sitting ⁽⁶⁴⁾.

49.3.1 Radical surgery and urinary diversion

Radical cystectomy is the standard treatment for localized MIBC. Recent interest in patients' quality of life has promoted the trend toward bladder-preserving treatment modalities, such as radio- and/or chemotherapy ⁽⁶⁴⁾. Performance status and life expectancy influence the choice of primary management, as well as the type of urinary diversion, with cystectomy being reserved for patients with a longer life expectancy without concomitant disease and a better performance status ⁽⁶⁵⁾.

A delay in radical cystectomy of more than twelve weeks since diagnosis has a negative impact on outcome and should be avoided ⁽⁶⁵⁾.

49.3.2 Radical cystectomy: indications

Traditionally, radical cystectomy was recommended for patients with MIBC T2-T4a, N0-Nx and M0 ⁽⁶⁶⁾. Other indications include high risk and recurrent non-muscle-invasive tumors, BCG-refractory, BCG-relapsing and BCG-unresponsive, T1G3 tumors, as well as extensive papillary disease that cannot be controlled with TURB and intravesical therapy alone ⁽⁶⁷⁾.

Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-UC (these tumors respond poorly to chemotherapy and RT) ⁽⁶³⁾. It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent visible hematuria. When there are positive LNs, in the case of N1 involvement (metastasis in a single node in the true pelvis) orthotopic neobladder can still be considered, but not preferable option in N2 or N3 tumors ⁽⁶³⁾.

49.3.3 Urinary diversion after radical cystectomy

From an anatomical standpoint, three alternatives are currently used after cystectomy ⁽⁶⁸⁾:

- Abdominal diversion, such as an uretero-cutaneostomy, ileal or colonic conduit, and various forms of a continent pouch;
- Urethral diversion, which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion.
- Rectosigmoid diversions, such as uretero-(ileo-) rectostomy.

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix.

Ideal urinary diversion method should be selected for each patient considering the patient, urinary tract, oncological and anesthetic factors to minimize the perioperative morbidity and maintain long term oncological and functional outcomes ⁽⁶⁸⁾.

49.3.4 Lymphadenectomy: role and extent

Regional LNs have been shown to consist of all pelvic LNs below the bifurcation of the aorta. The optimal extent of LND has not been established to date ⁽⁶⁹⁾.

Standard lymphadenectomy in BC patients involves removal of nodal tissue cranially up to the distal inch of the common iliac artery, with the ureter being the medial border, and including the internal iliac, obturator fossa and external iliac nodes down to the lymph node of Cloquet.

The number of lymph nodes removed during radical cystectomy is ranged from 15-20 nodes from both sides. Lymphadenectomy should be bilateral. Less than 10 LN is considered inadequate procedure.

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Extended lymphadenectomy includes all LNs in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the LN of Cloquet, as well as the area described for standard lymphadenectomy.

A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery.

No difference in outcome was reported between extended and super-extended LND. Removal of at least ten LNs has been postulated as sufficient for evaluation of LN status ⁽⁶⁹⁾.

Table 42: Recommendations for radical cystectomy and urinary diversion

Recommendations	Strength rating
1. Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality	Strong
2. Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
3. Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection.	Strong
4. Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit Select men for sexual-preserving techniques based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck	Strong
5. Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time to bowel recovery.	Strong

6. Offer pharmacological prophylaxis, such as low molecular weight heparin to RC patients, starting the first day postsurgery, for a period of 4 weeks.	Strong
7. Offer RC in T2-T4a, N0M0, and high-risk non-muscle-invasive bladder cancer.	Strong
8. Perform a lymph node dissection as an integral part of RC.	Strong
9. Do not preserve the urethra if margins are positive for malignancy	Strong

49.4 Unrespectable tumors

49.4.1 Palliative cystectomy for muscle-invasive bladder carcinoma

Locally advanced tumors (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction ⁽⁷⁰⁾. These patients are candidates for palliative treatments, such as palliative RT.

Palliative cystectomy carries the greatest morbidity and should be considered for symptom relief only if there are no other options ⁽⁷⁰⁾. Urinary diversion in this occasion should be as simple as required to alleviate the symptoms and minimize the morbidities.

49.4.1.1 Obstruction of the upper urinary tract

Unilateral (better kidney) or bilateral nephrostomy tubes provide the easiest solution for UUT obstruction ⁽⁷¹⁾, but patients find the tubes inconvenient and prefer ureteral stenting. However, stenting may be difficult to achieve in many occasions.

Another possible solution is a urinary diversion with, or without, a palliative cystectomy; supravescical diversion using uretero-cutaneous anastomosis or palliative ileal conduit diversion ⁽⁷¹⁾.

49.4.1.2 Bleeding and pain

In the case of bleeding, the patient must be screened first for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumor or with a bleeding tumor ⁽⁷²⁾. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective. It can usually be done without any anesthesia. Radiation therapy is another common strategy to control bleeding and is also used to control pain and control of hematuria ⁽⁷²⁾.

49.5 Bladder-sparing treatments for localized disease

49.5.1 Transurethral resection of bladder tumor

TURB alone in patients with muscle-invasive bladder tumors is only possible as a therapeutic option if tumor growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumor ⁽⁷³⁾.

TURB alone should only be considered as a therapeutic option for muscle-invasive disease after radical TURB, when the patient is unfit for cystectomy, or refuses open surgery, or as part of a multimodality bladder-preserving approach ⁽⁷³⁾.

Table 43: Bladder sparing treatment should not be considered as an equivalent to radical cystectomy

Recommendations	Strength Rating
1. Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong
2. Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong
3. Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	Strong
4. Offer surgical intervention or multimodality treatments (MMT) as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
5. Offer MMT as an alternative to selected, well-informed and compliant patients, especially for whom radical cystectomy is not an option.	Strong

49.5.2 External beam radiotherapy

Current RT techniques with soft-tissue matching result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target dose for curative EBRT in BC is 64-66 Gy, with a subsequent boost using external RT or interstitial RT ⁽⁷⁴⁾.

EBRT can be an alternative treatment in patients unfit for radical surgery, as it can be used to control bleeding ⁽⁷⁵⁾.

49.5.3 Systemic chemotherapy

Chemotherapy alone rarely produces durable complete remissions. In general, a clinical complete response rate of up to 56% is reported in some series, which must be weighed against a staging error of > 60% ⁽⁷⁶⁾.

Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival although it may be confounded by patient selection ⁽⁷⁷⁾.

Several groups have reported the effect of chemotherapy on resectable tumors (neoadjuvant approach), as well as unresectable primary tumors.

49.5.4 Multimodality bladder-preserving treatment

Multimodality treatment (MMT) or trimodality treatment combines TURB, chemotherapy and RT ⁽⁷⁸⁾. The rationale to combine TURB with RT is to achieve local tumor control in the bladder and adjacent nodes. The addition of systemic chemotherapy or other radiosensitisers is aimed at the potentiation of RT ⁽⁷⁹⁾. Micrometastases are targeted by platinum-based combination chemotherapy. The aim of MMT is to preserve the bladder and QoL without compromising oncological outcome. There are no completed RCTs comparing the outcome of MMT with RC, but MMT has been shown to be superior to RT alone.

49.6 Adjuvant therapy

49.6.1 Role of adjuvant platinum-based chemotherapy

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate ⁽⁸⁰⁾.

49.6.1.1 The general benefits of adjuvant chemotherapy include ⁽⁸⁰⁾:

- Chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micrometastases is avoided
- No delay in definitive surgical treatment.

49.6.1.2 The drawbacks of adjuvant chemotherapy are ⁽⁸¹⁾:

- Assessment of *in vivo* chemosensitivity of the tumor is not possible and overtreatment is an unavoidable problem;
- Delay or intolerance of chemotherapy, due to post-operative morbidity

49.6.2 Role of adjuvant immunotherapy

To evaluate the benefit of PD-1/PD-L1 checkpoint inhibitors, a number of randomised phase III trials comparing checkpoint inhibitor monotherapy with atezolizumab, nivolumab or pembrolizumab have been performed but no data have been presented so far ⁽⁸²⁾. This line of treatment is still in its infancy and should be tried in high volume centers within controlled trials.

49.6.3 Critical consideration in management of MIBC

Patient informed consent is always needed in all the treatment modalities and enough time should be allowed to the patient and his family explaining the disease, the outcome, morbidity and quality of life (QoL) for each treatment option.

Laparoscopic and robotic radical cystectomy may be utilized but never replace the standard open approach. The use of such techniques is still in its infancy in Egypt and should be restricted to a well experienced surgeon who would be able to treat any unexpected complications.

The patient should be well informed about the technique without any bias from the surgeon and the operation should be performed in a well-equipped place.

Radical cystectomy and urinary diversion should be strictly performed by a high volume surgeon, (at least 30-50 cystectomy per year) in a well-equipped hospital, high caliber anesthetic team, ICU, Blood transfusion, well trained nursing staff, stoma therapist, nutritionist, and preferably social or psychiatric support team.

50 Metastatic bladder cancer

Approximately 50% of patients with muscle-invasive UC relapse after RC, depending on the pathological stage of the primary tumor and the nodal status ⁽⁸³⁾. Local recurrence accounts for 30% of relapses, whereas distant metastases are more common. Ten to fifteen percent of patients are already metastatic at diagnosis ⁽⁸³⁾.

The patient and his family should be informed about such natural history of metastatic outcome, QoL and survival rate.

50.1 First line systemic therapy for metastatic disease

50.1.1 Standard first-line chemotherapy for fit patients

Methotrexate, vinblastine, Adriamycin plus cisplatin (MVAC) and GC prolonged survival compared to monotherapy and older chemotherapy combinations ⁽⁸⁴⁾.

High-dose intensity MVAC (HD-MVAC) combined with granulocyte colony-stimulating factor (G-CSF) is less toxic and more efficacious than standard MVAC in terms of dose density, complete response (CR), and survival rate ⁽⁸⁴⁾.

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard ⁽⁸⁵⁾.

50.1.2 Non-platinum combination chemotherapy

Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments ⁽⁸⁶⁾. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines ⁽⁸⁶⁾.

50.1.3 Single-agent chemotherapy

Response rates to single-agent first-line chemotherapy vary. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several phase II trials ⁽⁸⁷⁾. Responses with single agents are usually short-lived, complete responses are rare, and no long-term DFS has been reported.

50.1.4 Immunotherapy in first-line treatment

Several randomised phase III trials are currently investigating the use of checkpoint inhibitors in the first-line setting for cisplatin-eligible and ineligible patients using combinations with chemotherapy or CTLA-4 inhibitors as well as monotherapy ⁽⁸⁸⁾.

50.2 Second-line systemic therapy for metastatic disease

50.2.1 Second-line chemotherapy

Second-line chemotherapy data are highly variable and mainly derive from small single-arm phase II trials apart from a single randomised phase III study which for the first time established prognostic factors ⁽⁸⁹⁾.

A reasonable strategy has been to re-challenge former cisplatin-sensitive patients if progression occurred at least six to twelve months after first-line cisplatin-based combination chemotherapy.

Second-line response rates of single agent treatment with paclitaxel (weekly), docetaxel, nab-paclitaxel oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% ⁽⁹⁰⁾. Gemcitabine has also shown good response rates in second-line use but most patients receive this drug as part of their first-line treatment.

50.3 Post-chemotherapy surgery and oligometastatic disease

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with LN metastases only, good performance status and adequate renal function ⁽⁹¹⁾.

The role of surgery of residual LNs after chemotherapy is still unclear. Although some studies suggest a survival benefit and QoL improvement, the level of evidence supporting this practice is mainly anecdotal ⁽⁹²⁾.

In the absence of data from RCTs, patients should be evaluated on an individual basis and discussed by an interdisciplinary tumor board.

50.4 Treatment of patients with bone metastases

The prevalence of metastatic bone disease in patients with advanced/metastatic UC is 30-40% ⁽⁹³⁾. Skeletal complications due to bone disease have a detrimental effect on pain and QoL and are also associated with increased mortality.

Bisphosphonates such as zoledronic acid (ZA) reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption, as shown in a small pilot study ⁽⁹⁴⁾.

50.5 Follow-up in metastatic bladder cancer

An appropriate schedule for disease monitoring should be based on natural timing of recurrence; probability and site of recurrence; functional monitoring after urinary diversion and the potential available management options ⁽⁹⁵⁾.

50.5.1 Site of recurrence

50.5.1.1 Local recurrence

Local recurrence takes place in the soft tissues of the original surgical site or in LNs ⁽⁹⁶⁾.

Contemporary cystectomy has a 5-15% probability of pelvic recurrence which usually occurs

during the first 24 months, most often within 6 to 18 months after surgery. However, late recurrences can occur up to five years after RC.

Risk factors described are pathological stage, LNs, positive margins, extent of LND and peri-operative chemotherapy ⁽⁹⁶⁾. Patients generally have a poor prognosis after pelvic recurrence.

50.5.1.2 Distant recurrence

Distant recurrence is seen in up to 50% of patients treated with RC for MIBC. As with local recurrence, pathological stage and nodal involvement are risk factors. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with LN involvement (range 52-70%) ⁽⁹⁷⁾.

The most likely sites for distant recurrence are LNs, lungs, liver and bone. Nearly 90% of distant recurrences appear within the first three years after RC, mainly in the first two years, although late recurrence has been described after more than 10 years ⁽⁹⁷⁾.

50.5.1.3 Urethral recurrence

After RC, the incidence of new urethral tumors was 4.4% (1.3-13.7%) ⁽⁹⁸⁾. Risk factors for secondary urethral tumors are urethral malignancy in the prostatic urethra/prostate and bladder neck (in women). Orthotopic neobladder was associated with a significant lower risk of urethral tumors after RC ⁽⁹⁸⁾.

There is limited data, and agreement, about urethral follow-up, with some authors recommending routine surveillance with urethral wash and urine cytology and others doubting the need for routine urethral surveillance.

However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptotically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence.

50.5.1.4 Metachronous upper urinary tract urothelial carcinoma

UTUC occurs in 4-10% of cases and represents the most common sites of late recurrence ⁽⁹⁹⁾. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Frozen section of the lower cut end of the ureter is preferable to be examined especially if the tumor is of high grade, multifocal, invading the trigone or with concomitant CIS ⁽⁹⁹⁾.

50.5.2 Time schedule for surveillance

Although, based on low level evidence only, some follow-up schedules have been suggested, guided by the principle that recurrences tend to occur within the first years following initial treatment ⁽¹⁰⁰⁾.

A schedule suggested by the EAU Guidelines Panel includes a CT scan (every 6 months) until the third year, followed by annual imaging thereafter. Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC, which can develop

late (> 3 years) ⁽¹⁰⁰⁾. In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used for imaging of the UUT.

The exact time to stop follow-up is not well known and recently a risk-adapted schedule has been proposed, based on the interaction between recurrence risk and competing health factors that could lead to individualized recommendations and may increase recurrence detection ⁽¹⁰¹⁾. Elderly and very low-risk patients (those with NMIBC or pT0 disease at final cystectomy report) showed a higher competing risk of non-BC mortality when compared with their level of BC recurrence risk. On the other hand, patients with locally advanced disease or LN involvement are at a higher risk of recurrence for more than 20 years ⁽¹⁰¹⁾.

50.6 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients with a urinary diversion need functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow-up ⁽¹⁰²⁾. This rate increases over time, and exceeds 54% after 15 years of follow-up. Therefore, long-term follow-up of functional outcomes is desirable.

The functional complications are diverse ⁽¹⁰²⁾ and include: vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis, stenosis of uretero-intestinal anastomosis, stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction. Especially in women approximately two-thirds need to catheterize their neobladder, while almost 45% do not void spontaneously at all. Recently a 21% increased risk of fractures was also described as compared to no RC, due to chronic metabolic acidosis and subsequent long-term bone loss. Since low vitamin B12 levels have been reported in 17% of patients with bowel diversion, in case of cystectomy and bowel diversion, vitamin B12 levels should be measured annually.

51 Summary:

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered. Proper staging and grading are the cornerstone in management of Urinary bladder tumors. Management may differ from endoscopic resection to a radical cystectomy based on the nature, extent and depth of invasion of the tumor

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Committee VI

Prostate Cancer



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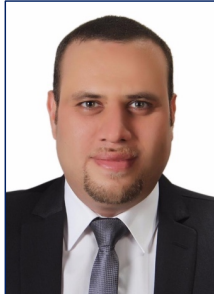
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53 Abbreviations

AS	Active surveillance
ADT	Androgen deprivation Therapy
ARTA	Androgen Receptor Targeting Agents
CRPC	Castration-resistant Prostate Cancer
dMMR	Defective Mismatch Repair
DRE	Digital Rectal Examination
ePLND	Extended Pelvic Lymph Node Dissection
eLND	Extended Pelvic Lymph Node Dissection
EBRT	External-Beam Radiation Therapy
HRQoL	Health Related Quality of Life
HIFU	High Intensity Focused Ultrasound
HDR	High-Dose Rate
HRD	Homologous Recombination Deficiency
HFX	Hypofractionation
IMRT	Intensity Modulated Radiotherapy
IPSS	International Prostatic Symptom Score
LAPC	Locally advanced prostate cancer
LDR	Low-Dose Rate
LN	Lymph Node
LND	Lymph Node Dissection
MRI	Magnetic Resonance Imaging
MFS	Metastasis Free Survival
PCa	Metastatic Castration-Resistant
mHSPC	Metastatic Hormone Sensitive Prostate Cancer
MSI	Microsatellite Instability
mpMRI	Multiparametric Magnetic Resonance Imaging
NEPC	Neuroendocrine Prostate Cancer

NGI	Next-Generation Imaging
OMPC	Oligometastatic Disease
PLND	Pelvic Lymph Node Dissection
PARP	PolyADP-Ribose Polymerase
PET	Positron Emission Tomography
PCa	Prostate Cancer
PSA	Prostate-Specific Antigen
RP	Radical Prostatectomy
RT	Radiotherapy
SRE	Skeletal-Related Events
TURP	Transurethral Resection Of The Prostate
VMAT	Volumetric Arc External-Beam Radiotherapy
WW	Watchful Waiting

54 Abstract

2.1.Objectives.

The Urologic Egyptian Guidelines on prostate cancer aim to help and guide clinical practitioners to have knowledge of the incidence, standard definitions, diagnosis, therapy, and follow-up of prostate cancer patients

2.2.Methods

Databases searched included Medline, Cochrane Libraries, EAU guidelines, AUA and NICE guidelines, from January 2018 and September 2020.

Review of several meta-analyses, leading institutional protocols and relevant Egyptian publications were taken into consideration. All statements were graded according to Strength Rating of recommendation. Each statement was given a Strength Rating rating (strong or weak).

2.3.Results

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

2.4.Conclusions.

These guidelines provide practical evidence-based guidance on the clinical aspect of prostate cancer. The main target is entirely focused on assessment and treatment, reflecting the recommended clinical practice. This can provide the basis for thinking through patient's management and also for planning and designing clinical services.

Prostate cancer is a complex disease, in which disease characteristics, age, comorbidities and individual patient preference will impact treatment choice. All available management options need to be discussed, in full, with the patient.

55 Introduction

Prostate cancer is the most frequent male cancer above the age of 50 years. In Egypt, it's the 6th most common male cancer according to the National population based Registry program of Egypt 2008-2011, but the exact prevalence depends on the frequent use of PSA and DRE for males above age of 50 years. Prostate cancer is very heterogenous and complexed disease that necessitates individualized treatment including patient's preferences through MDT.

This Guideline covers the diagnosis and management of prostate cancer based on revision of many Guidelines like EAU, NICE and NCCN guidelines that use the best evidence and recommendation.

Professional and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients. It is not mandatory to apply the recommendations, and this guideline does not override the responsibility to make decisions appropriate to the circumstances' of the individual, in consultation with them and their families.

This guideline also takes in consideration values and believes of Egyptian patients and the economic status of Egypt as a low resource country.

56 Screening and early detection of prostate cancer

Pca is a common disease, it grows so slowly and rarely causes symptoms, so most men die of other causes before the disease becomes clinically or impact the survival. At the same time, Increased detection of prostate cancer subjects some patients to the risks associated with treatments that may not prolong life and have risks of morbidity. So, screening for early detection of PCa is one of the most controversial topics in the urological literature

4 1. Benefits and harms prostate cancer screening

- Cochrane review and others reported that screening increases the detection of prostate cancer and reduces the rates of advanced disease at the time of diagnosis. ^(1,2,3)
- Effect of screening on mortality “the most controversial topic”, Some noted a greater decline in prostate cancer mortality rate, ^(4,5,6). Others reported there was no difference in prostate cancer mortality between the screened and non-screened in the (PLCO) trial. ⁽⁷⁾ Also Schröder FH from (ERSPC) trial reported that with extended follow up, the mortality reduction remains unchanged. ⁽⁸⁾ at the same time a Cochrane review reported that screening have no benefit on PCa-specific survival and overall survival. ⁽³⁾
- There is over diagnosis and treatment. Schröder et al, 2014 reported that to prevent one Pca death we would need to screen 781 men and diagnose an additional 27 men at a median follow-up of 13 years. ⁽⁸⁾ the same result obtained from (PLCO) trial.
- False-result of PSA. It may be abnormal even if there is no Pca such patients may have anxiety about their test result and/or may at risks related to prostate biopsy, and it may be normal even if there is Pca.
- Risk of prostate biopsy
- Risk of treatment

4.2. Screening for early detection

The American College of Preventive Medicine recommends against routine population screening⁽⁹⁾. Shared decision-making (Patients and clinicians should engage in shared decision)

Points that must be discussed in shared decision-making

- Benefits and harms of screening
- Use nomograms to help with decision making, predict biopsy results, predict pathological stage and predict risk of treatment failure
- Screening is done with a PSA test which is repeated every 1-2 years.
- Additional tests may be done to assess elevated PSA. No available tests can accurately determine which men have a cancer that may cause health problems.

- Prostate biopsy may be needed any may be repeated
- Discuss all treatment options and their risks and benefits in an objective, unbiased manner

Table 44: Recommendations for screening for early detection

Recommendation	Strength Rating
1. Screening should be in shared decision-making	Strong
2. Systematic population-based screening for Prostate cancer	Weak

4.3 Approach for Screening

PSA testing alone or in combination with Digital rectal examination. ⁽¹⁰⁾

- If DRE was performed, PSA can be measured immediately as DRE leads to minimal transient PSA elevations of 0.26 to 0.4 ng/mL
- Patient who is repeating PSA test to evaluate a result that was close to a cutoff should abstain for at least 48 hours from activities that induce perineal trauma (eg, ejaculation or bicycling).

Table 45: Reasons to temporarily defer PSA testing

Causes	Time to defer
Bacterial prostatitis	6-8 weeks after symptoms resolve
Urethral instrumentation	2 weeks
Prostate biopsy or (TURP)	6 weeks

PSA derivatives:

PSA derivatives are used to increase the specificity of PSA testing and improve detection of Pca. They are of no benefit in men with PSA >10 ng/mL or less than 4 ng/mL. They include: PSA density, PSA density of the transition zone, PSA velocity, age-specific PSA, f/t ratio, free PSA isoforms and complexed PSA forms

Table 46: Recommendations for PSA derivatives

Recommendation	Strength Rating

1. PSA in combination with DRE is the most appropriate test for screening.	Strong
2. Men with abnormal DRE should be referred to biopsy, regardless PSA result.	Strong
3. A man taking a 5-ARI the PSA should corrected before interpretation.	Strong

4.4. Age to begin discussing screening

- At age 50 or 55 years to 69 years for average-risk men as long as life expectancy is at least 10- 15 years
- At age 40 or 45 years old for higher-risk men
- BRCA1 or BRCA2 genetic mutations, black men, men with a family history of prostate cancer, particularly in a first-degree relative who was diagnosed at age <65 years and men with a PSA > 1 ng/mL at 40 years or > 2 ng/mL at 60 years

Table 47: Recommendations for Age to Begin Discussing Screening

Recommendation	Strength Rating
1. Men screened for Pca should have a life expectancy of at least 10 -15 years	Strong
2. Race, age, and family history are used to identify risk for prostate cancer	Strong
3. In average-risk men, initiate discussion of screening is at age 50 or 55 years	Strong
4. Men at higher risk, initiate discussion of screening is at age 40 or 45 years	Strong

4.4.1 Frequency of screening

No specific screening interval. Expert guidelines vary as to screening interval recommendations.

Some recommend repeating PSA testing every two years whereas others repeat PSA annually. Based on the ERSPC, screening intervals of two years preserve the majority of the benefits and reduce over-diagnosis and false positives.

Other recommend to adjust the frequency of testing based on the prior PSA result, with less frequent retesting in men with lower initial PSA levels and annual testing in those with higher PSA levels that are still below a cutoff for biopsy. ^(11,12)

4.4.2 Discontinuing screening

- Patients have a life expectancy of <10 to 15 years.
- Most clinicians offer screening up to age 70 years

Table 48: Recommendations for Discontinuing Screening

Recommendation	Strength Rating
1. Screening interval of one to two years	Strong
2. Screening up to age 70 years, stopping earlier if comorbidities limit life expectancy to less than 10 years	Strong

4.5 Prostatic biopsy

4.5.1 Baseline biopsy

- (US)-guided is the standard of care. It is performed by trans-rectal or trans-perineal approach. Cancer detection rates, when performed without prior (MRI), are comparable between the two approaches. ⁽¹³⁾
- TURP should not be used as a tool for biopsy. ⁽¹⁴⁾
- The decision for biopsy is based on elevated PSA and/or suspicious DRE and/or imaging. Recently, prostate cancer risk calculators have been developed to estimate the risk of prostate cancer from multiple parameter, thereby reducing the number of unnecessary biopsies. Common calculator used are: the PCPT cohort: PCPTRC 2.0 the ERSPC cohort: <http://myprostatecancerrisk.com/>, the ERSPC cohort: <http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators> and a local Canadian cohort: <https://sunnybrook.ca/content/?page=asure=calc>

4.6 Elevated PSA

- It should not prompt immediate biopsy. It should be verified after a few weeks, in the same laboratory, using the same assay under standardized conditions (i.e. no ejaculation, manipulations, and [UTIs]). ^(15,16)
- Empirical use of antibiotics in an asymptomatic patient to lower the PSA not recommended. ⁽¹⁷⁾
- PSA depravities and new biological markers such as TMPRSS2-ERG fusion, PCA3 or kallikreins as Phi or 4Kscore tests increase sensitivity and specificity of PSA, so avoiding unnecessary biopsies. ⁽¹⁸⁻²¹⁾
- For people who have a raised PSA and MRI Likert score of 1 or 2, omit biopsy based on shared decision making with the patient, repeat PSA test at 3 to 6 months and:
 - If there is a strong suspicion of prostate cancer (for example, PSA density greater than 0.15 ng/ml/ml or PSA velocity greater than 0.75 ng/year, or strong family history), offer prostate biopsy considering their life expectancy and comorbidity
 - If the level of suspicion is low; advise PSA to follow up at 6 months and then every year, and set a PSA level to biopsy based on PSA density (0.15 ng/ml/ml) or velocity (0.75 ng/year).

4.7 Abnormal DRE

An abnormal DRE is associated with an increased risk of a higher ISUP grade and is an indication for biopsy. ^(22,23)

4.8 Imaging

- Grey-scale TRUS and ultrasound-based techniques is not reliable at detecting PCa. ⁽²⁴⁾
- Multiparametric magnetic resonance imaging (mpMRI)
- Because of its low specificity, mpMRI in very low-risk patients would result in an inflation of false-positive findings and subsequent unnecessary biopsies. so mpMRI must not be used in patients who do not have an indication for prostate biopsy based on their family history and clinical and biochemical data.
- Cochrane meta-analysis and others reported that (mpMRI) has good sensitivity for the detection and localization of ISUP grade ≥ 2 cancers. ⁽²⁵⁻²⁸⁾, also it reported that (mpMRI) is poor sensitive in identifying ISUP grade 1 PCa. ⁽²⁵⁾
- MRI-TBx improve the detection of ISUP grade ≥ 2 as compared to systematic biopsy especially in patients with prior negative systematic biopsy, but not in biopsy-naïve men. In biopsy-naïve patients, the difference is to be less marked; it is not significant in all series, but remains in favor of MRI-TBx in some studies. ^(25, 29-33)
- MRI-TBx reduce the detection of ISUP grade 1 PCa as compared to systematic biopsy. So, MRI-TBx significantly reduces over-diagnosis of low-risk disease, as compared to systematic biopsy. ^(25,31-33)
- Combined target and systemic biopsy of the lobe with the MRI lesion increase the detection of csPCa (ISUP grade ≥ 2) in compare with target biopsy alone from 73.5% to 96%. ⁽³⁴⁾
- csPCa can be missed because of MRI failure (invisible cancer or reader's misinterpretation) or because of targeting failure (target missed or undersampled by MRI-TBx).
- Limitations of the 'MR pathway' are the moderate inter-reader reproducibility of mpMRI and the lack of standardisation of MRI-TBx (minimum number of targeted cores to be obtained as a function of the prostate volume, lesion size and location), as well as the fact that its inter-operator reproducibility has not been evaluated.

Sampling sites and number of cores

- Where no prior imaging with mpMRI, or where mpMRI has not shown any suspicious lesion, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland.
- Additional cores should be obtained from suspect areas.

- At least eight systematic biopsies are recommended in prostates with a size of about 30 cc. Sextant biopsy is no longer recommended.
- Ten to twelve core biopsies are recommended in larger prostates
- Saturation biopsy (> 20 cores):
 - It may be performed with the trans-perineal technique, which detects an additional 38% of PCa. The rate of urinary retention is high (10%)
- Seminal vesicle biopsy:
 - Not recommended due to low its value.
 - Its added value compared with mpMRI is questionable.
- Transition zone biopsy during baseline biopsies has a low detection rate and should be limited to repeat biopsies

4.9 Repeat biopsy after previously negative biopsy

- The PCA3 assay and PHI is not recommended in people having investigations for suspected prostate cancer who have had a negative prostate biopsy
- The decision for repeat the biopsy has to be considered when there is high probability of Pca despite negative initial biopsy as in: rising and/or persistently elevated PSA, suspicious DRE, 5-30% PCa risk (35,36), positive (mpMRI) Likert score of 3 or more, ASAP, 31-40% PCa risk on repeat biopsy, ^(37,38) extensive (> 3 site) (HGPIN), ~30% PCa risk ^(38,39), a few atypical glands adjacent to (HGPIN), ~50% PCa risk. ⁽⁴⁰⁾, intraductal carcinoma, > 90% risk of associated high-grade PCa. ⁽⁴¹⁾
- For people who have a raised PSA, an MRI Likert score of 1 or 2, and negative biopsy, repeat PSA at 3 to 6 months and:
 - If there is a strong suspicion of prostate cancer (for example, PSA density greater than 0.15 ng/ml/ml or PSA velocity greater than 0.75 ng/year, or strong family history), offer prostate biopsy considering their life expectancy and comorbidities
 - If the level of suspicion is low; advise PSA follow-up every 2 years, and set a PSA level for re-biopsy based on PSA density (0.15 ng/ml/ml) or velocity (0.75 ng/year).

Table 49: Recommendations for Prostate Biopsy

Recommendation	Strength Rating
1. The initial biopsy is based on PSA and DRE. Do not automatically offer a prostate biopsy on the basis of serum PSA level alone	Strong

2. In asymptomatic men with normal DRE and elevated PSA between 4-10 ng /dl to avoid unnecessary biopsies, offer further risk-assessment by use one of the following tools: •Pca risk-calculator •Image (multiparametric MRI) •An additional serum or urine-based test.	Strong
3. Do not offer transition zone or seminal vesicle sampling at initial biopsies due to low detection rates	Strong
4. Do not use transurethral resection of the prostate as a tool for cancer detection	Strong
5. people decide whether to have an MRI or prostate biopsy by discussing: PSA level, DRE findings, any comorbidities, risk factors (including increasing age and black African-Caribbean family origin) and any history of a previous negative prostate biops	Strong
6. Do not use mpMRI as an initial screening tool.	Strong
7. Do not routinely offer mpMRI to people with prostate cancer who are not going to be able to have radical treatment	Strong
8. Adhere to PI-RADS guidelines for mpMRI acquisition and interpretation.	Strong

Table 50: Recommendations For Biopsy Naïve Patients

Recommendation	Strength Rating
1. Offer mpMRI as the first-line investigation before prostate biopsy for people with suspected clinically localized Pca.	Recommended
2. When mpMRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	Strong
3. When mpMRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient and repeat PSA test at 3 to 6 months. If person opts to have a biopsy, offer systematic prostate biopsy.	Recommended

Table 51: Recommendations for patients with prior negative biopsy

Recommendation	Strength Rating
1. Perform mpMRI before prostate biopsy.	Strong

2. When mpMRI is positive (i.e. PI-RADS > 3) repeat, the biopsy is mandatory but target biopsy only.	strong
3. When mpMRI is negative (i.e. PI-RADS < 2), and clinical suspicion of prostate cancer is high, perform systematic biopsy based on shared decision	Strong

57 Locally Confined Disease

Risk stratification is essential for appropriate management of patients with prostate cancer after initial diagnosis. Combination of DRE for clinical staging, serum total PSA, local and nodal staging through cross sectional imaging CT or mpMRI and metastatic work up evaluation as well as TRUS guided biopsy parameters (Gleason score, number of positive cores, percentage of core infiltration) are needed for assessment of prostate cancer risk and planning further management.

5.1 Risk Stratification of Locally Confined Prostate Cancer

Table 52: Definition of Different Risk Groups

Very Low-risk	Low-risk	Intermediate-risk	High-risk	
PSA <10ng/ml and GS<7 (ISUP grade 1) and cT1-2a and <34% of Bx cores +ve and no core >50% +ve and PSA density <0.15 ng/ml/cc	PSA < 10 ng/mL and GS<7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS>7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localized				Locally advanced
<i>GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.</i>				

Patients with prostate cancer should be managed after counseling with multidisciplinary team including urologists, medical and radiation oncologists, pathologists and radiologists. Patients should be informed on the effect of each treatment modality on the survival, oncologic control as well as treatment related adverse effects.

Table 53: Recommendations for Risk stratification of locally confined prostate cancer

Recommendation	Strength Rating
1. Risk stratification is essential for planning further management of patients diagnosed with prostate cancer	Strong
2. Bone scans should not be offered to asymptomatic very low or low-risk localized prostate cancer.	Strong
3. Discuss with prostate cancer patients all appropriate treatment modalities based on the risk stratification of prostate cancer	Strong
4. Management of prostate cancer should be after multidisciplinary team including urologist, medical and radiation oncologists, pathologists and radiologists	Strong

5. Counsel patients with prostate cancer on survival benefit, risk of progression and treatment related adverse effects of each treatment modality based on risk stratification	Strong

58 General guidelines for management of PCa

6.1. Deferred treatment

Watchful waiting is a conservative palliative management for patients with life expectancy < 10 years unfit or refusing active treatment, where patients are not offered any active treatment till the development of local or systemic progression or become symptomatic.

Active surveillance is a form of deferred treatment aiming at avoiding unnecessary treatment in patients with clinically localized disease with low risk for progression to avoid treatment related adverse effects with active intervention in presence of signs of disease progression.

Table 54: Difference between two forms of deferred treatment of prostate cancer

	Active surveillance ⁽⁴²⁾	Watchful waiting
Target patients	Low risk and some intermediate risk patients with life expectancy >10 years	All risk patients with life expectancy <10 years
Aim	Curative treatment with predefined follow up schedule to minimize treatment related side effects without compromising survival	Palliative treatment to selected patients with all risk stages to minimize side effects for patient not fit for active treatment

Watchful waiting should not be offered to asymptomatic patients with prostate cancer with life expectancy > 10 years or patients with high risk disease. ⁽⁴³⁾

Table 55: Recommendations for Asymptomatic Patients with Prostate Cancer

Recommendation	Strength Rating
1. Offer watchful waiting for selected asymptomatic patients with life expectancy <10 years if not accepting treatment related side effects after counseling on the patient for risk of progression	Weak
2. Active treatment should be recommended for patients with life expectancy > 10 years based on risk stratification and counseling of patients	Strong

6.2. Active treatment

Active treatment for prostate cancer include radical prostatectomy (RP), radiotherapy (RT), androgen deprivation therapy (ADT) and other minimally invasive techniques e.g High intensity focused ultrasound (HIFU), cryotherapy and focal therapy.

Active treatment should be offered to prostate cancer patients after appropriate counseling in absence of contraindication for this form of active treatment and accepting treatment related adverse effects.

Table 56: Recommendations for Active Treatment

Recommendation	Strength Rating
1. Inform patients that no active treatment modality has shown superiority over any other active or deferred treatment in terms of survival in low risk disease	Strong
2. Counsel patients on side effects of all active treatments and discuss with the patients' pros and cons of each treatment modality.	Strong
3. Discuss the effect of active treatment of prostate cancer on potency, fertility, urinary continence and bowel function.	Strong

6.2.1. Surgical treatment: radical prostatectomy

Radical prostatectomy (RP) should be offered for localized prostate cancer patients and selected patients with locally advanced disease based on risk stratification with or without extended pelvic lymph node dissection.

RP can achieve adequate cancer control in localized prostate cancer patients, however may jeopardize postoperative urinary continence, sexual function and health related quality of life (HRQoL). ⁽⁴⁴⁾

Different surgical approaches may be adopted during RP including open, laparoscopic and robotic techniques with equal oncologic and functional outcomes. ⁽⁴⁵⁾

Extended pelvic lymph node dissection should be done if risk of lymph node involvement is > 5% and there is no value for limited lymphadenectomy in the setting of radical prostatectomy. ^(46,47)

Nerve sparing radical prostatectomy and meticulous dissection at the apex of the prostate may improve postoperative functional outcomes; better sexual and urinary functions. If Nerve sparing RP is planned, a preoperative mpMRI should be done for detection of extracapsular extension and appropriate counseling of the patient. ^(48, 49)

Table 57: Recommendations for Surgical Treatment (Radical Prostatectomy)

Recommendations	Strength Rating
6. Inform patients that no surgical approach for radical prostatectomy (open, laparoscopic- or robotic) has clearly shown superiority in terms of functional or oncological results.	Strong
7. Inform the patient that in experienced hands laparoscopic and robotic surgery has less perioperative morbidity	Strong
8. Perform an extended pelvic lymph node dissection (ePLND), when a LND is deemed necessary.	Strong
9. Do not perform pelvic lymphadenectomy with radical prostatectomy in very low and low risk prostate cancer	Strong
10. Do not offer nerve sparing surgery when there is a risk of extracapsular extension (based on imaging CT/mpMRI, ISUP grade, nomogram).	Strong
11. Preoperative mpMRI should be performed if nerve sparing radical prostatectomy is planned	Strong

58.1.1

7. Radiotherapy (RT)

7.1.1.1. External beam radiotherapy

Intensity-modulated radiotherapy (IMRT) and volumetric arc external-beam radiotherapy (VMAT) are the gold standard for EBRT using multi-leaf collimators so that each radiation beam can be continuously controlled providing adequate and precise radiation doses to particular parts of the radiation field optimizing radiation dose with reduction of treatment related side effects to neighbor tissues especially the rectum to avoid bowel related symptoms after EBRT. ^(50,51)

IMRT with of image guided radiotherapy can help to monitor organ movement allowing dose escalation with increased toxicity to normal surrounding tissues. ⁽⁵²⁾

The concept of hypofractionation (HFX) relies on delivering fewer fractions of higher single doses of radiotherapy ≥ 2.5 Gy per fraction increases treatment efficacy ⁽⁵³⁾, shortens treatment time and reduce treatment cost without increasing early or late adverse effects. ⁽⁵⁴⁾

7.1.1.2. Brachytherapy

There are two methods to deliver brachytherapy; Low-dose rate brachytherapy and High-dose rate (HDR) brachytherapy.

Low dose rate brachytherapy may be offered to selected low and intermediate risk patients; stage cT1b-T2a N0, M0; ISUP grade 1 with < 50% of biopsy cores involved with cancer or ISUP grade 2 with < 33% of biopsy cores involved with cancer; an initial PSA level of < 10 ng/mL; a prostate volume of < 50 cm³; an IPSS < 12 and maximal flow rate > 15 mL/min. ⁽⁵⁵⁾

High dose radiation can be delivered in single or multiple fractions and is usually used in combination with EBRT of > 45 Gy in patients with intermediate and high risk prostate cancer. ⁽⁵⁶⁾

Table 58: Recommendations for Radiotherapy (RT)

Recommendation	Strength Rating
1. Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
2. Offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy to the prostate, to carefully selected patients with localized disease.	Strong
3. Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.	Strong
4. Inform patients undergoing external beam radiotherapy of increased risk of colorectal cancer	Strong
5. Offer Low dose brachy therapy to selected patients with low or intermediate risk prostate cancer if not contraindicated	Weak

6. Offer High dose brachytherapy in combination with EBRT in intermediate and high risk prostate cancer	Strong
7. Offer radiotherapy in conjunction with ADT in intermediate and high risk prostate cancer	Strong

7.1.1.3. *Investigational therapies*

Various techniques for either whole gland ablation and/or focal therapy e.g high-intensity focused US (HIFU), cryotherapy and focal photodynamic therapy.

HIFU employs focused ultrasonic waves produced by a transducer to heat malignant tissues above 65°C to cause coagulative necrosis by cavitation ⁽⁵⁷⁾. It can be performed under general or regional spinal anaesthesia.

Cryotherapy depends on tissue freezing to induce dehydration of cells and protein denaturation, through direct destruction of cellular membranes by ice crystals and microthrombi resulting in ischaemic apoptosis ^(58,59)

Focal therapy to ablate malignant foci is a new alternative for standard treatment to minimize adverse effects of whole gland ablation. It can be applied through various techniques e.g. HIFU, cryotherapy, photodynamic therapy, or brachytherapy. ^(60,61)

Table 59: Recommendations for focal therapy

Recommendation	Strength Rating Rating Rating
1. Cryotherapy and high-intensity focused ultrasound should only be offered within a clinical trial setting.	Strong
2. Only offer focal therapy within a clinical trial setting.	Strong

8. Management of prostate cancer according to risk group stratification

8.1. Guidelines for first-line treatment of Very Low and Low risk disease

Patients with very low and low risk prostate cancer can choose either active surveillance or active treatment (radical prostatectomy or radiotherapy) after comprehensive counseling on the benefit and harms of each modality as well as survival benefit and disease progression.

No survival benefit for active treatment over active surveillance in this risk group, however active treatment reduce risk for disease progression and development of distant metastases compared to active surveillance. ⁽⁶²⁾

Active surveillance may maintain better urinary and sexual functions compared to radical prostatectomy and radiotherapy. Radical prostatectomy may jeopardize early postoperative urinary and sexual function with subsequent improvement over time. Radiotherapy has more adverse effect on bowel function compared to AS and RP.

Multiparametric MRI to people having active surveillance who have not had an MRI previously. If the MRI results do not agree with the biopsy findings, offer a new MRI-influenced biopsy. ⁽⁶²⁾

Selection criteria for AS:

Selection criteria are mostly driven from the DETECTIVE Study ⁽⁶³⁾

The criteria include: ISUP grade 1, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc ^(64,65)

Patients with prostate cancer on AS should be informed that active treatment may be necessary on evidence of disease progression (evidence of metastases or diagnosis of clinical T3 or T4 disease or need for long-term androgen deprivation therapy or rectal fistula or the need for a urinary catheter owing to local tumor growth). ⁽⁶²⁾

Disease progression may be suspected if there was:

- Any rise in prostate-specific antigen (PSA) >20% between consecutive measures at any time during follow-up or
- Any rise in PSA level of 50% or greater in any 12-month period confirmed by repeat tests or
- Any indication of the appearance of symptomatic systemic disease. ⁽⁶²⁾

Table 60: Recommended schedule for AS

	First year ⁽⁶²⁾	Second year and thereafter
PSA	PSA every 3-4 months Monitor PSA kinetics (PSA velocity and density)	PSA every 6 months Monitor PSA kinetics (PSA velocity and density)

DRE	Every 12 months
mpMRI	At 12-18 months then mpMRI and/or re-biopsy if clinical progression or PSA changes at any time.

Table 61: Recommendations of watchful waiting and active surveillance.

Recommendation		Strength Rating
Watchful waiting (WW)	1. Low Risk Prostate Cancer is to be diagnosed after at least 12 core prostate biopsies including TZ	Strong
	2. Offer a WW policy to asymptomatic patients with a life expectancy < 10 years (based on comorbidities).	Weak
	3. Patients with localized prostate cancer on watchful waiting having evidence of significant disease progression (rapidly rising PSA level or bone aches) should be re-evaluated and counseled on further management	Strong
Active surveillance (AS)	1. Offer AS Only to patients with very low risk PCa	Strong
	2. Offer (Discuss) AS to patients suitable for curative treatment but with low-risk PCa.	Strong
	3. Refrain from/Stop AS to patients having non-compliance issues	Strong
	4. Perform multiparametric magnetic resonance imaging (mpMRI) before a confirmatory biopsy, if not done before the first biopsy.	Strong
	5. Perform the combination of targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy at confirmatory biopsy.	Weak
	6. Base follow up on digital rectal examination, prostate-specific antigen (PSA) and repeated biopsies.	Strong
	7. Counsel (Inform) patients about the possibility of needing further treatment in the future.	Strong
	8. Offer radical treatment to people with localized prostate cancer who had chosen active surveillance and develop evidence of disease progression.	Strong

Patients with very low and low-risk prostate cancer should be counseled on various forms of active treatment; radical prostatectomy versus radical radiotherapy or other minimally invasive treatments for selected patients if not contraindicated.

Table 62: Recommendations for Patients with Very Low and Low Risk Prostate Cancer

Treatment	Recommendation	Strength Rating

Active treatment	Offer surgery and radiotherapy (RT) as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	Do not perform a PLND (estimated risk for pN+ < 5%). (very low and low risk PCa if Chose RP)	Strong
Radiotherapy	Offer low-dose rate (LDR) brachytherapy to patients with low-risk PCa, without a previous transurethral resection of the prostate (TURP) and with a good International Prostatic Symptom Score (IPSS) and a prostate volume < 50 mL.	Strong
	Use intensity-modulated radiation therapy (IMRT) with a total dose of 74-80 Gy or moderate hypo-fractionation (60 Gy/20 fx in four weeks, or 70 Gy/28 fx in six weeks), without androgen deprivation therapy (ADT).	Strong
Other options	Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound [HIFU], etc.) or focal treatment within a clinical trial setting. Focal therapy (Cryotherapy, HIFU, laser etc) should only be offered within clinical trial setting	Strong

8.2. Guidelines for treatment of intermediate risk disease

8.2.1. Surgery radical prostatectomy (RP)

- Based on SPCG-4 and PIVOT RCT comparing RRP vs. WW, Prostate Cancer Specific Death rate and Overall All-cause Mortality rate was significantly lower with RP than WW in the SPCG-4 and PIVOT respectively
- The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1% ⁽⁶⁶⁾.
- An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5%. ⁽⁶⁷⁾

8.2.2. Radiotherapy

The recommended treatment is IMRT or VMAT at an escalated dose (76-80 Gy) or a combination of IMRT or VMAT to optimize radiation dose to tumor and reduce damage to the surrounding organs.

Short-term ADT (4-6 months) is recommended with radiotherapy ⁽⁶⁸⁻⁷⁰⁾. Brachytherapy may be used in combination with radiotherapy in patients with intermediate and high risk prostate cancer if available.

Table 63: Recommendations for Intermediate-Risk Disease

Treatment	Recommendation	Strength Rating

Active surveillance	Offer AS to highly selected patients (< 10% Gleason pattern 4) accepting the potential increased risk of further metastases.	Weak
Radical prostatectomy (RP)	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease after counseling the patient.	Strong
Extended pelvic lymph node (LN) dissection (ePLND)	Perform an ePLND in intermediate-risk disease if the estimated risk for positive LNs exceeds 5%.	Strong
Radiotherapy	Offer EBRT to patients with a life expectancy <10 years or not fit for or refusing surgery	Strong
	For external-beam radiation therapy (EBRT), use a total dose of 76-78 Gy or moderate hypofractionation (60 Gy/20 fx in four weeks or 70 Gy/28 fx in six weeks), in combination with short-term neoadjuvant plus concomitant ADT (four to six months).	Strong
	Offer LDR brachytherapy to selected patients; patients without a previous TURP, with a good IPSS and a prostate volume < 50 mL.	Strong
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachy- therapy.	Weak
Other therapeutic options	Only offer whole gland treatment (such as cryotherapy, HIFU, etc.) or focal treatment within a clinical trial setting.	Strong
	Do not offer ADT monotherapy to intermediate-risk asymptomatic men unable to receive any local treatment	Strong

8.3. Guidelines for treatment of high risk disease

Patients with high risk prostate cancer should be adequately counseled on the possibility of local failure as well as risk distant metastases after initial treatment and a multidisciplinary management of high risk prostate cancer is recommended.

8.3.1. Surgery

Patients with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP. ⁽⁷¹⁾

Radical prostatectomy may be recommended to patients with surgically fit high risk prostate cancer who have life expectancy of > 10 years and no pelvic lymph node metastases as a part of multimodal treatment with further adjuvant treatment according to final pathological staging.

Extended PLND should be performed in all high-risk PCa cases undergoing RP as the estimated risk for positive LNs is > 5%. ⁽⁶⁷⁾

Nerve sparing radical prostatectomy should be avoided in high risk patients for adequate local cancer control especially be extracapsular extension is suspected in imaging studies.

8.3.2. Radiotherapy

Radiotherapy may be recommended for patients with high risk prostate cancer who are surgically unfit for radical prostatectomy, having expectancy <10 years as a part of multimodal treatment.

For high-risk localized PCa, use a combined modality approach, consisting of dose-escalated IMRT or VMAT, plus long-term ADT FOR 2-3 years.

Patients with local failure after radiotherapy and ADT may need salvage radical prostatectomy.

Table 64: Recommendations for High-Risk Disease

Recommendation		Strength Rating
Radical prostatectomy (RP)	Offer RP to patients with high- risk localised PCa and a life expectancy of > 10 years (only as part of multi-modal therapy) (Indicate that adjuvant therapy is possible)	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk disease.	Strong
Radiotherapy	1. In patients with high-risk localised disease, use ERBT with 76-78 Gy in combination with long-term ADT (two to three years).	Strong
	2. In patients with high-risk localised disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (two to three years).	Weak
	3. Do not offer brachytherapy monotherapy to people with high-risk localised prostate cancer.	Strong
Other options	1. Do not offer either whole gland or focal therapy to high-risk patients.	Strong
	2. Do not use ADT monotherapy in asymptomatic patients.	Strong
	3. Do not offer Active surveillance for high risk prostate cancer	Strong

8.4. Guidelines on Locally advanced prostate cancer (LAPC)

8.4.1. Definition

LAPC is defined as histologically diagnosed prostate cancer that extends beyond the prostate gland (cT3-4); extracapsular extension (T3a), seminal vesicles infiltration (T3b), or invading adjacent organs; bladder or rectum (T4), or any prostate cancer disease with clinically positive pelvic L.N (cN+) regardless PSA level and/or Gleason score with no evidence of distant metastases. ⁽⁷²⁾

8.4.2. Diagnosis of LAPC

Evaluation of local extension as well as nodal and/or distant metastases is essential for diagnosis LAPC and exclusion of metastatic disease.

8.4.2.1. *Comprehensive medical history*

Presence of hematuria, bleeding per rectum or hemospermia in patients with high risk prostate cancer may denote locally advanced disease.

8.4.2.2. *Digital rectal examination (DRE)*

Fixed prostate or hard seminal vesicles during rectal examination may suspect LAPC (T3b/T4 disease).

8.4.2.3. *Imaging studies*

A cross-sectional contrast study is needed for evaluation of local extension of disease; presence of nodal and/or distant metastases in high risk disease.

8.4.2.4. *Pelviabdominal CT with contrast*

CT with contrast may be used to detect nodal as well as distant metastases. Serum PSA level, Gleason score and clinical T-stage were statistically significant independent predictors for positive CT finding. ⁽⁷³⁾

8.4.2.5. *Multiparametric magnetic resonance imaging (mpMR)*

mpMRI has a high negative predictive value for extracapsular extension ⁽⁷⁴⁾ and is equivalent to pelviabdominal CT for pelvic L.N staging ⁽⁷⁵⁾

8.4.2.6. *^{99m}Tc-Bone Scan*

Bone scan can detect bony metastases with sensitivity and specificity of 79% and 83% respectively ⁽⁷⁶⁾. Bone scan should be done in patients with T1 with PSA > 20, T2 with PSA >10, patients with T3/T4, GS ≥8 or symptomatic patients. ⁽⁷⁷⁾

8.4.2.7. *Whole body MRI scans*

It is indicated in cases of indeterminate bone metastases. MRI has very high sensitivity and specificity for detection of bone metastases (98-100%) overperforming bone scan in detection of bony metastases. ⁽⁷⁸⁾

8.4.2.8. Positron emission tomography (PET) scan

8.4.2.8.1. Sodium Fluoride (18F-NaF) PET

has similar specificity but higher sensitivity to bone scan, but cannot detect L.N or visceral metastases ^(79,80)

8.4.2.8.2. Choline PET

is less sensitive but more specific than bone scan in detection of bony metastases (76).

Moreover, it can detect L.N and visceral metastases.

8.4.2.8.3. Prostate-specific membrane antigen-based (68Ga-PSMA) PET

It may play a role in initial staging of prostate cancer in selected cases (higher detection of metastases compared to bone scan and CT. ⁽⁸¹⁾

Table 65: Recommendations for Locally advanced prostate cancer (LAPC)

Recommendation	Strength Rating
1. Comprehensive history and digital rectal examination may suspect locally advanced disease	Strong
2. Cross-sectional pelvi-abdominal imaging and bone scan should be used for metastatic workup evaluation	Strong
3. mpMRI is equivalent to CT in detection of clinically positive lymphadenopathy (cN0)	Strong
4. Use PSMA-PET CT or whole body MRI in case of indeterminate bony lesions in bone scan	Weak
5. Use of PSMA-PET scan is currently not recommended at initial staging of Prostate cancer	Strong

8.4.3. Initial treatment of LAPC

A multidisciplinary management by urologists, medical and radiation oncologists should be adopted.

To date, there is no standard local treatment for LAPC; however multimodal treatment incorporating local and systemic therapies can provide better outcomes in generally fit patients with life expectancy ≥ 10 years. ⁽⁸²⁾

Patients with LAPC should be counseled on various available treatment modalities, oncological outcomes as well as treatment related complications especially urinary continence and sexual dysfunction.

Table 66: Recommendations for Initial treatment of LAPC

Recommendation	Strength Rating

1. Counsel patients with LAPC on various available treatment modalities at multidisciplinary meeting including urologists, medical and radiation oncologists.	Strong
2. Local as well as systemic therapy are usually needed in patients with LAPC as parts of multimodal therapy	Strong

8.4.3.1. Radical prostatectomy (RP)

Surgical intervention for LAPC (cT3) with no clinically detectable lymph node involvement (cN0) as part of a multimodal therapy in relatively young fit patients can be recommended in high-volume centers ⁽⁸³⁾. Laparoscopic RP may achieve comparable oncological outcomes to open RP in high volume centers, however open RP is preferred over laparoscopic and robotic approaches in LAPC.

Extended pelvic lymph node dissection (eLND) with dissection up to the common iliac arteries should be done in all patients with high risk or LAPC. ⁽⁸⁴⁾

Patients with LAPC should be informed for possibility of positive surgical margins and further adjuvant hormonal and/or radiotherapy (RT). PSA monitoring after radical prostatectomy is essential for prompt detection of candidates for salvage RT.

Table 67: Recommendations for Radical prostatectomy in LAPC

Recommendation	Strength Rating
1. Discuss open radical prostatectomy as a part of multimodal therapy for selected patients with LAPC (cT3); younger patients with no medical comorbidities	Strong
2. Offer only open radical prostatectomy for LAPC (cT3) in centers with high volume disease and surgical expertise as part of multimodal therapy	Strong
3. Laparoscopic radical prostatectomy should be offered to patients with LAPC (cT3) only at high volume centers and could achieve comparable oncologic outcomes	Strong
4. Nerve sparing radical prostatectomy is not recommended in the setting of LAPC.	Strong
5. Extended pelvic lymph adenectomy should be done during radical prostatectomy	Strong

8.4.3.2. Radiotherapy (RT)

One of the treatment options of locally advanced prostate cancer, is combined neoadjuvant / concomitant and adjuvant ADT with radiation therapy, with 24-36 months of adjuvant ADT, this protocol improves disease free survival, metastatic free survival and overall survival especially in patients with GS 8-10. ⁽⁸⁵⁾

Radiation therapy preferably with new techniques for instance Intensity modulated radiotherapy (IMRT) and Volumetric-modulated arc therapy (VMAT) can be delivered either by conventional

fractionation 78-80 Gy over 39-40 fractions or hypo-fractionated schemes 60 Gy over 20 fractions or 72 Gy over 30 fractions. ⁽⁸⁶⁾

In locally advanced disease in patients with good performance status chemotherapy in addition to ADT and radiation could be a valid option as it improves the PFS and marginally improves the OS. ⁽⁸⁷⁾

For patients with lymph node positive disease, the addition of radiation therapy to the standard of care (ADT) improves both overall survival and prostate cancer specific survival, so it is recommended to add radiotherapy to either long term ADT and lifelong ADT. ⁽⁸⁸⁾

In patients with LN positive disease the addition of abiraterone acetate to radiotherapy and ADT improves OS and failure free survival. ⁽⁸⁹⁾

Patients with locally advanced disease who underwent radical prostatectomy should receive adjuvant radiotherapy

if they have high risk features including positive margin, positive LNs, extracapsular extension or detectable PSA. ⁽⁹⁰⁾

Patients with pLN positive disease should receive adjuvant ADT in combination with radiation therapy. ⁽⁸⁹⁾

Table 68: Recommendations for Radiotherapy in Locally advanced prostate cancer (LAPC)

Recommendation	Strength Rating
1. Discuss radiotherapy in combination with ADT as alternative for radical prostatectomy in surgically unfit patients or patients refusing surgical intervention	Strong
2. Radiotherapy should be delivered with the highest available technique when feasible with either conventional dose not less than 76 Gy or hypo-fractionated schedule 60-72 Gy	Strong
3. Adjuvant ADT after radiotherapy should be continued for 24-36 months	Strong
4. Patients with clinically positive LNs should receive radiotherapy plus ADT as standard of care	Weak
5. Patient with LAPC should receive adjuvant radiation after RP if they have any high-risk features (SV involvement, pLN +, ECE or detectable PSA)	Strong
6. Offer adjuvant ADT with RT for patients with pathological LN+ after RP.	Strong
7. Offer RT with adjuvant ADT for LAPC after RP in patients with other risk factors rather than pLN + (SV involvement, ECE or detectable PSA).	Strong

8.4.3.3. Androgen deprivation Therapy (ADT)

Combined RT and ADT is recommended for LAPC; especially with positive nodal involvement.

ADT alone should be only offered to patients with LAPC refusing or unable to receive local treatment (radical prostatectomy or RT) with PSA-doubling time < 12 months or a PSA > 50 ng/mL, or a poorly differentiated tumor. ⁽⁹¹⁾

Table 69: Recommendations for Androgen deprivation therapy (ADT) in LAP

Recommendation	Strength Rating
1. Offer ADT in combination with radiotherapy in surgically unfit patients or patients refusing surgical intervention	Strong
2. Only offer ADT monotherapy to selected patients refusing or unfit for radical prostatectomy and radiotherapy; who are either symptomatic or asymptomatic, but with a PSA-doubling time (DT) < twelve months or a PSA > 50 ng/mL, or a poorly differentiated tumor.	Strong

8.4.3.4. Active surveillance (AS) and watchful waiting

AS should never be offered to patients with high risk prostate cancer or LAPC due to high risk of disease progression and distant metastases

Watchful waiting with deferred ADT monotherapy could be offered to asymptomatic LAPC patients with a PSA-DT > twelve months, a PSA < 50 ng/mL and well differentiated tumor, who are unwilling or not candidates for radical prostatectomy or RT. ⁽⁹²⁾

Table 70: Recommendations for Active surveillance (AS) and watchful waiting in LAP

Recommendation	Strength Rating
1. Do not offer AS for patients with LAPC	Strong
2. Watchful waiting with deferred ADT monotherapy may be offered to asymptomatic patients with a PSA-DT > twelve months, a PSA < 50 ng/mL and well differentiated tumor refusing local therapies.	weak

8.4.3.5. Adjuvant treatment after initial management of LAPC

8.4.3.5.1. No nodal metastases (pN0) after RP with ePLND

Adjuvant RT to the surgical field should be offered to patients at increased risk of local relapse: pT3-4 pN0 with positive margins (highest impact), and/or invasion of the seminal vesicles. ⁽⁹³⁻⁹⁵⁾

No role for prompt Adjuvant ADT in pN0 LAPC for patient who underwent radical prostatectomy and ePLND.

8.4.3.5.2. LN metastases (pN+) after RP with ePLND

Early adjuvant ADT in pN+ after RP for LAPC improves CSS and OS. ⁽⁹⁶⁾

Patients with pN+ disease after an ePLND, should be counseled for adjuvant therapy based on nodal involvement characteristics:

- Offer adjuvant ADT for node-positive (pN+).
- Offer adjuvant ADT with additional radiotherapy.
- Offer observation (expectant management) to a patient after ePLND and < 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension. ⁽⁹⁷⁾

Table 71: Recommendations for Adjuvant treatment after initial management of LAPC

Recommendation	Strength Rating
1. Do not offer neoadjuvant ADT for patients with LAPC	Strong
2. Offer adjuvant RT for selected patients with LAPC and positive surgical margins	Strong
3. Counsel patients with pN+ who underwent ePLND for further management; adjuvant ADT, Adjuvant ADT with RT or expectant management (≤ 2 L.N+ with microscopic involvement, PSA < 0.1 ng/ml and no extra nodal involvement)	Strong

9. Management of biochemical recurrence after primary treatment

9.1. Biochemical recurrence after initial radical prostatectomy

9.1.1. Definition:

Biochemical recurrence after radical prostatectomy defined as patients who achieve an undetectable PSA level after radical prostatectomy with subsequent detectable PSA level that increases on 2 or more subsequent measurements more than 0.2 ng/ml (recurrent disease); or patients with PSA level didn't fall to undetectable levels after RP (persistent disease).^(98,99)

9.1.2. Diagnostic workup

1. Calculation of PSA doubling time for prognosis and risk stratifications⁽¹⁰⁰⁾
2. Prostate imaging: MRI
3. Bone imaging: Bone scan / 18F PET/CT – 11C PET/CT.⁽¹⁰¹⁾
4. Chest, abdomen and pelvis CT.
5. If available and negative conventional imaging, consider 68Ga PSMA PET/CT.⁽¹⁰²⁾
6. Biopsy if imaging revealed prostate bed recurrence.

9.1.3. Treatment options

8.1.3.1. Salvage radiotherapy:

For men with a greater than 10-year life expectancy, which is the vast majority of men with BCR, PSADT less than 6 months, early salvage radiotherapy improves PFS, 5 years and 10 years bRFS, the definition of early salvage RT is controversial, but AUA recommend starting salvage RT while PSA is less than 1 ng/ml, many other studies recommend starting salvage radiotherapy while PSA between 0.2 – 0.5 ng/ml.^(103,104)

Radiotherapy dose: 64 – 71 Gy.⁽¹⁰⁵⁾

Radiotherapy field: Prostate bed ± pelvic LNs.⁽¹⁰⁶⁾

8.1.3.2. ADT with salvage radiotherapy:

Both bicalutamide 150 mg for 24 months or LHRH agonist for 6 months with SRT is valid options.^(107,108)

8.1.3.3. Observation:

Patients with life expectancy less than 5 years and PSADT more than 6 months may be considered for observation as they are unlikely to benefit from SRT.⁽⁹⁹⁾

9.2. Biochemical recurrence after initial Radiotherapy:

9.2.1. Definition of BCR after RT

BCR is defined as any PSA increase greater than or equal to 2 ng/mL higher than the PSA nadir.
(109)

9.2.2. Diagnostic workup

The same as BCR after radical prostatectomy.

9.2.3. Treatment options:

- Radical prostatectomy. (110)
- Cryotherapy. (111,112)
- High-Intensity Focused Ultrasound (HIFU). (113)
- ADT: both continues and intermittent ADT (114,115)
- Brachytherapy. (116,117)
- Observation: especially in patients with negative TRUS biopsy.

Table 72: Recommendations for Management of biochemical recurrence after primary treatment

Recommendation	Strength Rating
1. BCR after radical prostatectomy defined as either detectable PSA after 4 – 6 weeks post-operatively or detectable PSA level more than 0.2ng/ml in two consecutive measurements after undetectable PSA.	Strong
2. BCR after definitive radiotherapy ± hormonal therapy defined as PSA increase more than 2 ng/ml after nadir.	Strong
3. Diagnostic and metastatic workup should include bone scan, CT chest, pelvis and abdomen.	Strong
4. In highly selective patients, with doubtful conventional imaging results and long-life expectancy we can consider ⁶⁸ Ga PSMA PET/CT.	Weak
5. Treatment for patients with BCR after RP, patients should be stratified according to life expectancy and PSADT.	Strong
6. For patients with life expectancy less than 5 years and PSADT more than 6 months, observation should be considered the preferred option.	Strong
7. For patients with life expectancy more than 5-10 years and PSADT less than 6 months, treatment should be started as early as PSA level less than 0.5ng/ml.	Strong
8. Treatment should include salvage radiotherapy to dose between 64-72 Gy	Strong
9. Addition of hormonal treatment together with salvage/adjuvant radiation in rapidly progressing disease, either LHRH agonist for 6 months or in patients with concern regarding the toxicity of LHRH agonist we may consider bicalutamide for 24 months or no hormonal treatment.	Weak
10. Treatment of patients with BCR after definitive RT ± hormonal treatment,	Strong

patient should be stratified according to life expectancy, performance status and their understanding and accepting of different toxicities.	
11. Observation may be considered in patient with short life expectancy and patients with negative TRUS biopsy.	Strong
12. Radical prostatectomy is a valid option for selective fit, young patients with long life expectancy (more than 10 years) and no major comorbidities after counseling them with the expected urinary and sexual toxicities.	Strong
13. High-Intensity Focused Ultrasound (HIFU), may be considered in selected cases in experienced centers when trans-perineal template prostate mapping (TPM) is available or multi-parametric MRI with matched TRUS biopsies, especially in patients with concerns regarding bowel and urinary toxicities.	Weak
14. Brachytherapy and cryotherapy are alternative options, but due to lack of centers providing both modalities and expected cost, both options may be considered in selected patient when feasible centers are available.	Weak
15. Androgen deprivation therapy should be considered in patient not eligible for RP or not accepting its toxicities, especially with PSADT less than 6-9 months, those patients should start early ADT within 8 weeks of diagnosis of BCR, and intermittent ADT should be discussed with the patient to decrease the likelihood of ADT toxicities.	Strong
16. Patient must be counseled and discussed in each management step, and receive clear, understandable information about the pro and con of each treatment option, and the patient preference must be taken seriously in the treatment decision.	Strong
17. Counseling the patient regarding radiation toxicity, emphasizing on rectal and sexual toxicity is a fundamental step before proceeding for radiotherapy	Strong
18. Counseling the patient regarding radical prostatectomy toxicity, emphasizing on urinary incontinence, sexual toxicity and quality of life is a fundamental step before proceeding for surgery.	Strong

10. Management of Metastatic Hormone Sensitive Prostate Cancer (mHSPC):

10.1. Introduction & Evidence Based Medicine:

Since Charles Huggins established the critical role of androgens in stimulating prostate cancer growth in 1941, androgen deprivation therapy (surgical or medical) was considered to be the primary management of advanced/metastatic prostate and maintained to be the cornerstone of effective therapy across decades in all guidelines ^(118,119). Many controversial issues do exist regarding the intermittent versus continuous (most commonly adopted) ADT, while immediate treatment upon diagnosis is generally preferred to delayed onset treatment due to the survival advantage. ^(120,121)

Despite of being palliative in metastatic disease state, ADT can normalize serum levels of prostate-specific antigen (PSA) in over 90 percent of patients and can produce objective tumor responses in 80 to 90 percent with antitumor activity improving quality of life by reducing pain and other disease related complications, however, the duration of response is highly variable, and most prostate cancer patients eventually experience disease progression into castrate resistant disease with ultimate fatality. The development of additional therapies; cytotoxic therapies & androgen receptor targeting agents (ARTA) with survival advantage, has led to their earlier use in combination with ADT for initial therapy of metastatic disease aiming at improving castration quality to achieve positive influential effect on survival outcome. ⁽¹²²⁾

In the recent years with incorporation of chemotherapeutics and ARTA early in the upfront treatment of mHSPC, there is a growing emphasis upon defining the subset of patients who could gain the maximum benefit in terms of median Overall Survival based on the tumor burden or volume present (High versus low), where many definitions were existing based on clinical trials populations as shown in below table 29.

Table 73: Definition of high & low disease volume used in different clinical trials adding chemotherapy or ARTA to ADT for upfront management of mHSPC

Trial	High Volume	Low Volume
Glass et al	Extensive Disease: Appendicular skeletal metastases and/or visceral metastases	Minimum Disease: Nodal and/or axial skeletal metastases
CHAARTED Trial	>4 bone metastases with one or more outside the vertebral bodies and pelvis and/or visceral metastases (Extranodal)	All others
STAMPEDE Trial	Same as the CHAARTED trial	Same as the CHAARTED Trial

GETUG-AFU15	Same as the CHAARTED trial	Same as the CHAARTED Trial
LATITUDE Trial	2 or more the following: Visceral metastases, >3 bone metastases, Gleason score > 8	Only one of the following: Visceral metastases, > 3 bone metastases, Gleason Score > 8

Moreover, and more recently, a newer term applied for those patients with oligometastatic disease (OMPC) aiming at exploring the role of local therapy namely radiation therapy plus ablation of the few number of lesions present in metabolic while not seen in conventional imaging. However, more controversial issues emerged for the definition and how to diagnose oligometastatic disease as shown in table 30^(123,124). The most widely accepted definition of OMPC is "The low-volume tumor burden up to 3–5 metastases in bone and/or lymph nodes on conventional imaging".⁽¹²⁵⁾

Table 74: Different definitions used to describe oligometastatic mHSP

Study	Cutoff Number of Oligometastases	Location of metastases	Imaging Modality
Singh et al	< 5	Any	Isotopic Bone Scan
Berckovic et al	< 3	Bone or L. N	Isotopic Bone Scan, Choline and FDG PET/CT
Schick et al	< 4	NR	Isotopic Bone Scan, Choline and FDG C-Acetate/CT
Decaestecker et Al	< 3	Bone or L. N	FDG and Choline PET/CT
Jereczek-Fossa et Al	1	L.N	FDG and Choline PET/CT, CT
Ost et al	< 3	Any	FDG and Choline PET/CT
Ost et al	< 3	Any	Choline PET CT Scan

For the time being and based on 6 phase III trials: CHAARTED, LATITUDE, ARCHES, ENZAMET, TITAN & STAMPEDE trials; 4 Agents (Docetaxel, Abiraterone Acetate, Enzalutamide & Apalutamide) were approved to be added to the benchmark ADT for mHSPC in both low and high tumor burden based on overall survival advantage except Docetaxel which showed the benefit only in high tumor burden disease. The choice to add which pharmaceutical is controversial since the pooled data and network meta-analysis failed to show superiority for any in relation to others in terms of OAS. The choice between the recently approved agents (All are Category 1 Evidence) plus ADT can be suggested based on many factors as duration of treatment, profile of anticipated complications and disease parameters as shown in table 31.⁽¹²⁶⁾

Table 75: How to choose between up-front treatments in mHSPC

	DOCETAXEL	ABIRATERONE	ENZALUTAMIDE /APALUTAMIDE
Duration of Treatment	Short term	Long term	Long term
Toxicities	Peripheral neuropathy, hair loss, nail changes	Liver enzymes & Electrolytes	Seizures, Falls
Corticosteroids	Yes	Yes	No
Settings	High Tumor Burden	Any	Any

In developing countries with low national financial resources, the most cost effective treatment should be elected as an up-front treatment of mHSPC. Based on a recent publication by EUA, ADT plus Docetaxel is considered to most cost benefit effective as compared to ADT plus Abiraterone Acetate despite modest superiority of Abiraterone Acetate in network meta-analysis. (127)

A consensus on management of OMPC in daily clinical practice is limited by scarcity of evidence from clinical studies. Phase 3 STAMPEDE trial had shown significant difference in terms of Failure Free but not Overall Survival. Management is best within the context of clinical trial or via Multidisciplinary Team approach where the facility of PSMA PET CT Scan should be present. Management of OMPC via external beam radiation therapy to the primary and ablative radiation therapy to few metastatic lesions detected only by PSMA PET CT can be considered. It is included under management of low tumor burden mHSPC in NCCN guidelines while not specified in EUA guidelines. (128,129)

Suggested National Guidelines for The Management of Metastatic Hormone Sensitive Prostate Cancer (mHSPC), Table 32

Table 76: Summary of therapeutic interventions according to the clinical situation and according to level of national recommendations

Clinical Situation	Intervention	Strength Rating
• mHSPC • Low volume of Disease) • Asymptomatic	Immediate and Continuous ADT	Strong
	Delayed ADT*	Weak
	Intermittent ADT*	Weak
• mHSPC • (Low Volume of Disease) • Symptomatic	Immediate and Continuous ADT plus ARTA (Abiraterone Acetate, Enzalutamide or Apalutamide)	Strong

	Palliative External Beam Radiation Therapy	Strong
• mHSPC • High Volume of Disease • Symptomatic or Asymptomatic	Docetaxel	Strong
	ARTA**: •RTA**:dedico Acetate •cetateoedico •edicoeodico	Strong
	Palliative External Beam Radiation Therapy (in Symptomatic osseous disease)	Strong
* Certain clinical situations ** Approved upon tumor board in treating tertiary center for certain clinical and re-embarrassment situations.		

1. Achieve castrate level of serum testosterone (< 50 ng/ml): (Category 1)

- Immediate onset of treatment unless:
 - a. Life expectancy is < 5 years.
 - b. Asymptomatic patient.
 - c. The presence of uncontrolled comorbid disease (Cardiac, Central Nervous, Metabolic disorders).
- Continuous ADT is generally preferred to intermittent approach unless the patient is willing for non-continuous treatment and having low tumor volume, asymptomatic and well informed about the pros and cons of having continuous treatment.
- Surgical versus medical castration (LHRH agonists and antagonists) is to be decided following discussion with the patient taking into consideration the cost of treatment, patient's compliance and well.

2. Adding Approved Agents with Survival Advantage:

Based on extent of volume of systemic disease:

a. Low Tumor Volume:

- Careful monitoring by serum testosterone and PSA every 3 months after the nadir. (Preferred)
- Palliative external beam radiation therapy in a symptomatic patient.
- In symptomatic patients, also ARTA can be considered:

- i. Abiraterone Acetate (Category 1)
- ii. Enzalutamide (Category 1)
- iii. Apalutamide (Category 1)

b. High Tumor Burden:

- Docetaxel 75 mg/m² every 21 days for 6 courses provided of adequate hematological recovery and within normal ranges organ functions especially symptomatic patients with rapidly progressing disease and the presence of visceral metastases. (Preferred – Based on Cost Benefit Study).
- ARTA with survival advantages can be considered:

i. Abiraterone Acetate (Category 1)

ii. Enzalutamide (Category 1)

iii. Apalutamide (Category 1)

The use of 1st generation anti-androgen (e.g. Bicalutamide) is only used currently for a month with the start of LHRH analogue to prevent flare phenomenon, however it can be used according to local authority and tumor board in a tertiary service center based on the economic issues (National Practice).

Palliative EBRT is still a valid option for persistent bony pains due to metastases.

3. Special Situations:

Patients proven to have few metastatic sites by PSMA – PET Scan after being negative in conventional imaging (Oligometastatic Disease):

- Continue on ADT only (Preferred).
- If within the context of Clinical Trial or MDT approach; local EBRT to primary tumor and ablative SBRT to metastatic sites (Optional).

Patients should be considered to have bone-remodeling agents (Zoledronic Acid or Denosumab) to protect against therapy associated bone loss every 3 – 6 months with Calcium and Vitamin D supplementation to reduce skeletal related events.

If an impending fracture or spinal cord compression would be encountered, a prophylactic surgical fixation should be attempted without delay.

The help of clinical nutritionist, physiotherapist and psychiatrist would be highly appreciated to maintain the quality of life particularly with hormonal manipulation.

Careful attention should be given to the drug to drug interactions between the anti-neoplastic agents and the commonly used medications in this age group.

Follow up strategy included regular serum Testosterone and PSA every 3 months unless otherwise indicated due to new or recurring symptoms to detect evolution of castrate resistant phase, while radiologic images would be attempted if serum PSA started to show successive rises or clinical suspicion of having a complicated or progressing case.

11. Castration-resistant Prostate Cancer (CRPC)

11.1. Definition of Castration-resistant PCa

Ensure a castrate serum testosterone < 50 ng/dL plus either;

- Biochemical progression: Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or,
- Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) ^(130,131)

Table 77: Castrate-resistant disease definition

Recommendation	Strength Rating
Ensure testosterone levels are < 50 ng/dL to diagnose CRPC	Strong

11.2. Non-metastatic castration-resistant PCa

11.2.1. Definition:

The occurrence of biochemical progression with no overt clinical metastases detected via bone scan and CT-scan (conventional imaging as referred to in APCCC) ⁽¹³²⁾ remains till now the standard description for this state.

Next-generation imaging (NGI), positron emission tomography [PET], PET/CT, PET/MRI, or whole-body MRI) can be offered in M0CRPC if a change in management is anticipated but data in this area remains scarce. ⁽¹³³⁾

Eventually, progression to an evident metastatic state occurs in a third of the M0CRPC patients within 2 years. Risk factors for converting to a metastatic state are a high PSA and a rapidly rising PSA. ⁽¹³⁴⁾

In patients with unfavorable PSA kinetics (doubling time ≤ 10 months during continuous ADT and total PSA level ≥ 2 ng/ml) and nonmetastatic by conventional imaging 3 randomised phase 3 clinical trials (PROSPER, SPARTAN, and ARAMIS) have identified new treatment standards for patients with M0 CRPC ⁽¹³⁵⁻¹³⁷⁾ with the addition of enzalutamide, apalutamide, or darolutamide to on-going ADT. The metastasis free survival (MFS) and recently OS were met by all 3 trials and severe toxicity was low. Most patients (around 70%) in the 3 trials had a DT ≤ 6 month making this group of higher bearing to receive these novel therapies, but generally it was beneficial in the whole cohort. At the moment darolutamide is not available in Egypt and thus was not included in the current recommendations, table 34.

Table 78: Recommendations for Non-metastatic castrate-resistant disease

Recommendations	Strength Rating
1. Propose apalutamide or enzalutamide to patients with M0 CRPC with a	Strong

PSA-DT≤ 6 months and a high risk of developing metastasis	
2. Propose apalutamide or enzalutamide to patients with M0 CRPC with a PSA-DT 6 to≤ 10 months and a high risk of developing metastasis	Strong

11.3. Metastatic castration-resistant PCa

Ultimately men with PCa will progress despite castration. Despite this, androgen suppression should be continued in these patients. The treatment landscape here is affected by previous incorporation of agents into the castration naïve phase or M0CRPC. Furthermore, it is even more challenging to sequence approved therapies and sometimes logistics have the upper hand in this decision.

11.3.1. First-line treatment of mCRPC abiraterone, enzalutamide, docetaxel, Sipuleucel-T

The first line options have earned their place through prospective randomized phase 3 trials against comparators that are currently not considered standard of care. A survival benefit was appreciated in asymptomatic men with abiraterone, enzalutamide, and sipuleucel-T, radium-223 in symptomatic men with bone metastases and docetaxel in either asymptomatic or symptomatic cases. ⁽¹³⁸⁻¹⁴⁷⁾

Sipuleucel-T is not available outside the USA, whilst radium-223 is not available in Egypt. (not included in table 31)

In an expert consensus conference half of the panellists regarded bicalutamide and dexamethasone inappropriate for treating mCRPC if abiraterone and enzalutamide are available. ⁽¹⁴⁸⁾

Thus recognizing the financial constraints internationally and locally it would seem wise to propose these measures in the context of limited resources only if life prolonging agents were not available by any means with docetaxel use being encouraged in fit chemo-naïve patients as a more economic approach when feasible.

11.3.2. Second-line treatment for mCRPC

Progression in mCRPC unfortunately is inevitable and only prospective randomised data for second-line treatment in men who have received docetaxel as first-line treatment for mCRPC. Abiraterone, cabazitaxel, enzalutamide, and radium-223 have demonstrated an OS benefit. ^(147, 149-153)

* Cabazitaxel

A reduced dose of 20 mg/m² cabazitaxel was found to be equivalent in OS to 25 mg/m², but less toxic. Hence, the lower dose should be selected in the second-line setting. ⁽¹⁴⁹⁾

Treatment post- docetaxel / one line of hormonal treatment for mCRPC

Third line treatment after docetaxel and a single hormonal treatment for mCRPC is generally less beneficial than with earlier use ^(154,155). Given the possible evidence of cross-resistance between

enzalutamide and abiraterone, radium-223 or cabazitaxel seem to be valid choices. Docetaxel rechallenge may be considered. ⁽¹⁵⁶⁻¹⁵⁸⁾

Third-line treatment with either cabazitaxel or alternative AR-targeted therapy (enzalutamide or abiraterone) in post- docetaxel patients whose mCRPC had progressed rapidly (within a year) on their first AR-targeted therapy was addressed by the CARD trial and results seemed to favor cabazitaxel use. ⁽¹⁵⁹⁾

In the era of precision medicine and the quest for an actionable target has indeed extended to PC. ⁽¹⁶⁰⁾ Guidelines such as the NCCN currently recommend considering tumour genomic profiling for patients with regional or metastatic disease. These include tests for microsatellite instability (MSI)/defective mismatch repair (dMMR), and for variants involving other DNA repair genes, such as BRCA1/2, PTEN, ATM and CDK12. ⁽¹³⁸⁾

Men possessing somatic homologous recombination deficiency (HRD) exhibited high response rates, up to 88%, with polyADP-ribose polymerase (PARP) inhibitors in the post docetaxel and at least one novel hormonal agent arena. [32] Regulatory approval was obtained for olaparib after a significant clinical benefit to men with BRCA1/2 or ATM-mutated mCRPC was demonstrated. ⁽¹⁶²⁾

Alternatively, Platinum based chemotherapy may be offered to patients unable to receive a PARP inhibitor in the setting of limited resources but studies are needed to substantiate this use. ⁽¹³⁸⁾

Deficient MMR or MSI high mCRPC may be given pembrolizumab if feasible. ⁽¹³⁸⁾

Neuroendocrine prostate cancer (NEPC) development may be suspected if progressive disease with frequent visceral metastases is encountered with a low or moderately elevated serum PSA. This aggressive variant has a poor prognosis and requires tissue biopsy to confirm its diagnosis. Similarly, to small-cell lung cancer, platinum- based chemotherapy regimens may be deployed in therapy as it does not express the androgen receptor rendering it hormone refractory. ^(138, 163)

11.4. Monitoring of treatment

After thorough baseline history and clinical examination necessary laboratory values are noted (PSA, FBC, KFT, LFTs, ALP) along with a bone scan and CT of chest, abdomen and pelvis. ⁽¹⁴⁸⁾

The incorporation of novel imaging such as Choline or PSMA PET CT scans for progressing CRPC is probably not as beneficial as in cases with BCR or hormone naïve disease and remains ill defined. ^(130,148)

Additionally, relying on PSA solely to monitor CRPC may be misleading as visceral metastases have been recorded in cases lacking PSA elevation or neuroendocrinal differentiation. ^(164,165)

This led expert recommendations from the PCWG2 and APCCC to use a combination of bone scintigraphy, CT scans, PSA level and clinical benefit in evaluating men with CRPC, with the later stressing the need for radiological assessment even in the absence of clinical indication at least every 6 months. ^(148, 166)

11.5. When to change treatment

At least two of the three criteria (PSA progression, radiographic progression and clinical decline) should be fulfilled to discontinue treatment. ⁽¹⁶⁶⁾

11.6. Bone metastases/bone Health in CRPC

Painful bone metastases are common in CRPC. Surgical intervention is warranted in case of spinal cord compression (if feasible) which is considered an oncological emergency, along with high dose corticosteroids and subsequent external beam radiotherapy. Radiotherapy plays an integral part in skeletal secondaries and may be given as a single dose or multiple fractions. ^(167,168)

11.7. Preventing skeletal-related events

11.7.1. Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE), however prospective trials failed to demonstrate a survival benefit. ⁽¹⁶⁹⁾

11.7.2. RANK ligand inhibitors

The efficacy and safety of denosumab vs. zoledronic acid in metastatic CRPC was initially found to be superior in delaying or preventing SREs in a phase III trial but later a post-hoc review of these end-points found denosumab displayed identical results. ^(170,171) Again, these findings were not associated with any survival benefit.

The potential toxicity (e.g., osteonecrosis of the jaw) of these drugs must always be kept in mind (5-8.2% in M0 CRPC and mCRPC, respectively) and monitoring of serum calcium and renal function is necessary ⁽¹⁷²⁾. Thorough dental examination before initiating therapy for fear of jaw necrosis is obligatory as it is increased by a history of trauma, dental surgery or dental infection. Preventative treatment is advised with these agents (e.g. supplemental calcium, Vitamin D) and for SRE in CRPC patients. ⁽¹³⁰⁾

Table 79: Recommendations of Metastatic castrate-resistant disease therapies & supportive care

Recommendations	Strength Rating
1. Treatment with life-prolonging agents should be encouraged <i>if available</i> . First-line therapy choice depends on the performance status, symptoms, comorbidities, location and extent of disease, patient preference, previous treatment in the hormone-sensitive metastatic PCa (HSPC) phase (alphabetical order: abiraterone, docetaxel, enzalutamide,).	Strong
2. Treat eligible patients with docetaxel	Strong
3. Second-line treatment options <i>if available</i> for mCRPC rely on pre-treatment performance status, symptoms, patient preference, comorbidities and extent of disease (alphabetical order: abiraterone, cabazitaxel, docetaxel and enzalutamide.	Strong
4. Rechallenge with Docetaxel if 1 year interval of disease stability had been achieved and if no other options are suitable/available.	Weak

5. Third line cabazitaxel is favoured for men previously treated with docetaxel and progressing within 1 year of therapy on abiraterone or enzalutamide.	Strong
6. HRR gene-mutated mCRPC, germline or somatic, after treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy may be offered a PARP inhibitor/Olaparib	Strong
7. Metastatic CRPC men with bone secondaries require bone protective agents to avoid SRE.	Strong
8. Patients on bisphosphonates or denosumab must receive calcium and vitamin D supplementation with regular calcium level and renal function monitoring	Strong

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Committee VII

Upper Urinary Tract Trauma



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Egyptian Urological Guidelines on Urologic Upper Tract Trauma

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59 List of Abbreviations

AAST	American Association for the Surgery of Trauma
AUA	American Urologic Association
CT	Computed Tomography
EUA	European Urologic Association
IVU	Intra-venous Urography
MOH	Egyptian Ministry of Health
PUJ	Pelvi-ureteric Junction
US	Ultrasound

60 Abstract

60.1 Introduction

This document integrates recent international guidelines with local experience and environmental and socioeconomic circumstances. The latter are dominated by a rich bioecological environment, specific demographics and social constraints, limited financial resources.

60.2 Methodology

Our recommendations are the outcome of integrating 4 resource categories:

1. Two guidelines (including their latest updates), namely European Urological Association [EUA], American Urologic Association [AUA]
2. Review of several guides, position statements, meta-analyses and leading institutional protocols.
3. Relevant Egyptian publications.
4. A panel of 4 Urology trauma surgeons representing most trauma referral centers in Egypt

60.3 Results.

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

60.4 Conclusions.

These guidelines provide practical evidence-based guidance on the clinical aspect of upper urinary tract trauma including the kidney and the ureter. The main target is entirely focused on assessment and treatment, reflecting the recommended clinical practice.

61 Guidelines

The kidney is the most commonly injured urologic organ from external trauma. Renal trauma can be classified into blunt, sharp, and iatrogenic.

61.1 Recommendations of trauma initial evaluation

- We strongly recommend taking detailed history including age, type of trauma, history of pre-existing renal disease, known solitary kidney, known pre-existing renal abnormality.
- We strongly recommend vital signs measurements, trauma assessment regarding airway, breathing, circulation, deformities, and exposure of other body parts.
- We recommend physical examination to assess the injury.
- We strongly recommend routine urine analysis, blood tests including hematocrit value, and renal function tests.

61.2 Recommendations of radiographic assessment

- We strongly recommend multi-phase CT scanning in trauma patients with
 - Visible hematuria
 - Non-visible hematuria and one episode of hypotension
 - History of rapid deceleration injury and/or significant associated injuries
 - penetrating trauma
 - Clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness. ⁽¹⁾
- Advantages of CT outweigh the risks, which include contrast related complications, radiation exposure, and the dangers of transporting a patient away from the resuscitation environment. ⁽²⁾
- Standard intravenous pyelogram may be used in rare cases where CT is not available, but is inferior ⁽²⁾
- Ultrasound may be used in children, although CT is preferred. ⁽²⁾
- Ultrasound is not routinely used for assessment of solid organ injury as it is insensitive, operator dependent, does not define the injury well, and is inferior to CT. It is an option for follow-up. ⁽¹⁾
- An intraoperative one-shot IVP may be used to confirm that a contralateral functioning kidney is present in rare cases where the patient is taken to the operating room without a CT scan. ⁽²⁾
- MRI has diagnostic accuracy similar to CT. However, its logistics are not practical in the trauma setting. ⁽¹⁾
- Radionuclide scans has no role in the immediate evaluation of trauma patient.

61.3 Renal Injury Grading System

Based on contrast CT findings; renal injuries can be graded according to the AAST grading scale. The scaling system is validated, predicts morbidity and the need for intervention ^(3, 4)

Table 80: Renal injury grading system

Grade*	Description of injury
1	Contusion or non-expanding subcapsular haematoma No laceration
2	Non-expanding peri-renal haematoma Cortical laceration < 1 cm deep without extravasation
3	Cortical laceration > 1 cm deep (not reaching collecting system) without urinary extravasation
4	Parenchymal laceration: through corticomedullary junction into collecting system Or Vascular: segmental renal artery or vein injury with contained hematoma, or partial vessel laceration, or vessel thrombosis
5	Parenchymal: shattered kidney Or Vascular: renal pedicle or avulsion
*Advance one grade for bilateral injuries up to grade 3	

61.4 Recommendations on management of renal trauma patients:

- We strongly recommend that haemodynamic stability is the most important parameter for selecting patients to either non-surgical or surgical management
- A haemodynamically stable patient is one whose vital signs are stable and not consistent with shock with stable serial hematocrit values over time ⁽²⁾
- The management plan depends upon proper classification of injury using contrast CT whenever possible, otherwise an IVU is an alternative, and ultrasound is a weak imaging tool.
- In haemodynamically stable patient with G 1- 3 injuries the management is usually conservative with bed rest, blood transfusion, and ICU admission for monitoring and resuscitation if necessary. ⁽²⁾
- In hemodynamically stable patients with G4-5 injury management can also be conservative except for bilateral artery injuries or injuries involving a solitary functioning kidney. ⁽⁵⁾ If renal pelvis avulsion or proximal ureteral avulsion injury is present (suggested by the medial extravasation of dye and absence of contrast in the distal ureter); drainage of the kidney using nephrostomy tube or DJ stent may be promptly required to avoid urinoma formation. ⁽⁶⁾

- Selective angio-embolization is effective (when available) in high grade renal trauma with high success rates & can be used in severe polytrauma to embolize the main renal artery.⁽¹⁾
- When conservative management has been chosen according to haemodynamic stability and the grade of renal trauma, repeat imaging should be performed after 2-4 days after the injury.
- If an urinoma was found in follow up imaging; drainage of the kidney by nephrostomy/DJ stenting should be done according to the clinical situation along with placement of a percutaneous drain.
- Surgical treatment:
 - Indications for exploration include:
 - Non or transient response to initial fluid resuscitation
 - Grade 5 vascular injury
 - The need to explore for associated abdominal injuries
 - Expanding or pulsatile peri-renal haematoma at laparotomy
 - Operative findings & reconstruction:
 - Access:
 - Transperitoneal approach is recommended in most series ^(7,8)
 - Access to the renal pedicle is obtained by making an incision in the posterior peritoneum over the aorta, just medial to the inferior mesenteric vein, then placing a vascular clamp on the renal hilum. ⁽⁹⁾
 - Stable haematomas detected during exploration for associated injuries should not be opened. Central or expanding haematomas indicate injuries of the renal pedicle, aorta, or vena cava and are potentially life-threatening and require further exploration. ⁽¹⁰⁾
 - Renorrhaphy:
 - Repair of injured renal parenchyma is the most commonly performed reconstructive technique
 - Partial nephrectomy:
 - Removal of all non-viable renal tissues with watertight closure of the collecting system is strongly recommended. ⁽¹⁾
 - When available, the use of hemostatic agents and sealants is helpful. ⁽¹¹⁾
 - Vascular repair:
 - Should be attempted in solitary kidney or bilateral injuries, results are rarely effective^(12,13)
 - Dissection or bleeding of the main renal artery can be managed with a vascular stent⁽¹⁾
 - Nephrectomy:
 - Can be lifesaving in vascular injuries
 - Placement of a drain is a must after corrective surgery or nephrectomy.
- Follow up

- Follow up is strongly recommended after renal trauma to assess recovery of renal function and potential complications.
- Physical examination, blood pressure measurements, urinalysis, serum creatinine, and imaging studies including ultrasound, CT scans, and nuclear scans.

61.5 Special considerations in pediatric age group:

- Children are more prone than adults to renal injury after blunt trauma. A child's kidney is larger in relation to the rest of the body with less per-renal fat, weaker abdominal muscles, and finally less ossified compressible thoracic cage. ⁽¹⁴⁾
- Blood pressure cannot be a reliable measure of the renal involvement in pediatric trauma as children can maintain their blood pressure despite hypovolemia unlike adults. ⁽¹⁵⁾
- Use imaging in all children who have sustained a blunt or penetrating trauma with any level of hematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height. ⁽¹⁾
- Use rapid spiral computed tomography with delayed images scanning for diagnostic and staging purposes. ⁽¹⁾
- Manage most injured kidneys conservatively. ⁽¹⁾
- Offer surgical intervention in case of hemodynamic instability and a Grade V renal injury. ⁽¹⁾

61.6 Complications of renal trauma:

- Early:
 - Bleeding, infection, sepsis, perinephric abscess, urinary fistula, urinary extravasation and urinoma formation.
- Delayed:
 - Delayed bleeding, hydronephrosis, stone formation, chronic pyelonephritis, hypertension, AVF, and pseudoaneurysm.

61.7 Recommendations of medico-legal issues of renal trauma:

- We strongly recommend written documentation of the condition the patient was first assessed and the first aid, resuscitation measures performed, also keeping records of all investigations done during the evaluation of the patient. (1D)
- We strongly recommend detailed counselling with the patient and relatives whenever applicable regarding options of management and documenting the counselling session. (1D)
- We strongly recommend a fully informed consent whenever applicable from patient or relatives before deciding on a specific line of management. (1D)
 -
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Table 81: Recommendation for Management of Renal Trauma

Recommendation	Strength Rating
1. Assess haemodynamic stability upon admission.	Strong
2. Test for haematuria in a patient with suspected renal injury	Strong
3. Perform a multiphase computed tomography scan in vitally stable trauma patients with: • Visible haematuria; • Non-visible haematuria and one episode of hypotension; • A history of rapid deceleration injury and/or significant associated injuries; • penetrating trauma; • Clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness.	Strong
4. Manage stable patients with blunt renal trauma non-operatively with close monitoring and re-imaging as required	Strong
5. Use selective angioembolisation for active renal bleeding if there are no other indications for immediate surgical exploration.	Strong
6. Proceed with renal exploration in the presence of: • Persistent haemodynamic instability; • Grade 5 vascular or penetrating injury; • Expanding or pulsatile peri-renal haematoma.	Strong
7. Repeat imaging in high-grade injuries and in cases of fever, worsening flank pain, or falling haematocrit.	Strong
8. Follow-up approximately three months after major renal injury with: • Physical examination; • Urinalysis; • Individualised radiological investigation including nuclear scintigraphy; • Blood pressure measurement; • Renal function tests.	Weak
9. Measure blood pressure annually to diagnose renovascular hypertension.	Strong

62 Ureteral Trauma

Ureteral injuries represent 1-2.5% of all urinary tract injuries with those resulting from iatrogenic causes being far more common than accidents or external violence causes. Whereas the lower ureters are more involved in the earlier, the upper segments' injuries are more encountered in the latter. ^(16, 17, 18)

62.1 Iatrogenic ureteral trauma

62.1.1 Incidence

Traumatic injuries to the ureter during diagnostic or therapeutic maneuvers represent about 80% of all ureteral injuries. ⁽¹⁹⁾ The incidence of such injuries during different interventions is summarized in table 1 ^(20, 21, 22, 23, 24, 25)

Ureteral injuries have also been reported during laparoscopic and robotic interventions, minimally invasive hysterectomy, vaginal mesh surgeries, flexible uretero-rensoscopy (URS), laser lithotripsy and retrieval of neglected double J stents

62.1.2 Predisposing factors, grading and pathogenesis

Most of the iatrogenic ureteral injuries occur when they are least expected and the possibility of surgeons' negligence or overconfidence frequently cannot be ruled out. However, some predisposing factors could be cited including for instance prior surgery or irradiation, advanced malignancy, anatomical abnormalities, inflammations, colonic diverticulitis and endometriosis. ^(26, 27, 28)

Grading of ureteral trauma suggested by the American association for the surgery of trauma ⁽²⁹⁾ (table 2) has not gained wide acceptance as the case of renal trauma grading but it might help in academic reporting.

Table 82: Grading System of Ureteral Trauma

Grade	Type	Description
I	Haematoma	Contusion or Haematoma without devascularization
II	Laceration	< 50% transection
III	Laceration	> 50% transection
IV	Laceration	Complete transection with < 2cm devascularization
V	Laceration	Avulsion with > 2cm devascularization

Advance one grade for bilateral insults up to grade III

- The mechanism of iatrogenic ureteral injuries during open or laparoscopic interventions includes laceration, ligation or kinking, crushing, partial or complete transection, thermal injury and ischemic devascularization injuries.
- On the other hand, endoscopic manipulations might entail mucosal abrasions, submucosal false passages, ureteral perforation, resection, intussusception, avulsion and thermal or laser injuries.

62.2 Ureteral injuries during endoscopic manipulations:

62.2.1 Intra-operative diagnosis

- Ureteral injuries in such settings are frequently diagnosed by direct vision as a mucosal laceration, tear or complete perforation with peri-ureteral fat evident in the field.
- A retrograde ureterogram is quite conclusive when it reveals contrast extravasation into the retroperitoneum. ⁽²⁶⁾ **This mandates the availability of fluoroscopy during all endoscopic manipulations involving the ureter.** Any impression apart from free contrast flow up the ureter should raise suspicions because a false passage might allow contrast flow in a sleeve fashion in the ureteral sub-adventitia mimicking a normal ureter and deceiving the novice.
- The visualization of an intussuscepted part of the ureter into the bladder or the urethra is diagnostic for ureteral avulsion.
- Failure to diagnose an injured ureter during endoscopic manipulations may result in more extensive sequelae and complications: ^(22, 30) The manifestations, diagnosis and treatment of delayed presentation are described in **(4.8.1.5).**

62.2.2 Prevention:

- Sticking to the basic principles of endoscopic handling of the ureter minimizes the risk of ureteral injury. The following list summarizes most of these principles:
 - Preliminary passage of guide wires
 - The use of slippery guide wires when necessary
 - Fluoroscopic guidance
 - Proper dilation of the intramural ureter
 - The use of small caliber ureteroscopes
 - Maintaining a continuous irrigation
 - Hydraulic dis-impaction of stones
 - Under-vision introduction and withdrawal of ureteroscopes
 - Proper fragmentation of sizable stones
 - Judicious use of lithotripters and keeping them always under vision

- Judicious use of stone baskets and extractors
- The use of ureteral access sheaths when repeated endoscope introduction is anticipated

62.2.3 Treatment:

- Mild mucosal lacerations usually require no further treatment.
- Submucosal false passages should be managed by temporary ureteric stent/DJ.
- Perforations should be managed by temporary double J stenting (4-6 weeks). Thermal injuries may require longer term stenting (6-8 weeks).
- Later follow up by intravenous urography or retrograde pyelography should be taken into account to watch for the development of ureteral strictures.⁽³¹⁾
- Ureteral intussusception and/or avulsion should be surgically explored and ureteral gaps bridged as will be explained in (4.8.1.7).

62.3 Ureteral injuries during open or laparoscopic surgeries

62.3.1 Diagnosis:

- Often the urologist is consulted in a case without the leisure of previous knowledge of the patient's history or prior evaluation.
- A quick assessment of the available imaging studies can be informative about the preoperative status.
- Proper exposure of the suspected injured segment is usually the first advisable step.
- Ligatures might be cut only if they will not jeopardize hemostasis.
- If such an exposure is not feasible, the advisable options include:
- I.V. injection of indigo carmine and watching for the extravasating dye
- Cystoscopy and retrograde injection of indigo carmine or passage of a guide wire or a ureteric catheter into the involved ureter. Gentle manipulations are mandatory to avoid aggravating the injury.
- Intra-operative retrograde ureterography under fluoroscopy
- If none of the above is feasible, a small longitudinal ureterotomy may be performed through which a well lubricated ureteric catheter, a small caliber Nelaton catheter or a guide wire may be gently passed through the suspected injured site.

62.3.2 Prevention:

- It is advisable in complex surgeries in the vicinity of the ureter to have the ureters identified and secured away from clamps and ligatures.
- Mass cauterization, clamping and ligation should be strictly avoided.

- The possibility of having duplex systems should be put in mind during assessment of the available imaging studies prior to ureteric surgeries.
- The preliminary placement of ureteral stents prior to complex pelvic surgery has been debated whether it will guard against injuries or it will just facilitate intra-operative identification of the injury.^(23, 32, 33) However, the committee feels that prior stenting might facilitate identification of the ureter during surgery in patients with predisposing factors (prior surgery or irradiation, advanced malignancy, anatomical abnormalities, inflammations, colonic diverticulitis and endometriosis)

62.3.3 Treatment:

- Ureters mildly involved in sutures or ligatures may be managed by de-ligation and temporary ureteral stenting.
- Partial tears may be repaired with stenting.
- More severe injuries including crush injuries, thermal injuries and transection warrant resection of the involved segment and ureteral re-anastomosis (see 4.8.1.6) or resorting to one of the gap-bridging solutions according to the level of the injury (4.8.1.7).
- If the intra-operative circumstances do not permit proper ureteral reconstruction, a damage-control policy may be resorted to: proximal urinary diversion by a nephrostomy tube and ureteral ligation as distal as the injury would allow with a deferred plan for re-construction.⁽³⁴⁾
- If nephrostomy tube fixation is not feasible a ureteric catheter may be exteriorized to drain the involved ureter.

62.4 Iatrogenic ureteral injuries that passes undiagnosed intra-operatively:

62.4.1 Diagnosis:

- Ureteral ligation or intussusception injuries inflicted during surgical or endoscopic procedures and not identified intra-operatively may pass silently and stay unrecognized only to be diagnosed accidentally later on or even not at all.
- Otherwise, patients may present in the post-operative period similar to transection and perforation injuries with one or more of the following:
 - Fever and sepsis
 - Flank pain
 - Abdominal pains due to retroperitoneal urinoma or intraperitoneal collection
 - Anuria (in bilateral insults or in cases with jeopardized contralateral unit)
 - Urine leakage from the vagina, the rectum, the abdominal wound or the fixed drain.
 - Pneumaturia or fecaluria
 - Ischemic and thermal injuries frequently manifest later than transection injuries. A high level of suspicion should be kept in vague situations.

- The estimation of the creatinine concentration in the leaking fluid clarifies the nature of the fluid whether it is serum, lymph or urine; being almost ten-times the serum level in the latter situation.
- Abdominal ultrasonography is usually the initial diagnostic tool that should be re-enforced by contrast-enhanced abdomino-pelvic CT to identify the site of extravasation, the intra-abdominal collection and the presence of back pressure. Absence of the latter should not rule out ureteral trauma because acute complete ureteral ligation or crushing may result in acute renal shut down with negligible or even no pelvi-caliceal dilatation.
- Renal duplex studies with measurement of the arterial resistive index or renal radio-nuclide studies may be resorted-to in order to settle the diagnosis in such circumstances.^(35, 36)
- The sensitivity of IVU remains below that of CT in the diagnostic algorithm as it might miss up to 60% of the cases.^(19, 26)
- In doubtful cases, retrograde (or antegrade) uretero-pyelography should be performed to confirm the diagnosis.

62.4.2 Treatment:

- Cases diagnosed within one week of the injury without associated urinomas or infection may withstand an accelerated approach including trial for endoscopic stenting, or accelerated surgical reconstruction.⁽²⁶⁾
- Later diagnosis in the context of a mild injury, retro- or antegrade ureteral stenting may be tried. However, the success rates are quite limited.^(37, 38) Otherwise, US- or CT-guided percutaneous drainage of the urine collection and fixation of a nephrostomy tube for urine diversion are the most widely accepted approaches. A period of 3-6 months has been advocated to wait for re-assessment and surgical correction accordingly.

62.5 Broad principles for reconstruction of ureteral injuries:

- Debridement of necrotic tissue
- Avoid de-sheathing
- Spatulation of ureteral ends
- Watertight mucosa-to-mucosa anastomosis with absorbable sutures
- Tension-free anastomosis
- Internal stenting
- External drainage
- Isolation of injury with peritoneum or omentum

62.6 Methods of bridging ureteral gaps:

62.6.1 Lower or Middle ureter

- Uretero-neocystostomy (non-refluxing or refluxing techniques)
- Bladder psoas hitch
- Bladder Boari flap

62.6.2 Upper or Middle ureter

- Renal mobilization
- Trans-uretero-ureterostomy
- Pelvi-ureteric re-anastomosis
- Uretero-calicostomy

62.6.3 Extensive segments

- Ileal ureter replacement
- Renal auto-transplantation
- Buccal mucosal grafts (limited experience)

62.7 Non-Iatrogenic ureteral trauma

- Ureteral injury in external violence trauma is a rare entity. Their small size, their flexibility in the horizontal plane and their protection by surrounding bone, muscles and fat render them partially safe.
- Ureteral injuries may ensue as a result of rapid deceleration trauma with subsequent avulsion at the level of the PUJ or penetrating injuries due to stab wounds, fire arm or blast injuries.
- High velocity bullet injuries from gun rifles are of particular interest due to the cavitation wave they induce resulting in a wider field of impact than that expected from the bullet trajectory per se.
- The majority of penetrating ureteral injuries are associated with other organ injuries.

62.7.1 Diagnosis and treatment in the acute stage:

- A high degree of suspicion should be raised in patients with rapid deceleration injuries (e.g. road traffic accidents and falling from heights) and in penetrating injuries related to the course of either ureters even if no other injuries can be confirmed.
- Hematuria is a non-dependable finding.
- A contrast enhanced abdomino-pelvic CT with delayed films is more conclusive than a standard IVU to reach a reliable diagnosis.

- Finally, a retrograde uretero-pyelography may be required in unsettled situations.
- Most of the ureteral injuries, however, are associated with other vital organ injuries and are frequently diagnosed during laparotomy performed to handle these injuries (e.g. bleeding vessels, parenchymatous organ tears and intestinal injuries).
- Exclusion or confirmation of the injury during laparotomy might require adequate ureteral exposure, I.V. injection of indigo carmine or other maneuvers similar to those described for iatrogenic injuries occurring during open or laparoscopic surgeries (4.8.1.6).
- The treatment algorithm is also similar to that adopted for treating open iatrogenic ureteral injuries. However, a damage control policy is more frequently resorted to as dictated by the patient's stability and associated injuries (4.8.1.4).-c

62.7.2 Diagnosis and treatment in the late stage:

- If a ureteral injury passes un-noticed in its acute stage, the manifestations and diagnostic procedures are similar to those described for undiagnosed iatrogenic injuries (4.8.1.5).-a.
- The treatment algorithm also follows the same path (4.8.1.5).-b

Table 83: Recommendation for Management of Ureteral trauma

Recommendation	Strength Rating
Visually identify the ureters to prevent ureteral trauma during abdominal and pelvic surgery.	Strong
Beware of concomitant ureteral injury in all abdominal penetrating trauma, and in deceleration-type blunt trauma.	Strong
Use pre-operative prophylactic stents in pelvic surgeries with high risk of ureteral injury.	Strong
Repair iatrogenic ureteral injuries recognized during surgery immediately	Strong
Treat iatrogenic ureteral injuries with delayed diagnosis by nephrostomy tube/JJ stent urinary diversion.	Strong
Manage ureteral strictures by ureteral reconstruction according to the location and length of the affected segment.	Strong

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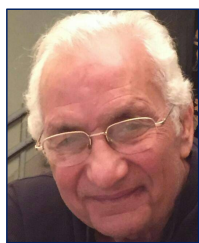
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Committee VIII

Lower Urinary Tract & Genitalia Trauma



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Egyptian Urological Guidelines of Lower Urinary Tract Trauma

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64 Abbreviations

Abbreviation	Detailed Name
EMBASE	Expected Media Data Base
EP	Extraperitoneal
IP	Intraperitoneal
MVAs	Motor vehicle accidents
PFUIs	Pelvic fracture urethral injuries
PUI	Posterior urethral injury
WHO	World Health Organization

65 Introduction:

65.1 Aim and objectives:

In this review, we tried to establish Egyptian Guidelines for the proper management of anterior urethral trauma to assist medical professionals.

It should be considered that guidelines constitute the best evidence-based available to the experts but following guideline recommendations will not necessarily result in the best outcome, and so the guidelines should never replace clinical expertise when making treatment decisions for individual patients.

65.2 Methods:

65.2.1 Evidence sources

During the preparation of these guidelines, new and relevant evidence sources were searched for, collected and evaluated through a structured assessment of the literature.

Databases searched included Medline, Expected Media Data Base (EMBASE), and the Cochrane Libraries, covering a time frame between 1/1/2018 till 31/12/2019. We also used data from the European Association of Urology (EAU) Guidelines for Urological Trauma and the American Urological Association Guidelines.

References used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence ⁽¹⁻³⁾:

- The magnitude of the effect.
- The inevitability of the results (exactness, reliability and heterogeneity).
- The balance between desirable and undesirable outcomes.
- The impression of patient values and predilections and the certainty of these values.

66 Definitions and Epidemiology of trauma:

2.1. Definition of trauma:

Trauma is defined as a physical injury or a wound to living tissue caused by an extrinsic agent due to diversity of mechanisms, such as traffic-related or transportation-related injuries, falls, assault, explosions, etc ⁽⁴⁾.

Globally, trauma is the sixth leading cause of death, with around 10% of all worldwide mortalities. This means around annual five million deaths even much more million disabilities ^(5, 6).

Nearly around half of the trauma related deaths occur in people aged 15-45 years and trauma can be considered as the leading mortality cause among this age group; especially among males ⁽⁵⁾. Death due to trauma is twice more common among males, compared to females; and this was more evident as regards motor vehicle accidents (MVAs) and interpersonal violence ⁽⁷⁾.

Therefore, trauma is a serious public health problem with substantial medical and socio-economic charge ⁽⁷⁾.

Isolated urologic injuries are usually infrequent because the kidneys, ureters, and bladder are well protected within the abdomen-pelvic cavity, and the penis and testes are physically mobile. Urologic injuries are not uncommon in case of multi-organ injuries; seen in around 10% of abdominal multi-organ traumatic injuries ^(4, 8, 9).

66.1 Classification of trauma

Traumatic injuries are classified by the World Health Organization (WHO) into intentional (such as interpersonal violence, war-related or self-injuries), and unintentional injuries (such as MVAs and falls). A specific type of unintentional injury is iatrogenic injuries which occurs during therapeutic or diagnostic procedures ⁽¹⁰⁾.

Traumatic injuries are usually divided into blunt or penetrating ones as these different mechanisms have different implications for management decisions and patients' outcomes. Explosion injuries may have features of penetrating and blunt trauma together ⁽⁴⁾. Penetrating injuries are further classified according to the velocity of the projectile into:

1. High-velocity projectiles (e.g. rifle bullets - 800-1,000 m/sec);
2. Medium-velocity projectiles (e.g. handgun bullets - 200-300 m/sec);
3. Low-velocity items (e.g. knife stab).

High-velocity weapons inflict greater damage due to temporary expansive cavitation that destroys a much larger area than the projectile tract itself. In lower velocity injuries, the damage is usually confined to the projectile tract. Blast injury is a complex cause of trauma which includes blunt and penetrating trauma and burns ⁽¹⁰⁾.

The most commonly used classification grading system is the AAST (American Association for the Surgery of Trauma) injury scoring scale. It is useful for managing renal trauma, but for the other urological organs, the injuries are commonly described by their anatomical site and severity (partial/complete) ⁽¹⁰⁾.

66.2 Genitourinary trauma

The kidney is the most commonly injured genitourinary organ. It is particularly susceptible to deceleration injuries because it is only fixed in space by the renal pelvis and vascular pedicle. Over eighty percent of renal injuries are due to blunt trauma; but penetrating trauma usually lead to more severe injuries ^(4, 11). Traumatic injuries to the renal vascular pedicle are uncommon but are usually associated with a multiple- organ injuries ⁽¹²⁾.

Ureteric trauma is the least common genitourinary trauma because of small size and high mobility of the ureter. The most common cause of ureteric injuries is iatrogenic trauma; accounting for about 75% of all ureteric injuries. The lower third of the ureter is most commonly injured ⁽¹³⁻¹⁵⁾.

Bladder injuries are uncommon and are usually associated with pelvic bone fractures ⁽¹⁶⁾.

The most common male external genital injuries include penile fracture, testicular rupture, and penetrating penile injury. If there is blood at the meatus or hematuria is found in addition to external genital injury, evaluation for urethral injury should also be performed ^(4, 15, 17).

67 General management principals

67.1 The Initial evaluation

The initial emergency assessment of a trauma patient is beyond the focus of these guidelines. It is usually carried out by emergency medicine and trauma specialized personnel following ATLS principles. Detailed further assessment involves cross-sectional imaging, laboratory analysis and specialist surgical input. The management of individual organ injury will follow in the sections below. Tetanus vaccine status should be assessed for all penetrating injuries ⁽¹⁸⁾.

67.2 Poly-trauma managed in major trauma centers leads to improved survival

Urological trauma is often associated with significant injuries in the poly traumatized patient. Lessons from civilian trauma networks, military conflict, and mass casualty events have led to many advances in trauma care. These include the widespread acceptance of damage control principles and trauma centralization to major trauma centers staffed by dedicated trauma teams. The re-organization of care to these centers has been shown to reduce mortality by 25% and length of stay by four days. Urologists increasingly understand their role in the context of polytrauma with the ultimate aims of improving survivability and decreasing morbidity in these patients ⁽¹⁹⁾.

67.3 Damage control

Damage control is a life-saving strategy for severely injured patients that recognizes the consequences of the lethal triad of trauma - hypothermia, coagulopathy and acidosis. The first of a three-phased approach consists of rapid control of hemorrhage and wound contamination. The second phase involves resuscitation in the intensive care unit (ICU), intending to restore normal temperature, coagulation, and tissue oxygenation. The final stage involves definitive surgery when more time-consuming reconstructive procedures are performed in the stabilized patient ^(20, 21).

Urological intervention needs to be mindful of the phase of management. Temporary abbreviated measures followed by later definitive surgery are required. Complex reconstructive procedures, including organ preservation, are not undertaken. The decision to enter damage control mode is taken by the lead trauma clinician following team discussion ⁽²⁰⁾.

67.4 Mass casualty events and Triage

A mass casualty event is one in which the number of injured people and the severity of their injuries exceed the capability of the faculty and staff. Triage, communication and preparedness are important components for a successful response. Triage after mass casualty events involves difficult moral and ethical considerations. Disaster triage requires differentiation of the few critically injured individuals who can be saved by immediate intervention from the many others

with non-life-threatening injuries for whom treatment can be delayed and from those whose injuries are so severe that survival is unlikely in the circumstances ⁽²²⁾ .

67.5 The role of thrombo-prophylaxis and bed rest

Trauma patients are at high risk of deep venous thrombosis (DVT). Concerns about secondary hemorrhage result in prolonged bed rest post-injury which effectively compounds this risk. Established prophylaxis measures reduce thrombosis and are recommended following systemic review. However, the strength of evidence is not high and as yet there is no evidence to suggest that mortality or pulmonary embolism risk is reduced. Compression stockings and low molecular weight heparins are favored. The risk of secondary hemorrhage is thought to be low and the practice of strict bed rest has waned in patients who can mobilize ^(23, 24) .

67.6 Antibiotic stewardship

Single-shot antibiotic doses are common in major trauma. The indication for continuing antibiotics is governed by injury grade, associated injuries and the need for intervention. Patients with urinary extravasation tend to be kept on antibiotics but there is no evidence base for this. Antibiotics should be avoided in lesser trauma e.g. Grade 1-3 renal trauma, and a regular review undertaken for those continued on regular dosing ⁽¹⁹⁾ .

67.7 Urinary catheterization

Prolonged catheterization is required in all forms of the bladder and urethral injury. Catheterization is not necessary for stable patients with low-grade renal injury. Patients with heavy hematuria, who require monitoring or ureteric stenting, benefit from catheterization. This can be removed once hematuria lightens and there is an improvement in the clinical situation. The shortest possible period of catheterization is advised ⁽¹⁹⁾ .

68 Anterior Urethral Trauma

68.1 Background:

Urethral injuries are uncommon and mostly affect male patients and are usually diagnosed following blunt trauma. Urethral injuries are divided into anterior and posterior injuries ^(25, 26).

The Goldman classification of urethral injuries includes five types of lesions aimed at discerning anterior from posterior and complete from incomplete and at determining whether posterior urethral injuries involve the bladder neck or the rectal wall ⁽²⁷⁾.

The main cause of anterior urethral injury is direct blunt trauma. Penetrating injuries to the anterior urethra are rare and are mainly caused by gunshot injuries ^(28, 29).

68.2 Anterior male urethral injury

Injuries to the male urethra are divided into injuries to the posterior urethra (at or above the membranous urethra) or anterior urethra (penile or bulbar urethra). Posterior urethral injuries are almost exclusively associated with pelvic fractures and occur between 1.5 and 10% of pelvic fractures ⁽³⁰⁾.

Anterior urethral injuries may be blunt (e.g., straddle injuries, where the urethra is crushed between the pubic bones and a fixed object) or penetrating, and the urethra may be lacerated, crushed, or disrupted ⁽³¹⁾.

The bulbar urethra is the most common site affected by blunt trauma. In bulbar injuries, the bulb is compressed against the pubic symphysis, resulting in rupture of the urethra at the site of compression ^(26, 28).

Possible mechanisms are straddle injuries or kicks to the perineum. A penile fracture can be complicated by a urethral injury in approximately 15% of cases. Penetrating anterior injuries are rare and are usually caused by gunshot wounds, stab wounds, dog bites, impalement of penile amputations ⁽³²⁻³⁴⁾.

Depending on the affected segment, penetrating injuries are usually associated with penile, testicular and/or pelvic injuries. Insertion of foreign bodies is another rare cause of anterior injury. It is usually a result of autoerotic stimulation or may be associated with psychiatric disorders ⁽³²⁻³⁴⁾.

Iatrogenic injury is the most common type of urethral trauma. The incidence of urethral injury during transurethral catheterization is 6.7 per 1,000 catheters inserted and can occur due to creation of a false passage by the tip of the catheter, inadvertent inflation of the anchoring balloon in the urethra or removal of the catheter with the anchoring balloon not fully deflated. A strict indication for every urethral catheterization is an important preventive measure. The

importance of catheter insertion training programs, to prevent urethral injury during transurethral catheterization, have been demonstrated ⁽³⁴⁻³⁷⁾.

Preliminary data suggest that guidewire led catheter insertion or use of a safety valve for balloon inflation may prevent urethral trauma in difficult catheterization cases. Instrumentation of the urethra (TURP, cystoscopy, etc.) can traumatize all segments of it. During penile prosthesis insertion (PPI), the risk of urethral perforation is 0.1-4%. Proximal urethral injuries are more common than distal ones ^(38, 39).

68.3 Female urethral injuries

Birth related injuries to the female urethra are rare and consist of a minor (peri)urethral lacerations during vaginal delivery. Pelvic fractures are the main cause of blunt trauma; however, PFUIs in females are rare and less common than in males. This is usually attributed to the flexibility provided by the vagina and the greater inherent elasticity of the female urethra, it may also be the result of less severe and more frequent stable pelvic fractures in females. In unstable pelvic fractures in females, a high suspicion for a urethral injury should be maintained ^(40, 41).

Female urethral injuries are classified into two types: longitudinal or partial (most frequent) injuries and transverse or complete injuries. Concomitant bladder or vaginal injury is possible; therefore, females are at risk of developing urinary incontinence and urethrovaginal fistula ^(40, 42).

Insertion of a synthetic sub-urethral sling for the treatment of female stress urinary incontinence is complicated by an intra-operative urethral injury in 0.2-2.5% of cases and is an important cause of iatrogenic urethral injury ⁽⁴³⁾.

68.4 Evaluation

68.4.1 Clinical signs

Blood at the meatus is the cardinal sign, but the absence of it doesn't rule out a urethral injury. Inability to void (with a palpable distended bladder) is another classic sign and is often associated with a complete rupture. Hematuria and pain on urination may be present in incomplete ruptures. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on the location and extent of the trauma. The presentation of these clinical symptoms may be delayed (> 1 hour) ^(42, 44).

Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases) and may reveal a 'high-riding' prostate, which is an unreliable finding. Failure to detect a rectal injury can cause significant morbidity and even mortality. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration. Another sign of urethral injury is difficulty or inability to pass a urethral catheter ^(42, 44, 45).

A female urethral injury should be suspected from the combination of an (unstable) pelvic fracture with blood at the vaginal introitus, vaginal laceration, haematuria, urethrorrhagia, labial

swelling, urinary retention or difficulties passing a urethral catheter. Vaginal examination is indicated to assess vaginal lacerations ⁽⁴⁶⁾.

68.4.2 Urethrography

Retrograde urethrography (RUG) is the standard in the early evaluation of a male urethral injury and is conducted by injecting 20-30 mL of contrast material while occluding the meatus. Films should be taken in a 30° oblique position ⁽⁴⁵⁾. Retrograde urethrography should be performed after pelvic or genital trauma especially when blood is seen at the urethral meatus ⁽⁴⁷⁾.

During RUG, any extravasation outside the urethra is pathognomonic for urethral injury. A typical image for incomplete rupture shows extravasation from the urethra which occurs while the bladder is still filling. A complete rupture is suggested by massive extravasation without bladder filling. Although RUG can reliably identify the site of injury (anterior vs. posterior), the distinction between a complete and partial rupture is not always clear. Therefore, any proposed classification system based on RUG is not reliable. In females, the short urethra and vulvar edema make adequate urethrography nearly impossible ^(42, 48).

Before deferred treatment, a combination of RUG and antegrade cystourethrography is the standard to evaluate the site and extent of the urethral stenosis and to evaluate the competence of the bladder neck ⁽⁴²⁾.

68.4.3 Cysto-urethroscopy

Flexible cystourethroscopy is a valuable alternative to diagnose an acute urethral injury and may distinguish between complete and partial rupture. Flexible cystourethroscopy is preferred to RUG in suspected penile fracture-associated urethral injury as RUG is associated with a high false-negative rate. In females, where the short urethra often precludes adequate radiological visualization, cystourethroscopy and vaginoscopy are the diagnostic modalities of choice. If before deferred treatment, the competence of the bladder neck is not clear upon antegrade cystourethrography, a suprapubic cystoscopy is advised ^(45, 48, 49).

68.4.4 Ultrasound and magnetic resonance imaging

In the acute phase, US scanning is used for guiding the placement of a suprapubic catheter ⁽⁵⁰⁾.

68.5 Management

68.5.1 Male anterior urethral injuries

68.5.1.1 Immediate exploration and urethral reconstruction

This is indicated for penile fracture-related injuries and non-life-threatening penetrating injuries. Small lacerations can be repaired by simple closure. Complete ruptures without extensive tissue loss are treated with an anastomotic repair. In the case of longer defects or apparent infection (particularly bite wounds), a staged repair with urethral marsupialization is needed ^(33, 34).

Penetrating injuries require peri- and postoperative antibiotic treatment. The role of immediate urethroplasty in blunt injuries is controversial. Patients who underwent immediate urethroplasty had a failure rate that was not significantly different compared to those who underwent delayed urethroplasty after initial suprapubic diversion. The time to spontaneous voiding was significantly shorter in the immediate urethroplasty group ⁽⁵¹⁾.

A stricture rate of 14.4% following immediate repair has been reported based on 23 studies with a total of 591 patients. An analysis of direct comparative studies showed a composite stricture rate of 20% for immediate repair vs. 44.2% for early endoscopic re-alignment, but at the expense of longer hospital stays and increased blood loss ⁽⁵²⁾.

Perforation of the distal urethra during penile prosthesis insertion needs to be repaired over a catheter; in this instance, the initial procedure should be abandoned ⁽⁵³⁾.

68.5.1.2 Urinary diversion

Blunt anterior urethral injuries are associated with spongiosal contusion. Evaluation of the limits of urethral debridement in the acute phase might be difficult and as a consequence, it is reasonable to start with urinary diversion only ⁽⁵⁴⁾.

If urinary diversion is performed, the therapeutic options are suprapubic diversion or a trial of early endoscopic re-alignment with transurethral catheterization ⁽⁵⁴⁾, there is conflicting evidence as to which intervention is superior ⁽⁴⁷⁾.

Urinary diversion is maintained for one to two weeks for partial ruptures and three weeks for complete ruptures. Satisfactory urethral luminal recanalization may occur in up to 68% after partial ruptures but is rare (14%) after complete ruptures ⁽⁴⁷⁾.

A review of 49 Chinese studies (1,015 patients), reported a 57% success rate for endoscopic re-alignment of blunt anterior injuries ⁽⁵²⁾. The wide range in success rate most likely reflects a mix of partial and complete ruptures which was not further specified in the review. Transurethral or suprapubic urinary diversion are treatment options for iatrogenic or life-threatening penetrating injuries. Minor iatrogenic urethral injuries and urethral contusions do not require urinary diversion ^(15, 55).

68.5.2 Female urethral injuries

Emergency room management of urethral injuries in females is the same as in males; however, subsequent management differs. Treatment options are:

- Early repair (less than or equal to seven days): Complication rate is the lowest with the early repair; therefore, this strategy is preferred once the patient is hemodynamically stable.
- Delayed repair (greater than seven days): Delayed repair often requires complex abdominal or combined abdominal-vaginal reconstruction with an elevated risk of urinary incontinence and vaginal stenosis ⁽⁴⁰⁾.

The approach (vaginal, abdominal or combined) for early repair depends on the location of the injury. Distal urethral injuries can be left hypospadiac since they do not disrupt the sphincter mechanism, but a concomitant vaginal laceration must be closed. In the case of urethral injury during synthetic sub-urethral sling insertion, immediate repair is warranted with the abortion of sling insertion ^(43, 45, 48).

68.6 Summary of Guidelines for the Evaluation and Management of Urethral Trauma

Table 84: Guidelines for Evaluation and Management of Urethral Trauma

Guidelines	Strength Rating
1. Good training of urinary catheter insertion for persons involved in urethral catheterization can reduce the rate of complications	Strong
2. Retrograde urethrography should be done for patients with blood at the urethral meatus after pelvic trauma	Strong
3. Male urethral injury is detected as contrast extravasation during urethrography or as a mucosal laceration during cystourethroscopy	Strong
4. Voiding cystourethrography can miss up to 50% of female urethral injury	Strong
5. Female urethral injuries should be assessed with combined cystourethroscopy and vaginoscopy	Weak
6. During emergency laparotomy, if an urethral injury is suspected, it should be investigated directly whenever feasible	Strong
7. Transurethral or suprapubic urinary diversion are the treatment options for iatrogenic anterior urethral injuries	Weak
8. With urinary diversion, urethral luminal re-canalization will succeed in up to 68% of cases after partial blunt anterior urethral ruptures	Weak
9. Complete blunt anterior urethral ruptures cannot be cured with urinary diversion alone, and urethroplasty is mandatory.	Strong
10. For complete blunt anterior urethral rupture, immediate and delayed urethroplasty has equal success rates.	Weak
11. Type of urethral reconstruction should be considered according to the length of the urethral stricture. Urethral strictures longer than 3 cm are suitable for augmented urethral reconstruction.	Weak

Guidelines	Strength Rating
12. Repetitive endoscopic treatments after failed re-alignment delay the time to definitive cure and increase the incidence of adverse events	Weak
13. 13. Clinicians should monitor patients for complications (e.g., stricture formation, erectile dysfunction, incontinence) for at least one year following urethral injury.	Weak

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69 Posterior urethral injury (PUI)

69.1 Anatomical consideration

69.1.1 Posterior urethra is the sphincteric portion of the urethra and it is not covered by the corpus spongiosum.

It extends from the bladder neck to the perineal membrane.

It includes prostatic and membranous urethra.

69.1.2 Prostatic urethra:

In adults, it is about 3 cm in length

It extends from the bladder neck till the upper border of the Urogenital diaphragm (UGD)

The prostate lies deep in the pelvis, retropubic, and its apex is located at the lower border of pubic bone, while in children, it is small and located in the retropubic space at the upper border of pubic bone.

69.1.3 Membranous urethra:

In adults, it is about 2 cm and it's devoid of any cover.

It is located within the urogenital diaphragm.

It starts from the anterior surface of the prostate near to the apex to the lower end of UGD

It is surrounded by inner smooth muscle and outer striated Rhabdosphincter (external urinary sphincter).

Oelrich stated that the prostate occupies the upper one third the length of urethra that extends from bladder neck to the inferior border of UGD (posterior urethra) in neonates and infants. By process of growing and mild development of the external sphincter, the prostate occupies two third of this length while in adult, with well-development of the prostate and maturation of externa sphincter, the prostate occupies the whole length above UGD and the bladder, the prostate and the UGD act as one unit.

Khan et al stated that there is a part of the urethra below the UGD and it is not covered by corpus spongiosum like the anterior urethra and so it is the inferior extension of membranous

urethra that is called infra-diaphragmatic portion of the membranous urethra or the bare area of the urethra.

Also, in the modern anatomy of UGD, there is no superior fascia of UGD and only the inferior fascia covers the UGD called perineal membrane

Also, the external sphincter is not oriented in transverse fashion but in a vertical one to reach the prostate and the bladder base, this explains why in children the injury occurs to the supradiaphragmatic urethra while in adult occurs to infra-diaphragmatic urethra.

Parts of membranous urethra are:

- Supra-diaphragmatic
- Intra-diaphragmatic
- Infra-diaphragmatic

Based on these anatomical considerations, you must consider the following:

In neonates and children, the most common site of injury of the posterior urethra is the supradiaphragmatic urethra as well as the bladder as it is exposed directly to the upper border of the symphysis pubis. This injury is usually in the form of:

- Open book injury: extends vertically from the anterior bladder wall to the anterior wall of the prostate and to the urethra.
- Uncommonly it may occur in a transverse fashion that result in complete avulsion of the bladder from the prostate or transprostatic injury or in very conditions, double level injury compromising complete separation of the prostate from the bladder above and the urethra below.

In adults, usually the injury occurs infra-diaphragmatically in the infra-diaphragmatic urethra at the bulbo-membranous junction with sparing of the external urinary sphincter and it may extend to the bulbar urethra. In rare conditions, the injury associated with pelvic fractures may injure the bulbar urethra only.

69.2 Causes of posterior urethral injury

It may be blunt trauma or penetrating trauma

- **Blunt trauma:** is associated with anterior pelvic ring fractures such as fracture of pubic bone or pelvic diastasis (wide separation of symphysis pubis) or stove in fractures (tetrameric fractures of the pubic bone) usually associated with high risk injury of the lower urinary tract especially the posterior urethra. This is called stable pelvic fracture.
- **Disruption of anterior pelvic ring:** as well as the posterior pelvic ring, such as sacroiliac ligament laxation or separation is usually associated with high incidence of urethral injury. This is called unstable pelvic fractures or malgaigne fracture.

N.B: It is well known that the elasticity or the young's modulus of the pelvic bone is higher than the intrapelvic soft tissue. So, with anteroposterior injury of the pelvis, the pubic bone is pushed posteriorly, as well as the soft tissue behind it towards the sacrum, then it will return anteriorly by its elasticity, however, bone return back to its normal position faster than soft tissue, this results in tears of all ligaments as the pubo-prostatic ligament and other soft tissue due to traction force.

So, the presence of undisplaced anterior pelvic ring fracture doesn't mean absence of associated injuries and you must do ascending urethrogram before any catheterization in any patient with anterior pelvic ring fracture.

- **Penetrating injury:** Gun shots, transurethral resection of the prostate (TURP)

69.3 Incidence:

10 -15 % of pelvic fractures are associated with urethral injuries while 85- 90% of posterior urethral injuries are associated with pelvic fractures.

69.4 Signs and symptoms:

- Bleeding at the external urinary meatus is the pathognomonic sign of posterior urethral injury.
- Hematuria
- Inability to void with suprapubic fullness

69.5 Examination:

With any road traffic accident, car or train accident with the suspicion of lower urinary tract injury, you must do the following:

1. Assessment of the general condition
2. Examination of bony pelvis by:
3. Compression of both iliac bones medially
4. Palpation of symphysis pubis to detect its wide separation or stove in fracture.
5. Look for unequal lengths of the lower limbs that may be associated with vertical sheer of the bony pelvis with unstable pelvic fracture.
6. Inspect, palpate and percuss the renal angle to detect retroperitoneal hematoma.
7. Inspect and examine the perineum, rectum and scrotum (vagina in females) for any associated injuries.
8. PR examination must be done to detect:

- The integrity of anal sphincters that denote good intact pelvic nerve.
- The presence or absence of the prostate as it is sometimes displaced upward and backward in association with the urethral injury as it is displaced by a pelvic hematoma that gives the sensation of a boggy mass on examination.

9. Bimanual examination to detect: full bladder, pie in sky bladder or expanded large sized pelvic floor hematoma.

69.6 Lab investigations:

As in all emergency cases, a blood sample must be taken for all routine lab investigations especially ABO group, CBC, Blood urea and creatinine.

69.7 Radiological examination:

There are situations where you face a poly-trauma patient and there is inadequacy of radiological equipment in your hospital, so:

69.7.1 If the patient is stable with good vital signs:

- Do plain x-ray first for the bony pelvis or CT to detect the type and the nature of the pelvic fracture.
- Then, if you have a suspicion of associated urethral injury, do an ascending urethrogram before any catheterization.
- The orthopedic state of the patient may not allow the steep lateral position to do the ascending urethrogram so the C-arm is a good choice to do a urethrogram without mobilization of the patient.
- If the urethra is intact on the ascending urethrogram insert a urethral catheter and do ascending cystogram with post voiding film to detect associated posterior bladder wall injury.

69.7.2 Unstable patients as well as poly-trauma patients

You must resuscitate them first and maintain their vital signs then you may be faced with one of the following probabilities:

- The patient passed to the OR for emergency control of their bleeding from the associated injury as ruptured spleen or liver. So, you can take a look to inspect the distended bladder as well as the pelvic hematoma and just insert the suprapubic tube and drain without any disturbance from the pelvic floor hematoma.
- If the patient resuscitated and the vital signs recover inside the OR theatre, you could do an ascending urethrogram under fluoroscopy before catheterization to detect the presence of associated urethral injury.

N.B:

- The direction of extravasated dye doesn't denote the site of injury as the dye pass through the weakest lacerated facial planes.
- The degree of the trauma to the lower urinary tract is correlated with the direction and the force of the trauma itself.

69.7.3 Ascending urethrogram:

The cornerstone for the diagnosis of any urethral injury is the ascending urethrogram in steep lateral position, which means:

- a) The patient is tilted 30 degrees on x-ray table with a supporting cushion.
- b) The lower hip and knee must be flexed while the upper hip and knee is in normal extended position.

-Stretch the penis towards the anterior superior iliac spine of the patient and insert a small part of a 10 french polyethylene catheter stem about 3 cm (till the fossa navicularis) after lubrication using sterile KY gel,

-Then press hold the catheter in the fossa navicularis by hand and inject 15 cc of the contrast dye slowly to fill the anterior urethra

-then ask the patient to relax the anal sphincters with simultaneous injection of 5 cc of contrast to fill the posterior urethra with simultaneous x-ray exposure.

69.8 Classification of posterior urethral injuries

Depending on the ascending urethrogram, urethral injuries could be classified into:

1-Colapinto-McCallum:

They classified posterior urethral injury into 3 types:

Type 1: in which puboprostatic ligaments are torn and the prostate and the bladder are displaced upward and backward causing stretching of intact urethra

Type 2: Injury of the urethra at the prostatomembranous junction with intact urogenital diaphragm resulting in intrapelvic extravasation of the dye.

Type 3: Injury of the posterior urethra with disruption of the urogenital diaphragm and the extravasation of the dye found intrapelvic as well as in the perineum.

2-Goldman classification:

He differentiated between the injury of the posterior urethra to above and below an intact urogenital diaphragm and he added a separate type including the bladder neck injury associated with the anterior bladder wall injury (vertical tear with the presence of the extra peritoneal extravasation as well as around the bladder neck). Also, he included bulbar urethral injury in his classification as well as bladder base injury that mimic posterior urethral injury.

3- some authors classified urethral injury as stretch, partial or incomplete or complete injury for simplicity where:

- a- **Urethral stretch:** the dye reaches the bladder without any extravasation, but with elongation of the urethral length.
- b- **Partial injury:** the dye reaches the bladder on ascending urethrogram with limited extravasation at the site of injury.
- c- **Complete injury:** of the urethra, the dye never reaches the urinary bladder and extravasation occurs which may be completely intrapelvic or perineal only or both (intra-pelvic and perineal).

Direction of extravasation on ascending urethrogram:

It depends on:

- Site of injury
- Integrity of UGD
- Opened fascial planes with trauma

So, the results may be;

- Intra-pelvic extravasation due to supra-diaphragmatic urethral injury with intact UGD
- Perineal or extra-pelvic extravasation due to infra-diaphragmatic urethral injury with intact UGD
- Combined both intra and extra-pelvic extravasation with any urethral injury associated with disrupted UGD

You must know that:

- The dye may not reach to the bladder due to external urinary muscle spasm from associated pain from trauma or fracture itself so , you must look to the shape of bulbar cone , is it is smooth taper end as normal or shoulder shape
- With complete separation of prostate and bladder from UGD it gives a picture of pie-in the sky appearance of the urinary bladder in the cystogram

69.9 Initial management of posterior urethral injuries:

There are controversies regarding initial management of posterior urethral injuries either early or delayed management

It includes the following:

- 1- Urethral stretch: no treatment or urethral catheter if the bleeding is considerable
- 2- Partial injuries: just do SP tube or endoscopic urethral catheter insertion with SP tube for 3 weeks

3- Complete injuries: one of the following lines of treatment:

69.9.1 Suprapubic tube alone:

It is just insertion of suprapubic catheter surgically with a drain without any disturbance of the pelvic floor hematoma.

In this technique, long segment pelvic fracture distraction defect is common (PFDD) with a lower incidence of incontinence and impotence.

69.9.2 Immediate suture repair

It is only indicated in the following situations:

- Any type of bladder neck injuries (partial injury associated with anterior bladder wall injury or complete avulsion of the bladder neck).
- Trans-prostatic urethral injury in children
- Associated rectal injuries needs colostomy

69.9.3 Immediate realignment either through surgery or endoscopy.

It is only indicated in stable patient with supra-diaphragmatic urethral injury and intact UGD

It is contraindicated in patient with disrupted UGD as it will result in prolapse of the prostate through the perineum

Usually, this technique is associated with a high incidence of incontinence and impotence due to disturbed pelvic floor hematoma to visualize both ends of urethra.

It also results in short pelvic fracture distraction defect or urethral stricture.

It can be performed by sound to sound, sound to finger or catheter to catheter

Trial of fixation of the prostate to the intact UGD to maintain realignment can be done by suture of the its capsule to the periosteum of the pubic bone, pass the suture through an intact UGD to the perineum or applying weight traction on the urethral catheter

The catheter is left for 6-8 weeks and closed SP tube for another one week to be sure from good micturition

69.10 Recommendations for the evaluation and management of urethral trauma

Table 85: Recommendations for evaluation and management of urethral trauma

<i>Recommendation</i>	<i>Strength Rating</i>
1. Provide appropriate training to reduce the risk of traumatic catheterization	<i>Strong</i>
2. Evaluate male urethral injuries with flexible cysto-urethroscopy and/or retrograde urethrography	<i>Strong</i>
3. Evaluate female urethral injuries with cysto-urethroscopy and vaginoscopy	<i>Strong</i>
4. Treat iatrogenic anterior urethral injuries by suprapubic or urethral catheterisation	<i>Strong</i>
5. Treat partial blunt anterior urethral injuries by suprapubic or urethral catheterisation	<i>Strong</i>
6. Treat complete blunt anterior urethral injuries in males by immediate urethroplasty	<i>Weak</i>
7. Treat pelvic fracture urethral injuries (PFUIs) in hemodynamically unstable patients by transurethral or suprapubic catheterisation initially	<i>Strong</i>
8. Perform early endoscopic re-alignment in male PFUIs when feasible	<i>Weak</i>
9. Do not repeat endoscopic treatments after failed re-alignment for male PFUIs	<i>Strong</i>
10. Treat partial posterior urethral injuries initially by suprapubic or transurethral catheter	<i>Strong</i>
11. Do not perform immediate urethroplasty (<48hours) in male PFUIs	<i>Strong</i>
12. Perform early urethroplasty (two days to six weeks) for female PFUIs with complete disruption in selected patients (stable, short gap, soft perineum, lithotomy position possible)	<i>Weak</i>
13. Manage complete posterior urethral disruption in male PFUIs with suprapubic diversion and deferred (at least three months) urethroplasty	<i>Strong</i>
14. Perform early repair (within seven days) for female PFUIs (not delayed repair or early re-alignment)	<i>Strong</i>

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70 Bladder trauma

70.1 Introduction

Bladder trauma can be caused by a direct blow to a distended bladder, high energy injury which disrupts the pelvis, penetrating, and iatrogenic injuries. Bladder injuries are divided into broad categories of extraperitoneal (EP), intraperitoneal (IP), or combined injuries which guide the management plan. Injuries to the bladder occur in up to 10% of abdominal trauma and may be associated with significant morbidity and mortality (10% to 22%).⁽¹⁾

70.2 Etiology

Motor vehicle accidents are the most common cause of blunt bladder injury, followed by falls and other accidents. Extraperitoneal injury is almost always associated with pelvic fractures^(2,3). The highest risk of bladder injury was found in disruptions of the pelvic circle with displacement > 1 cm, diastasis of the pubic symphysis > 1 cm, and pubic rami fractures^(4,5). Intraperitoneal injury is caused by a sudden rise in intravesical pressure of a distended bladder, secondary to a blow to the pelvis or lower abdomen. The bladder dome is the weakest point of the bladder and ruptures will usually occur there⁽⁵⁾.

There are challenges associated with consistent results regarding bladder trauma. There is evidence that approximately 85% of bladder injuries result from blunt trauma, while incident rates can account for up to 51% of injuries result from penetrating trauma.^(6,7,8) Other less common etiologies of bladder trauma include iatrogenic injuries most commonly during obstetric, gynecologic, or urologic procedures.^(7,9)

70.3 Epidemiology

Extraperitoneal (EP) and intraperitoneal (IP) and injuries occur with blunt and penetrating traumas, iatrogenic bladder injuries are well-documented as well. EP bladder injuries account for 60% of bladder traumas, while 30% are intraperitoneal, and 10% are combined.⁽¹⁰⁾ Iatrogenic IP bladder injuries are not uncommon. The bladder is the most frequently injured organ in obstetric/gynecologic procedures such as cesarean section and hysterectomies, with an incidence of 13.8 cases per 1000 procedures.⁽¹¹⁾

70.4 History and Physical Examination

Bladder trauma can be suspected in the presence of pelvic instability, blood at the meatus, significant abdominal and pelvic pain, suprapubic tenderness, high riding prostate, and gross hematuria. Peritoneal signs such as rigidity, guarding, and rebound tenderness should raise the suspicion not only for perforated viscus in the abdomen but also intraperitoneal bladder injury.

Evaluation of the genitals may reveal blood at the urethral meatus, in which case urethral injury needs to be ruled out before inserting an indwelling catheter. A high riding prostate on a rectal exam also concerns for urethral injury. Gross hematuria is seen in 67% to 95% of cases and is the most classical symptom associated with bladder trauma. ⁽¹²⁾

70.5 Evaluation

Basic labs such as complete blood count, metabolic panel, coagulation panel, and urinalysis should be obtained as part of the trauma work-up. Retrograde cystography, either computed tomography (CT) or conventional X-ray, is indicated for hemodynamically stable patients with gross hematuria, blood at the meatus, inability to void, pelvic fracture with microscopic hematuria, or penetrating injury to the pelvis, buttock, or lower abdomen. ⁽¹³⁾

According to the European Association of Urology guidelines for urogenital trauma, CT cystography is preferred over traditional X-ray cystography due to rapid turnover time and convenience and it is superior in detecting other intra-abdominal processes and bony fragments within the bladder ⁽¹⁴⁾

Imaging findings associated with EP bladder trauma are extravasation of contrast around the base of the bladder confined to the perivesical space and extravasation into the thighs, penis, perineum, or anterior abdominal wall if the urogenital fascia is violated in a complex injury. In IP bladder trauma, contrast extravasates into the peritoneal cavity, outlining the loops of bowel and filling paracolic gutters. ⁽¹³⁾

70.6 Treatment / Management

According to the American Urological Association (AUA) and EAU guidelines for bladder rupture,

70.6.1 Conservative management

Conservative treatment, which comprises of clinical observation, continuous bladder drainage and antibiotic prophylaxis ⁽¹⁵⁾, is the standard treatment for an uncomplicated extraperitoneal injury due to blunt ^(16,17,18) or iatrogenic trauma ⁽¹⁵⁾.

Conservative treatment is indicated for uncomplicated intraperitoneal injury after TURBT or other operations, but only in the absence of peritonitis and ileus ^(19,20). Placement of an intraperitoneal drain is advocated, especially when the lesion is larger ^(21,22). Penetrating extraperitoneal bladder injuries (only if minor and isolated) can also be managed conservatively ^(23,24,25).

70.6.2 Surgical management

Bladder closure is performed with absorbable sutures ^(23,26).

70.6.2.1 Blunt non-iatrogenic trauma

Most extraperitoneal ruptures can be treated conservatively, however bladder neck involvement, bone fragments in the bladder wall, concomitant rectal or vaginal injury or entrapment of the bladder wall necessitate surgical intervention ⁽¹⁶⁾. There is an increasing trend to treat pelvic ring fractures with open stabilisation and internal fixation. ⁽²⁷⁾ Likewise, an extraperitoneal rupture should be sutured during surgical exploration for other injuries, in order to decrease the risk of complications and to reduce recovery time ⁽²⁸⁾.

Intraperitoneal ruptures should always be managed by surgical repair ^(16,17) because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death ⁽²⁹⁾. Abdominal organs should be inspected for possible associated injuries and urinomas must be drained if detected. Laparoscopic suturing of the intraperitoneal rupture is also possible ⁽²³⁾.

70.6.2.2 Penetrating non-iatrogenic trauma

Penetrating bladder injury is managed by emergency exploration, debridement of devitalised bladder wall and primary bladder repair ^(31,32). A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters ^(23,31). In gunshot wounds, there is a strong association with intestinal and rectal injuries, usually requiring faecal diversion ^(31,24). Most gunshot wounds are associated with two transmural injuries (entry and exit wounds) and the bladder should be carefully checked for these two lesions ⁽³¹⁾. As the penetrating agent (bullet, knife) is not sterile, antibiotic treatment is advised ⁽³²⁾.

70.6.2.3 Iatrogenic bladder trauma

Perforations recognised intra-operatively are primarily closed ⁽³³⁾. Bladder injuries not recognised during surgery or internal injuries should be managed according to their location. The standard of care for intraperitoneal injuries is surgical exploration and repair ⁽³⁴⁾. If surgical exploration is performed after TURBT, the bowel must be inspected to rule out concomitant injury ⁽³⁵⁾. For extraperitoneal injuries, exploration is only needed for perforations complicated by symptomatic extravescical collections. It requires drainage of the collection, with or without closure of the perforation ⁽³⁶⁾. If bladder perforation is encountered during mid-urethral sling or transvaginal mesh procedures, sling re-insertion and urethral catheterisation (two to seven days) should be performed ⁽³⁷⁾.

70.6.3 Follow-up

After operative repair of a simple injury in a healthy patient, the catheter can be removed after five to ten days without cystography ^(38,39). In cases of complex injury (trigone involvement, ureteric re-implantation) or risk factors of impaired wound healing (e.g. steroids, malnutrition) cystography is advised ^(163,207). For conservatively treated internal IBT, catheter drainage, lasting five days for extraperitoneal and seven days for intraperitoneal perforations, is proposed ^(41,42).

The first cystography is planned approximately ten days after injury ⁽²³⁾. In case of ongoing leakage, cystoscopy should be performed to rule out bony fragments in the bladder, and a second cystography is warranted one week later ⁽¹⁶⁾

70.6.4 Recommendations for management of Bladder Injury

Table 86: Recommendations for management of Bladder Injury

<i>Recommendation</i>	<i>Strength Rating</i>
1. Perform cystoscopy in the presence of visible hematuria and pelvic fracture	<i>Strong</i>
2. Perform cystoscopy in case of suspected iatrogenic bladder injury in the post-operative setting	<i>Strong</i>
3. Perform cystoscopy with active retrograde filling of the bladder with diffuse contrast (300-350 ML)	<i>Strong</i>
4. Perform cystoscopy to rule out bladder injury during retropubic sub0urethral sling procedures	<i>Strong</i>
5. Manage uncomplicated blunt extraperitoneal bladder injuries conservatively	<i>Weak</i>
6. Manage blunt extraperitoneal bladder injuries operatively in cases of bladder neck involvement and/or associated injuries that require surgical intervention	<i>Strong</i>
7. Manage blunt intraperitoneal injuries by surgical exploration and repair	<i>Strong</i>
8. Manage small uncomplicated intraperitoneal bladder injuries during endoscopic procedures conservatively	<i>Weak</i>
9. Perform cystoscopy to assess bladder wall healing after repair of a complex injury in case of risk factors for wound healing	<i>Strong</i>

70.7 Differential Diagnosis

- Penile trauma
- Testicular trauma
- Vaginal trauma
- Urethral trauma
- Pelvic fractures – acetabular, open book, straddle, or pelvic avulsion
- Retroperitoneal hemorrhage
- Renal trauma

- Ureteral trauma

70.8 Prognosis

Patients with bladder injuries may also present with a wide variety of concurrent traumatic injuries. A single-center retrospective study at a level I trauma center found a mortality rate of 10.8% among patients with bladder rupture undergoing laparotomy for trauma.[40] Untreated bladder rupture can lead to complications such as peritonitis, severe sepsis, and fistulas. Successful management requires timely evaluation, accurate diagnosis, and proper management based on the location and severity of the rupture. Most patients recover normal bladder function. Severe trauma involving the neck of the bladder, the urethra, and/or pelvic floor muscles may lead to urinary incontinence that may or may not be amenable to surgery.

70.9 Complications

- Urinary incontinence
- Wound dehiscence; drainage from wound site should not be confused with urine leak
- Decreased bladder capacity from over-debridement
- Persistent urinary extravasation
- Hemorrhage can occur with violation of pelvic hematoma
- Pelvic abscess can develop from infected hematoma
- Intraabdominal infection
- Fistula
- Urinary tract infection
- Urinary urgency

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Pediatric Congenital Anomalies



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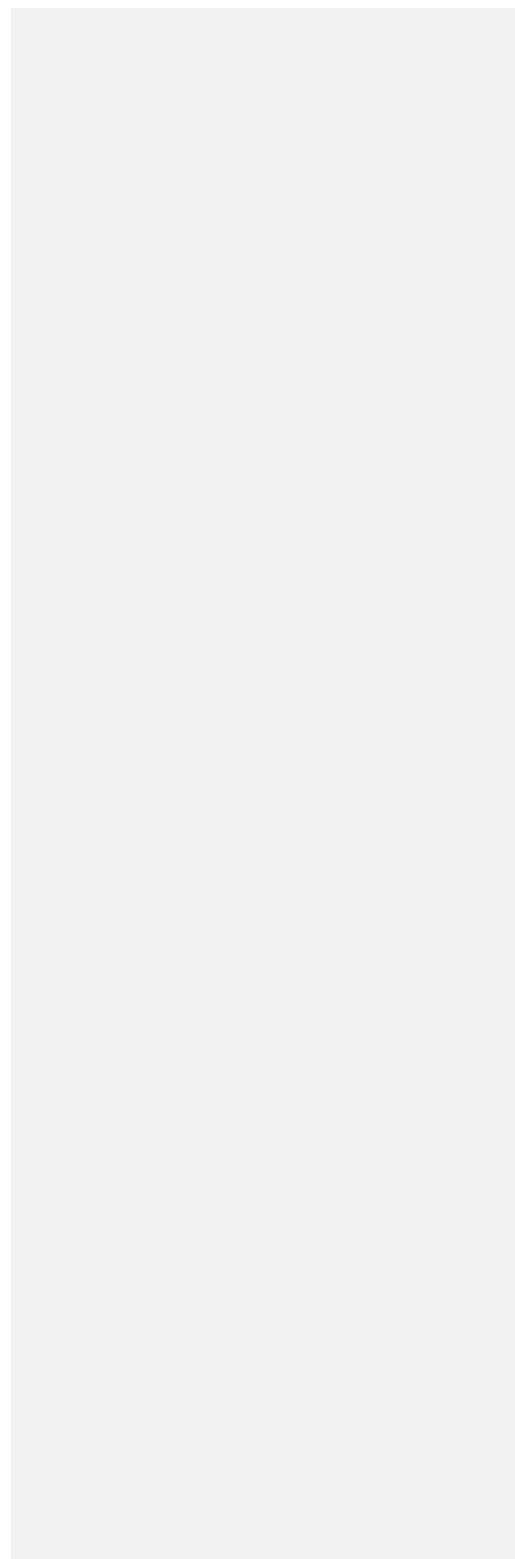


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71 Abbreviations

AAP	American Academy of Pediatrics
AUA	American Urological Association
ARM	Anorectal Malformation
BBD	Bladder And Bowel Dysfunction
BOO	Bladder Outlet Obstruction
CIS	Carcinoma In Situ
CAIS	Complete Androgen Insensitivity Syndrome
CAH	Congenital Adrenal Hyperplasia
CAP	Continuous Antibiotic Prophylaxis
DO	Detrusor Overactivity
DMSA	Dimercaptosuccinic Acid
DSD	Disorders Of Sex Development
EAU	European Association of Urology
ESPU	European Association of Pediatric Urology
5Fr	Five French
GnRH	Gonadotrophin Releasing Hormone
hCG	Human Chorionic Gonadotrophin

HSP	Henoch-Schonlein purpura
IV	Intravenous
MACE	Malone Antegrade Continence Enema
MAGPI	Meatoplasty And Glans Plasty
MIP	Megameatus Intact Prepuce
MCUG	Micturating Cystourethrogram
MGD	Mixed Gonadal Dysgenesis
MRI	Magnetic resonance imaging
PAIS	Partial Androgen Insensitivity Syndrome
PUV	Posterior Urethral Valves
US	Ultrasound
UDT	Undescended Testis
UPJ	Ureteropelvic Junction
UVJ	Ureterovesical Junction
UTIs	Urinary Tract Infections
VUR	Vesicoureteral Reflux
VUDS	Videourodynamics
VCUG	Voiding Cystourethography
WBCs	White Blood Cells

72 Introduction:

This guideline document is based mainly on the guidelines compiled by the European Association of Urology (EAU), The European Association of Pediatric Urology (ESPU) as well as the American Urological Association (AUA) guidelines. It is not intended to cover the entire field of pediatric urology but rather a number of common clinical pathologies in pediatric urological practice. It integrates some local experts' opinions based on Egyptian healthcare practice and socioeconomic circumstances.

73 SCROTAL:

73.1 Cryptorchidism or Undescended testis*:

A true undescended testis is on its normal path of descent but is halted on its way down to the scrotum. Depending on the location, the testes may be palpable or not, as in the case of testes arrested in the inguinal canal.

Cryptorchidism or undescended testis (UDT) is one of the most common pediatric disorders identified at birth. The main reasons for treatment are increased risks of impairment of fertility potential and testicular malignancy. Successful scrotal relocation of the testis (orchiopexy), may reduce but does not totally prevent these potential long-term sequelae.

The most useful classification of undescended testes is into palpable and non-palpable testes. Approximately 80% of all UDT are palpable.

The current standard of therapy according to the European and North American guidelines is orchiopexy. Hormonal therapy which played an important role in the past, has very few advocates.

73.2 Diagnosis:

1. History obtained from obstetric notes at time of delivery.
2. Scrotal palpation of testes for quality (size and consistence) and position.
3. Primary care providers (pediatrician, family physician) should refer infants with a history of cryptorchidism (detected at birth), who do not have spontaneous testicular descent by six months to an appropriate surgical specialist for timely evaluation.
4. All phenotypic male newborns with bilateral, nonpalpable testes should be evaluated for possible DSD (disorder of sexual development), particularly those with severe types of hypospadias.
5. Imaging studies cannot determine with certainty that a testis is present or not. Ultrasound (US) lacks the diagnostic sensitivity to detect the testis confidently or establish the absence of an intra-abdominal testis. Consequently, the use of different imaging modalities, such as US or Magnetic resonance imaging (MRI), for undescended testes is limited and only recommended in specific and selected clinical scenarios (e.g. identification of Müllerian structures in cases with suspicion of DSDs).
6. In boys with retractile testes, the position of the testes should be monitored annually to check for secondary reascent.

73.3 Management:

73.3.1 Undescended Testes:

Timing of surgery: Because undescended testes rarely descend after the age of 6 months, treatment should be started at that age, and should be finished by twelve months, or eighteen months at the latest, to avoid progressive loss of germ cells and Leydig cells.

Hormonal treatment: most of the studies on hormonal treatment have been of poor quality, with heterogeneous and mixed patient populations, testis location, schedules and dosages of hormonal administration. Additionally, long-term data are almost completely lacking. Short-term side effects of hormonal treatment include increased scrotal erythema and pigmentation, the general consensus is that hormonal treatment is not recommended. ⁽¹⁾

Human chorionic gonadotropin Human chorionic gonadotropin stimulates endogenous testosterone production and is administered by intramuscular injection. Several dose and administration schedules are reported. There is no proven difference between 1.5 IU and weight-based doses up to 3.0 IU every other day for fourteen days. Similar response rates were achieved with 500 IU once weekly and 1.50 IU three times weekly. However, there is evidence that dosing frequency might affect testicular descent rates. Fewer lower dose injections per week for five weeks seem to be superior to one higher dose every seven to ten days for three weeks with regard to testicular descent.

Gonadotropin-releasing hormone Gonadotropin-releasing hormone analogues (e.g., buserelin and gonadorelin) are available as nasal sprays, thus avoiding painful intramuscular injections. A typical dosage regimen consists of 1.2 mg per day in three divided doses, for four weeks. Success rates are wide ranging, from 9 to 60%, due to multiple treatment strategies and heterogeneous patient populations

Medical therapy for fertility potential Hormonal treatment may improve fertility indices and therefore serve as an additional tool to orchidopexy. There is no difference in treatment with GnRH before (neo-adjuvant) or after (adjuvant) surgical orchidolysis and orchidopexy in terms of increasing fertility index, which may be a predictor for fertility later in life. It is still unknown whether this effect on testicular histology persists into adulthood but it has been shown that men who were treated in childhood with buserelin had better semen analyses compared with men who had childhood orchidopexy alone or placebo treatment ⁽¹⁾

It is reported that hCG treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells, including acute inflammatory changes in the testes and reduced testicular volume in adulthood.

Palpable undescended testes: Surgical management (orchidofunicolysis via inguinal or scrotal approach) is the mainstay of treatment.

Inguinal orchidopexy Inguinal orchidopexy is a widely-used technique with a high success rate of up to 92%. Important steps include mobilisation of the testis and spermatic cord to the level of the internal inguinal ring, with dissection and division of all cremasteric fibres, to prevent secondary retraction and detachment of the gubernaculum. The patent processus vaginalis needs to be ligated proximally at the level of the internal ring, because an unidentified or inadequately repaired patent processus vaginalis is an important factor leading to failure of orchidopexy]. Any additional pathology has to be taken care of, such as removal of an appendix testis (hydatid of Morgagni). At this moment, the size of the testis can be measured and the connection of the epididymis to the testis can be judged and described in the protocol. Some boys have a significant dissociation between testis and epididymis which is prognostically bad for fertility. Finally, the mobilised testicle needs to be placed in a sub-dartos pouch within the hemi-scrotum without any tension. In case the length achieved using the above-mentioned technique is still inadequate, the Prentiss manoeuvre, which consists of dividing the inferior epigastric vessels and transposing the spermatic cord medially, in order to provide a straight course to the scrotum, might be an option. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature. ⁽²⁾

Scrotal orchidopexy Low-positioned, palpable undescended testis can be fixed through a scrotal incision including division of the gubernaculum, and the processus vaginalis needs to be probed to check for patency. Otherwise, fixation in the scrotum is carried out correspondingly to the inguinal approach. In up to 20% of cases, an inguinal incision will be compulsory to correct an associated inguinal hernia. Any testicular or epididymal appendages can be easily identified and removed. A systematic review shows that the overall success rates ranged from 88 to 100%, with rates of recurrence and post-operative testicular atrophy or hypotrophy < 1%.⁽³⁾

Non-palpable testes (20% of undescended testes, the aim is to determine whether a testis is present or not. If a testis is found, the decision has to be made to remove it or bring it down to the scrotum. It is essential to have a thorough re-examination under general anesthesia, since a previously non-palpable testis might be identifiable and subsequently change the surgical approach to standard inguinal orchidopexy. Otherwise, the easiest and most accurate way to locate an intra-abdominal testis is diagnostic **laparoscopy**. Subsequent removal or orchidolysis and orchidopexy can be carried out using laparoscopy and a scrotal incision. If an ipsilateral scrotal nubbin is suspected, and contralateral compensatory testicular hypertrophy is present, a scrotal incision with removal of the nubbin, thus confirming the vanishing testis, is an option avoiding the need for laparoscopy. ⁽³⁻⁵⁾

Among the 20% of non-palpable testes, 50-60% are intra-abdominal, canalicular or peeping (right inside the internal inguinal ring). The remaining 20% are absent and 30% are atrophic or rudimentary. Orchidopexy of an intra-abdominal testis is a surgical challenge. Usually, testes lying > 2 cm above the internal inguinal ring may not reach the scrotum without division of the testicular vessels. Under such circumstances, a Fowler-Stephens orchidopexy may be an option. The key feature of the procedure is proximal transection of the testicular vessels, with

conservation of the collateral arterial blood supply, via the deferential artery and cremasteric vessels. Transection of the testicular vessels puts the testis at risk of hypotrophy or atrophy if the collateral blood supply is insufficient. The testicular survival rate in the one-stage Fowler-Stephens technique varies between 50 and 60%, with success rates increasing up to 90% for the two-stage procedure. The advantages of two-stage orchidopexy, with the second part done usually six months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility. In addition, preservation of the gubernaculum may also decrease the chance of testicular atrophy. ⁽³⁻⁵⁾

73.3.2 Ectopic Testes:

If the position of a testis is outside its normal path of descent and outside the scrotum, the testis is considered to be ectopic. The most common aberrant position is in the superficial inguinal pouch. Sometimes an ectopic testis can be identified in a femoral, perineal, pubic, penile or even contralateral position. Usually, there is no possibility for an ectopic testis to descend spontaneously to the correct position; therefore, it requires surgical intervention. In addition, an ectopic testis might not be palpable due to its position. ⁽³⁻⁵⁾

73.3.3 Retractable Testes:

Retractable testes are one which have completed its descent into a proper scrotal position but can be found again in a suprascrotal position along the path of their normal descent. This is due to an overactive cremasteric reflex. Retractable testes can be easily manipulated down to the scrotum and remain there at least temporarily. There is no indication for orchidopexy in truly retractile testes. However, since one third can ascend (testicular reascent), they should be monitored carefully. ⁽⁶⁾

73.3.4 Undescended Testes after Puberty:

In a study on 51 men diagnosed with inguinal unilateral undescended testis and a normal contralateral one, with no previous therapy, significant germ cell activity at different maturation levels was found in nearly half of them. More importantly, the incidence of intratubular germ cell neoplasia was 2%. The Panel consensus of the ESPU recommends orchiectomy in post-pubertal boys with an undescended testis and a normal contralateral one in a scrotal position. ⁽⁶⁾

73.3.5 Undescended Testes and Malignancy:

In a landmark Swedish study, with a cohort of almost 17,000 men treated surgically for undescended testes and followed long term, it was found that management of undescended testes before the onset of puberty decreased the risk of testicular cancer. The relative risk of testicular cancer was reduced from 5.4 to 2.2 compared to the Swedish general population among those who underwent orchidopexy before thirteen years of age (2.2) and those treated after thirteen years of age (5.4). A systematic review and meta-analysis of the literature have also concluded

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that pre-pubertal orchidopexy may reduce the risk of testicular cancer and that early surgical intervention is indicated in boys with undescended testes.

73.3.6 Complications of surgical Therapy:

Surgical complications are usually uncommon, with testicular atrophy being the most serious. A systematic review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for one-stage Fowler-Stephens procedure, and 8.2% for the two-stage approach. Other rare complications comprise testicular ascent and vas deferens injury besides local wound infection, dehiscence, and hematoma. ⁽⁵⁾

Table 87: Recommendations for management of undescended testis

Recommendations	Strength Rating
1. In boys with retractile testes, providers should assess the position of the testes at least annually to monitor for secondary ascent.	Strong
2. Do not offer medical or surgical treatment for retractile testes until puberty.	Strong
3. Perform surgical orchidolysis and orchidopexy before the age of twelve months, and by eighteen months at the latest.	Strong
4. Evaluate male neonates with bilateral non-palpable testes for possible disorders of sex development.	Strong
5. Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of boys with cryptorchidism prior to referral, as these studies rarely assist in decision making.	Strong
6. Perform a diagnostic laparoscopy to locate an intra-abdominal testicle.	Strong
7. In prepubertal boys with nonpalpable testes, examination under anesthesia should be performed to reassess for palpability of testes. If nonpalpable, surgical or laparoscopic exploration and, if indicated, abdominal orchidopexy should be performed.	Strong
8. In boys with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a boy has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age.	Weak
9. Hormonal therapy in unilateral undescended testes is of no benefit for future paternity.	Weak
10. Offer endocrine treatment in case of bilateral undescended testes.	Weak
11. Inform the patient/caregivers about the increased risk of a later malignancy and infertility with an undescended testis in post-pubertal boys or older.	Weak

73.4 References:

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74 Hydrocele:

Hydrocele is defined as a collection of fluid between the parietal and visceral layers of the tunica vaginalis. Primary hydrocele results from patency or incomplete obliteration of the processus vaginalis. This may result in the formation of various types of communicating hydrocele; a large open processus vaginalis allowing passage of abdominal viscera results in clinical hernia. If complete obliteration of the processus vaginalis occurs with patency of mid-portion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are also encountered in newborns. Non-communicating hydroceles, based on an imbalance between the secretion and re-absorption of this fluid, are found secondary to minor trauma, testicular torsion, epididymitis or varicocele operation (due to ligation of the lymphatics). ⁽¹⁻³⁾

74.1 Diagnosis:

Diagnosis is based on history taking and physical examination with transillumination. Hydroceles are not reducible but fluctuate in size and are not associated with symptoms. Ultrasound may be indicated if a hernia is suspected.

74.2 Management:

Hydroceles have a great tendency to resolve spontaneously and the risk of testicular damage on follow-up and observation is minimal or non-existent. Accordingly, there is no indication for surgical intervention before 12 to 18 months.

The operation consists of ligation of the patent processus vaginalis via inguinal incision and the distal stump is left open, whereas in hydrocele of the cord the cystic mass is excised or unroofed.

The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele. ⁽¹⁻³⁾

Table 88: Recommendations for Hydrocele management

Recommendation	Strength rating
1. In the majority of infants, observe hydrocele for twelve months prior to considering surgical treatment.	Strong
2. Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	Strong
3. Perform a scrotal ultrasound in case of doubt about the character of an intrascrotal mass.	Strong

74.3 References:

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75 Acute Scrotum:

Causes of acute scrotal pain and:

1. Ischemia:

- Torsion of the testis (synonymous with torsion of the spermatic cord); Intravaginal; extravaginal (prenatal or neonatal)
- Appendicular torsion, testis or epididymis
- Testicular infarction due to compressive hydrocele or hernia
- Testicular infarction due to other vascular insult (cord injury, thrombosis)

2. Trauma:

- Testicular rupture
- Intratesticular hematoma, testicular contusion Hematocele

3. Infectious conditions

- Acute epididymitis
- Acute epididymo-orchitis
- Acute orchitis
- Abscess (intratesticular, intravaginal, scrotal skin, cutaneous cysts)
- Gangrenous infections (Fournier's gangrene)

4. Inflammatory conditions:

- Henoch-Schönlein purpur (HSP) vasculitis of scrotal wall.
- Fat necrosis, scrotal wall

5. Hernia:

- Incarcerated, strangulated inguinal hernia, with or without associated testicular ischemia

6. Acute or chronic events:

- Spermatocele, rupture or hemorrhage
- Hydrocele, rupture, hemorrhage or infection
- Testicular tumor with rupture, hemorrhage, infarction or infection

75.1 Diagnosis:

It is of paramount importance to distinguish patients with torsion of the testis from those with epididymitis or torsion of the appendix testis to avoid testicular loss, which can occur in a few hours. Typically, patients with torsion of the testis or appendix testis, present with excruciating pain and vomiting. The duration of symptoms is relatively shorter in testicular torsion and torsion of the appendix testes, compared to epididymitis. Early on, the location of the pain can help in differentiation. In testicular torsion, the pain is localized to the testis, and to the upper pole of the testis in appendicular torsion, whereas it is localized to the epididymis in epididymitis/epididymo-orchitis

A horizontal position of the testis (involved and contralateral testis) is more frequent in testicular torsion than in epididymitis. Elevation of the scrotum may reduce pain in epididymitis, but not in testicular torsion. Fever occurs more often in epididymitis. A normal urinalysis does not exclude epididymitis, similarly, an abnormal urinalysis does not exclude testicular torsion.

When history and physical examination are still not conclusive, doppler US is useful to evaluate acute scrotum, with 63.6 -100% sensitivity and 97-100% specificity, a positive predictive value of 100% and negative predictive value of 97.5%. Doppler US may reduce the number of scrotal exploration but it may also show a misleading arterial flow in the early phases of torsion and in partial or intermittent torsion. Of key importance, persistent arterial flow does not exclude testicular torsion. So, at the end, in case of doubt it is always better to explore than to lose a testis. ⁽¹⁻³⁾

75.2 Management:

75.2.1 Testicular torsion:

Manual detorsion is done by outward rotation of the testis unless the pain increases or if there is evident resistance. If successful, there is immediate relief of pain and normal examination. This is followed by immediate bilateral orchiopexy. Torsion of the appendix testis can be managed non-operatively using anti-inflammatory analgesics, particularly in those presenting late.

It is re-emphasized that surgical exploration is strongly recommended in case of doubt, to avoid testicular loss.

Despite timely and adequate detorsion and fixation of the testicle, up to half of the patients may develop testicular atrophy, even when intraoperatively assessed as viable, and should be counselled accordingly. ⁽¹⁻⁵⁾

75.2.1.1 Epididymitis:

In pre-pubertal boys, apart from an underlying pathology in 25%, in the majority, the etiology is unclear, with a negative urine culture. Nevertheless, antibiotic treatment is often started.

Epididymitis is usually self-limiting and with supportive care (minimal physical activity and analgesics), it heals without any sequelae. Rarely, bacterial epididymitis can be complicated by abscess and surgical exploration is required. ⁽⁶⁾

Table 89: Recommendations for management of acute scrotum

Recommendation	Strength rating
1. Testicular torsion is a pediatric urological emergency and requires immediate treatment.	Strong
2. In neonates with testicular torsion perform orchidopexy of the contralateral testicle. In prenatal torsion; the timing of surgery is usually dictated by clinical findings.	Weak
3. Base the clinical decision on physical examination. The use of Doppler ultrasound to evaluate acute scrotum is useful, but this should not delay the intervention.	Strong
4. Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	Strong
5. Perform urgent surgical exploration in all cases of testicular torsion within 24 hours of symptom onset.	Strong

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76 Varicocele in children and adolescents*:

Varicocele is unusual in boys under ten years of age and becomes more frequent at the beginning of puberty. It results from venous reflux, leading to an abnormal dilatation of testicular veins in the pampiniform plexus. It is reported in 14-20% of adolescents (similar to incidence during adulthood). It is left sided in 90% of cases. Right-sided varicoceles are rather uncommon and usually noted with bilateral varicoceles and seldom occur as an isolated finding. Doppler US in the supine and upright position can detect venous reflux and this is classified as subclinical varicocele. ⁽¹⁻⁴⁾

76.1 Diagnosis:

Varicocele is usually noticed by the patient or his parents or discovered by the pediatrician at a routine visit. It is mostly asymptomatic and rarely causes pain. Diagnosis must rely on dilated veins detected clinically in the upright position with an impulse on Valsalva manoeuvre and not on detection of reflux by Doppler ultrasound which is considered as subclinical varicocele. ⁽¹⁻⁴⁾

76.1.1 Varicocele is classified into 3 grades:

- Grade I - Valsalva positive (palpable at Valsalva only)
- Grade II - palpable (palpable without Valsalva)
- Grade III - visible (visible at distance).

Testicular size should be assessed by ultrasound or an orchidometer. A testis that is smaller by > 2 mL or 20% compared to the other testis is considered to be hypoplastic.

It is not ethical to ask for a semen analysis in such age group and the decision to interfere is based only on the presence of testicular hypoplasia at the time of diagnosis or on follow-up.

76.2 Management:

The recommended indication criteria for varicocelectomy in children and adolescents are:

- Varicocele associated with a small testis.
- Additional testicular condition affecting fertility.
- Bilateral palpable varicocele.
- Pathological sperm quality (in late adolescents only).
- Symptomatic varicocele or a large varicocele, causing physical or psychological discomfort.
- Surgical intervention consists of ligation of the internal spermatic veins.

- Inguinal (or subinguinal) using optical magnification or microsurgical approach to avoid injury to the artery and lymphatics.
- Supra-inguinal ligation where less veins are found, with less liability of hydrocele formation but higher incidence of recurrence. Injury of the testicular artery at that level does not have a deleterious effect on the testis or its catch up growth.

The advantage of the former is the lower invasiveness of the procedure, while the advantage of the latter is a considerably lower number of veins to be ligated and safety of the incidental division of the internal spermatic artery at the suprainguinal level.

For surgical ligation, some form of optical magnification (microscopic or laparoscopic) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring. The recurrence rate is usually < 10%.

Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy development and to achieve a better testicular function according to the LHRH stimulation test. The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs

Microsurgical varicocele repair in adolescents with varicocele significantly increases paternity rates and decreases time to conception post-operatively. Patients with varicocele who underwent microsurgical varicocele repair had increased sperm parameters and 3.63 times greater odds of paternity than controls who did not undergo varicocele surgery. ⁽¹⁻⁴⁾

Table 90: Recommendations for varicocle management

Recommendations	Strength Rating
1. Examine varicocele in the standing position and classify into three grades.	Strong
2. Use scrotal ultrasound to detect venous reflux without Valsalva manoeuvre in the supine and upright position and to discriminate testicular hypoplasia.	Strong
3. In all pre-pubertal boys with a varicocele and in all isolated right varicoceles perform standard renal ultrasound to exclude a retroperitoneal mass.	Strong
4. Inform caregivers and patients and offer surgery for: • Varicocele associated with a persistent small testis (size difference of > 2 mL or 20%); • Varicocele associated with additional testicular condition affecting fertility (cryptorchidism, history of torsion, trauma); • Varicocele associated with pathological sperm quality (in older adolescents); • Symptomatic varicocele.	Weak
5- Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	Strong
6- Use lymphatic-sparing varicocelectomy to prevent hydrocele formation and testicular hypertrophy.	Strong

In a meta-analysis of twelve RCTs conducted by the ESPU it was found that varicocele treatment improved testicular volume and increased total sperm concentration when compared with observation. Lymphatic sparing surgery significantly decreased hydrocele rates. However, the ultimate effects on fertility potential and paternity remain unknown.

The complications include hydrocele formation which is the commonest complication, as well as, recurrence of varicocele (10%).

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77 PENILE:

77.1 Circumcision:

77.1.1 Epidemiology

Approximately two-thirds of circumcisions are performed for religious reasons, primarily among Muslims and Jews (in whom circumcision is nearly universal). Approximately 57% of newborn males are circumcised before discharge from the hospital, with the remainder undergoing circumcision in other settings (office based or surgical) or remaining uncircumcised. In 2012, the American Academy of Pediatrics (AAP) released its most recent policy statement and technical report on circumcision. The statement endorses the health benefits of newborn male circumcision, including a reduction in the risk of urinary tract infections (UTIs) in the first year after birth, reduction in the heterosexual transmission of HIV and other STDs, and reduction in the risk of penile cancer

(1,2)

77.1.2 Procedure, Postoperative Care, and Complications

Local anesthesia is administered as either a dorsal penile nerve block or a subcutaneous ring block with 1% plain lidocaine (other local anesthetics, such as bupivacaine, may also be used). Topical 4% lidocaine cream have also been used as analgesics during newborn circumcision. The most common contraindications to newborn circumcision are penile torsion, chordee, and penoscrotal webbing. Surgical circumcision is performed with general anesthesia, typically after 6 months of age. The inner and outer foreskin are marked circumferentially, and the skin is removed. Hemostasis is achieved with **bipolar** cautery, and the skin edges are approximated with fine absorbable sutures and/or surgical skin glue. It is common for the head of the penis to appear red and swollen for the first 1 to 2 weeks after circumcision. Fibrinous exudate and crusting on the glans are also common and are often mistaken for pus by parents.

Electrocautery should never be used during circumcision except if bipolar is used

Complications of circumcision include postoperative bleeding and/or hematoma, meatal stenosis, and removal of too much or too little foreskin, as well as rare but clinically significant complications, such as urethral injury or glans amputation. Complication rates were higher when the circumcision was performed by a nonmedical provider and for children aged 12 months to 12 years. Monopolar diathermy should be avoided in all cases ⁽¹⁻⁶⁾

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78 Hypospadias:

Hypospadias is the second most common birth defect in males, potentially affecting both urinary and sexual function of the penis. New understanding of the anatomy of hypospadias during the last 20 years has led to changes in both means for straightening associated ventral curvature and performing urethroplasty, while also improving cosmetic outcomes ^(1,2)

78.1 Anatomy:

Hypospadias represents arrested penile development. Consequently, the urethral opening can occur from the perineum, where fusion of urethral folds begins, to the proximal glans near the point this fusion normally is completed. The epithelial strip extending from the meatus to the tip of the glans is referred to as the urethral plate, representing tissues that should have completed urethral tubularization. The glans does not fuse ventrally under the meatus, resulting in two “wings” to either side of the urethral plate. Along the shaft, the corpus spongiosum diverges along the lateral margins of the urethral plate to join ipsilateral glans wings. Typically, there is no frenulum, and ventral preputial development is incomplete whereas the dorsal aspect is formed, creating a dorsal hood. A variant of distal hypospadias termed the megameatus intact prepuce (MIP) presents with a normal foreskin, and so may not be detected until circumcision is performed or the skin becomes retractable ⁽²⁾. Ventral curvature of the penis may be noted, especially with more proximal hypospadias. Ventral curvature is found in approximately 15% of boys with distal forms of hypospadias, and in over 50% of those with the meatus on the proximal penile shaft or in the scrotum or perineum. Bending in distal cases most often is less than 30 degrees and will not prevent intercourse, whereas curvature greater than 30 degrees more often found in proximal cases may preclude penetration. Proximal cases additionally may have deep midline clefts in the scrotum and/or transposition of the scrotum higher than usual alongside the penile shaft. Defects in the hormonal processes of masculinization have long been implicated in hypospadias. ^(1,2)

78.2 Preoperative hormone stimulation:

No study confirms benefits of preoperative androgen therapy before hypospadias repair. Use has been advocated for the small appearing penis and/or glans, to potentially reduce ventral curvature, and to improve vascularity to skin before reoperations. Both topical and parenteral testosterone therapy have been used, with no apparent advantage to either route of administration. Parenteral regimens utilize testosterone enanthate 2 mg/kg given IM 5 and 2 weeks preoperatively, or every 3–4 weeks for three injections. Testosterone enanthate 2 mg/kg/wk can be administered topically twice daily for 3 weeks

Timing of surgery: . ⁽³⁾

A report from the American Academy of Pediatrics in 1996 suggested the optimal time for elective male genital surgery is between 6 and 12 months

78.3 Surgical repair:

78.3.1 Distal Hypospadias:

A recent survey of pediatric urologists indicated the most commonly used technique for distal repairs is TIP. This procedure involves tubularization of the urethral plate facilitated by midline incision to achieve a satisfactory neourethra caliber without skin flaps. meatoplasty and glans plasty (MAGPI) or flip-flap are less widely used nowadays. ^(1,2)

78.3.2 Proximal Hypospadias:

TIP can also be used to correct midshaft hypospadias and many cases with more proximal defects. The main contraindication is ventral curvature resulting in urethral plate transection to facilitate straightening. The main alternative to TIP when the urethral plate is maintained is onlay flap, but if the plate is transected either a 1-stage tubularized prepucial flap (Duckett) or 2-stage graft urethroplasty is required. ⁽⁴⁻⁶⁾

78.3.3 Correcting Penile Curvature:

When the penis develops with curvature, all tissues on the ventral aspect may be relatively shortened, including shaft skin, dartos, corpus spongiosum, urethral plate, and corpus cavernosa. Most apparent curvature resolves when the shaft skin is released during degloving, sometimes facilitated by excision of dartos. While excision of the corpus spongiosum and urethral plate may also lessen curvature, in most cases some extent of curvature persists due to corpora cavernosa disproportion. Bending less than 30 degrees can be readily straightened by midline dorsal plication popularized by Baskin. Typically, curvature greater than 30 degrees after degloving and excision of dartos has led to transection of the urethral plate with subsequent ventral corporal grafting or using just 3 transverse incisions in the ventral tunica from 3 to 9 area without grafting. ⁽⁷⁻¹²⁾

Table 91: Recommendations for Hypospadias management

Recommendations ⁽¹¹⁾	Strength Rating
1. At birth, differentiate isolated hypospadias from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	Strong
2. Counsel caregivers on functional indications for surgery, aesthetically feasible operative procedures (psychological, cosmetic indications) and possible complications.	Strong

3. In children diagnosed with proximal hypospadias and a small appearing penis, reduced glans circumference or reduced urethral plate, pre-operative hormonal androgen stimulation treatment is an option but the body of evidence to accentuate its harms and benefits is inadequate.	Weak
4. For distal hypospadias, offer Duplay-Thiersch urethroplasty, original and modified tubularised incised plate urethroplasty; use the onlay urethroplasty or two-stage procedures in more severe hypospadias. Correct significant (> 30 degrees) curvature of the penis.	Weak
5. Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, ejaculation disorder, and to evaluate patient's satisfaction.	Strong
6. Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	Strong

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79 NEUROGENIC BLADDER DYSFUNCTION/ SPINAL DYSRAPHISM:

79.1 General principles:

- Patients with spinal dysraphism should be managed with a multidisciplinary approach and offered lifelong follow-up.
- A child born with spinal dysraphism should be offered urologic care once the diagnosis is established. Without appropriate urologic management, 60-80% may develop urological problems within the first few years of life and less than 5% become continent.
- There are two prevalent general philosophies for the urologic management of children born with spina bifida: a proactive and an expectant approach. A proactive approach is recommended. Every bladder should be considered as a potentially hostile high-pressure bladder. Therefore, the bladder should be drained with an indwelling catheter until the spinal defect is closed. Clean intermittent catheterization (CIC) practice and training should be initiated shortly after spinal closure and patient stabilization ⁽¹⁻³⁾. CIC is better tolerated by patients and accepted by their families if started early in life. More importantly, early proactive management was shown to decrease the risk of renal damage and UTI, improve continence and reduce the need for later bladder augmentation ^(2, 4, 5). CIC can be later discontinued in patients with underactive sphincter and those with low postvoid residual (PVR) and no signs of bladder outlet obstruction (detrusor-sphincter dyssynergia) on urodynamics (UDS), but a very close follow-up is still warranted as the bladder dynamics may change overtime ⁽¹⁾.
- Closure of the spinal defect should be performed as early as possible. Prompt postnatal closure is essential to prevent infection and protect the exposed neural tissues from additional trauma. Prompt repair of open spina bifida is associated with decreased risk of neurogenic bladder, neurodevelopmental delay and ventriculoperitoneal shunt infection ⁽⁶⁻⁹⁾.
- Treatment is tailored according to the pattern of lower urinary dysfunction determined by urodynamic studies. The type, level and severity of neurological lesion have poor correlation with the pattern of lower urinary tract dysfunction. Figure 1 provides summary for the scheme of management of neurogenic bladder according to the pattern of detrusor and sphincter dysfunction ⁽¹⁰⁾

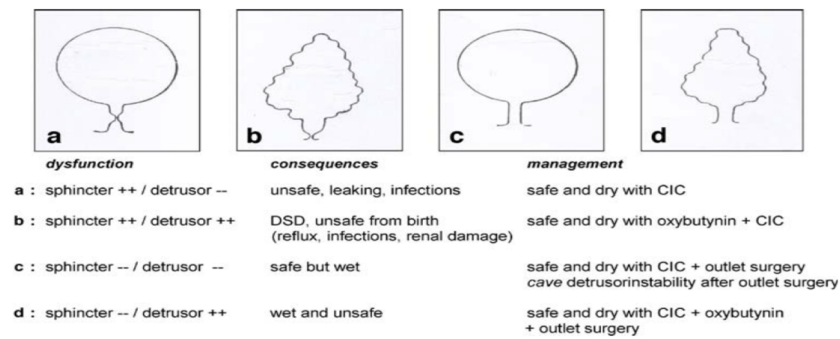


Figure 1: Management of Neurogenic bladder dysfunction/spinal dysraphism

79.2 Baseline evaluation:

(Open/Closed Spina Bifida, Anorectal Malformation (ARM), Spinal cord injuries, others):

79.2.1 Open Spina Bifida:

- Basic evaluation of a child born with spinal dysraphism should include renal bladder ultrasound at birth, renal function testing after the first week of life, voiding cystourethrogram (VCUG) after closure of the spinal defect and urodynamic testing or preferably videourodynamics (VUDS) between 2-3 months of birth ^(1, 10, 11).
- Urodynamic reporting should include information on the bladder capacity, maximal detrusor pressure, the presence of detrusor overactivity (DO) and detrusor leak point pressure ^(10,12).
- Interpretation of UDS in the newborn period may be difficult and reference ranges do not exist ⁽¹⁾.

79.2.2 Closed Spinal Dysraphism:

- Patients with suspicion of closed spinal dysraphism should be investigated with spinal ultrasound and MRI in children < 3 months and MRI in older children ^(11,13). If Spinal ultrasound is a good screening test in infants < 3 months. If spinal ultrasound is abnormal, equivocal or limited, in infants <3months, a spinal MRI should be ordered ^(14, 15).
- In patients with closed spinal dysraphism, baseline UDS should be performed before spinal cord untethering surgery. Any change of baseline urodynamic information is considered a sign of cord tethering and warrant neurosurgical intervention ^(11,16)

- UDS should also be performed if there is a strong suspicion of neurogenic bladder in older children (voiding pattern, incontinence, upper or lower urinary tract changes) ([1,11](#)).

79.2.3 Anorectal Malformation and Cloacal Anomalies (ARM):

- Patients with anorectal malformation should be investigated in the neonatal period with renal and spinal ultrasound due to the likelihood of associated renal and intraspinal abnormality ([17,18](#)). Baseline UDS should be obtained in the first few months of life after initial colostomy or definitive pull-through is performed. Repeat UDS is required if the patient suffers persistent or worsening urinary and/or fecal incontinence, upper tract damage or UTI on subsequent follow-up. A change of baseline UDS warrants spinal MRI and possibly spinal cord-untethering.

79.3 Medical treatment:

79.3.1 Anticholinergic medications:

- Patients with detrusor overactivity and/or elevated detrusor pressure on urodynamic studies should be started on anticholinergic medications, even within the first months of life ([1,3,11,19](#)). Oxybutynin is the only well-investigated anticholinergic drug in children and has been safely used in this age group (dosage 0.1 – 0.2 mg/kg body weight/8 hours). The use of oral anticholinergics is associated with dose-dependent adverse effects, more commonly: dry mouth, facial flushing and constipation ([20,21](#)). Anticholinergics are known to treat detrusor overactivity, lower the bladder storage pressure, decrease upper tract damage and the need for bladder augmentation. Other anticholinergic medications (e.g. tolterodine, solifenacin, trospium chloride and propiverine) have been safely used off-label in children ([24-28](#)).

79.3.2 β_3 agonists (e.g. mirabegron):

- Could be used as an alternative to or in combination with anticholinergics in patients with detrusor overactivity, but there are limited reports on their use in children ([29,32](#)).

79.3.3 α -Adrenergic antagonists:

- Can theoretically decrease bladder outlet resistance, facilitate bladder emptying and lower the bladder pressure. In reality, α -adrenergic antagonists are ineffective in children with neurogenic bladder. In a randomized, double-blind, placebo-controlled trial, different dosage regimens of tamsulosin did not result in a significant reduction of the detrusor leak point pressure, compared to placebo ([33](#)).

79.3.4 Continuous Antibiotic Prophylaxis:

- There is no strong evidence to support the routine use of **continuous antibiotic prophylaxis** (CAP) in patients maintained on CIC. The use of CAP is associated with increased bacterial resistance without decreasing the risk of UTIs and new renal scarring ⁽³⁴⁻³⁶⁾. However, it may be prudent to consider antibiotic prophylaxis for patients with high-grade VUR, recurrent UTIs or unfavorable bladder dynamics ⁽³⁾.

79.3.5 Bowel Management:

- Bowel management is an integral part of the care of a child with neurogenic bladder. Regular bowel emptying should be ensured in children with neurogenic bladder. Bowel management improves fecal continence, social integration and the patient's quality of life, and could potentially reduce the risk of UTIs. A graduated approach for bowel management is recommended. Bowel management should start with laxatives, rectal suppositories, retrograde enemas, digital evacuation, transanal irrigation systems or Malone antegrade continence enema stoma should be considered ⁽³⁷⁻⁴¹⁾.

79.3.6 Follow-up:

- Children with neurogenic bladder should be offered lifelong multidisciplinary follow-up. The frequency of urological follow-up, however, varies. Close follow-up is recommended during infancy and in adolescence. Children are at a higher risk of developing spinal cord tethering during these periods of rapid growth ^(42,43). The rapid growth rate is reduced once they become toddlers. Toddlers and adults born with spina bifida can be followed on annual or biannual bases ⁽⁴⁴⁾. Basic evaluation during follow-up should include: history, physical examination and renal-bladder ultrasound. Further testing with VCUG, UDS or DMSA is considered if there is a change in the severity of hydronephrosis or bladder wall thickening, change of continence or recurrent UTIs.
- During follow-up, history should focus on voiding or CIC frequency, urine leakage, symptoms suggestive of UTI, medication compliance, bowel habits and any changes of the neurological status.
- In patients with deterioration of the upper and/or lower urinary tract function, neurological evaluation including a total spine MRI, is warranted to exclude secondary tethered cord or worsening of hydrocephalus. ^(42,43).

79.4 Urinary tract infection:

- The diagnosis of **urinary tract infection** in patients on CIC is problematic. There are no universally accepted criteria to define UTI in patients maintained on CIC. The diagnosis of UTI should be based on a positive urine analysis and a positive urine culture of properly collected urine specimen in a symptomatic patient ⁽⁴⁵⁾. **Only patients with symptomatic**

UTI should receive antibiotic treatment. Asymptomatic bacteriuria in patients maintained on CIC requires no treatment.

79.5 Principles of Surgical Management of Neurogenic Voiding Dysfunction:

79.5.1 Indications for surgery:

- Treatment of neurogenic bladder in children and adolescents is primarily conservative. Surgery should be considered only if there is upper tract damage, recurrent symptomatic UTIs or failure to achieve urinary continence despite maximal conservative management.
- Preserving the upper urinary tract should always be the primary goal of treatment of neurogenic bladder. Upper tract safety should not be compromised to achieve urinary continence.

Surgery for neurogenic bladder in children mainly aims at:

- improving the bladder storage characteristics (intra-detrusor botulinum toxin injection, bladder augmentation, continent or incontinent urinary diversion).
- increasing the bladder outlet resistance in patients with bladder outlet insufficiency pursuing continence.
- facilitation of intermittent catheterization (creation of continent catheterizable channels) in patients with difficult transurethral CIC.

Surgical intervention, except for incontinent diversion, does not eliminate the need for CIC. Conversely, CIC becomes even more crucial after bladder augmentation or procedures to increase bladder outlet resistance.

Major bladder or bladder outlet reconstruction should only be performed in centers with enough expertise in these complex reconstructive procedures with a well-structured follow-up plan.

79.6 Botulinum toxin A injection:

Botulinum toxin A (Botox A) injection into the detrusor muscle can be used in patients with low capacity,

overactive or poorly compliant bladders refractory to anti-muscarinic treatment. Botulinum toxin A injection is more effective in patients with detrusor overactivity (DO), relative to those with poor compliance and no DO.

There is weak evidence to support botulinum toxin A injection into the urethral sphincter to decrease urethral resistance as a temporary solution in patients with high bladder pressure who are not capable of or do not wish to perform CIC.

79.7 Bladder Augmentation:

A variable proportion (12-38%) of neurogenic bladder patients may require bladder augmentation. Bladder augmentation should be only considered if medical treatment or intra-detrusor botox injection fails to achieve favorable bladder storage characteristics.

The long-term risk of surgical and metabolic complications of bladder augmentation should be carefully weighed against its benefits

A continent catheterizable channel can be offered at the time of bladder augmentation for patients who are not able to perform transurethral CIC, due to anatomic problem, social circumstance or sensate urethras.

Patients who receive bladder augmentation should commit to lifelong follow-up owing to the well-known surgical and metabolic consequences including acid-base and electrolyte disturbance, vitamin B12 deficiency, loss of bone mineral density and affection of linear growth, change of bowel habits, increased risk of urinary stones and UTIs, renal deterioration and increased risk of malignancy.

Ureterocystoplasty can avoid the complications of enterocystoplasty in properly selected patients. Nevertheless, reaugmentation may be required in up to 73% of patients.

Autoaugmentation, with detrusor-myotomy or partial detrusorectomy, generally has a low success rate.

79.8 Incontinent Cutaneous Urinary Diversion:

Incontinent urinary diversion (cutaneous vesicostomy, ileal or colonic conduits, ileovesicostomy) is an option in patients with high pressure bladders who are unable or unwilling to perform CIC, due to anatomic problems or social circumstances.

Refluxing uretero-cutaneostomy can also be considered as a temporizing measure in patients with high-grade VUR and recurrent febrile UTIs.

Neurostimulation/neuromodulation and somatic-to-autonomic nerve anastomosis are still experimental in children with neurogenic bladder.

79.8.1 Procedures to Increase Bladder Outlet Resistance:

Weak or insufficient bladder outlet resistance is a safe situation for upper tract safety. No pharmacotherapy has proved efficient to increase bladder outlet resistance. Surgical procedures for bladder outlet insufficiency produce fixed resistance at the level of bladder outlet and may adversely change bladder dynamics, even in patients with Low bladder compliance has been reported in approximately one third and upper tract changes in about 50% of patients following procedures to increase bladder outlet resistance. These risks should be carefully discussed when counseling patients and families before bladder outlet surgery. Additionally, close and lifelong

follow-up is mandatory following these procedures. Simultaneous bladder augmentation should be considered in patients with poor preoperative bladder dynamics.

It is preferable to combine procedures to increase bladder outlet resistance with creation of continent catheterizable channel; since catheterization through a reconstructed a bladder neck or a urethra compressed by a sling is not sometimes easy.

Autologous or synthetic slings: provide a continence rate of 40-100% and are more successful in females. Sling procedures are usually combined with bladder augmentation or other bladder outlet procedures.

Bladder neck injection with a bulking agent generally has a low success rate (10-40%) and the results are not durable.

Bladder Neck Closure with a Continent Catheterizable Channel is usually kept as the last resort to achieve urinary continence after all other measures fail. Bladder neck closure has a high success rate, but patients should be warned against the risk of bladder stones, bladder perforation and upper tract deterioration if not compliant to CIC and regular bladder irrigations.

Surgical Treatment of Vesicoureteral Reflux: treatment of VUR in neurogenic bladder patients should primarily focus on improving bladder dynamics and lowering the risk of UTIs. Surgery for VUR is reserved for patients with recurrent symptomatic UTIs after bladder dynamics have been optimized. Endoscopic treatment of VUR has a high failure rate in patients with neurogenic bladder. Simultaneous ureteral reimplantation should be discussed in patients with high-grade symptomatic VUR undergoing bladder or bladder outlet reconstruction ^(46, 47).

Surgical Options For Bowel Management including Malone Antegrade Continence Enema (MACE), cecostomy buttons and diverting stomas should be discussed with a bowel specialist after failure of other measures to achieve fecal continence.

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80 Urinary Tract Infections

80.1 Introduction:

Urinary tract infections (UTIs) are the most common bacterial infection in children ⁽¹⁻³⁾. The incidence varies depending on age and sex. The prevalence is higher; there is a male predominance; infections not caused by *Escherichia coli* are more frequent; and there is a higher risk of urosepsis ^(4, 5).

Although urinary tract infection affects at least 3.6% of boys and 11% of girls, establishing the diagnosis is difficult in early childhood owing to the lack of specific urinary symptoms, difficulty in urine collection, and contamination of samples. Most children have a single episode and recover promptly ⁽⁶⁾.

80.2 Diagnosis:

80.2.1 Risk factors for urinary tract infection in children:

- Poor urine flow, dysfunctional voiding and/or constipation
- Previous urinary tract infection
- Recurrent fever of uncertain origin
- Antenatally diagnosed renal abnormality or evidence of spinal lesion
- Family history of vesicoureteric reflux or renal disease
- Enlarged bladder and/or abdominal mass
- Poor growth
- High blood pressure

80.2.2 Clinical symptoms and signs:

Urinary tract infection is considered in all infants and children with:

- (a) Unexplained fever of 38°C or higher after 24 hours at the latest.
- (b) Symptoms and signs suggestive of urinary tract infection, including ⁽⁶⁾:
 - Fever
 - **Non-specific symptoms**, such as lethargy, irritability, malaise, failure to thrive, vomiting, poor feeding, abdominal pain, jaundice (in infants)
 - **Specific symptoms**, such as frequency, dysuria, loin tenderness,

dysfunctional voiding, changes to continence, haematuria, and offensive or cloudy urine.

- Septic shock is unusual, even with very high fever.

Localization of site of urinary tract infection:

- Child with bacteriuria and fever of 38°C or higher is considered to have acute pyelonephritis or upper urinary tract infection.
- Child with fever lower than 38°C, loin pain or tenderness, and bacteriuria is considered to have acute pyelonephritis or upper urinary tract infection.
- All other children with bacteriuria but no systemic symptoms or signs are considered to have cystitis or lower urinary tract infection.

80.2.3 Physical examination:

- **Non-specific:** Throat, lymph node, temperature
- **Specific:**
 - Abdomen and flank (constipation, palpable and painful kidney, or palpable bladder).
 - Back (stigmata of spina bifida or sacral agenesis),
 - Genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis).

80.2.4 Urine sampling, analysis and culture:

80.2.4.1 Urine sampling:

(a) Clean catch urine collection, but if this is not possible, use Plastic bag attached to the cleaned genitalia but not cotton wool balls, gauze, or sanitary towels.

(b) If non-invasive techniques are not possible, use a catheter sample or suprapubic aspirate with ultrasound guidance.

If urine is to be cultured but cannot be cultured within 4 hours of collection, the sample should be refrigerated or preserved with boric acid immediately.

80.2.4.2 Urinalysis:

a) Dipsticks:

- Rapid, do not require microscopy, and are ready to use.
- The test is helpful when the result is positive, because it is highly specific.

b) Microscopy: ≥ 5 WBC/ μ L in centrifuged urine or > 10 WBC/ μ L in uncentrifuged urine have been demonstrated to be sensitive for UTI ⁽⁷⁾.

c) Flow imaging analysis technology: to classify particles in uncentrifuged urine.

80.2.4.3 Urine culture:

Definition of UTI in children depends on method of urine sampling:

- Urine specimen from suprapubic bladder puncture → Any number of cfu/mL (at least 10 identical colonies)
- Urine specimen from bladder catheterization → $> 10^3 - 10^5$ cfu/mL
- Urine specimen from midstream void →
 - $> 10^4$ cfu/mL with symptoms
 - $> 10^5$ cfu/mL without symptoms
- Indications for sending urine samples for culture:
- Upper urinary tract infection.
- Recurrent urinary tract infection.
- Under three years of age.
- No response to treatment within 48 hours.
- High to intermediate risk of serious illness.
- Positive result for leukocyte esterase or nitrite.
- Clinical symptoms and dipstick tests do not correlate.

80.2.5 Imaging strategies:

1. **Ultrasound:**

- An ultrasound scan is required on diagnosis for all atypical infections.
- In infants with febrile UTI: urinary tract ultrasound is advised within 24 hours to exclude obstruction.
- In toilet-trained children: Post-void residual (PVR) urine should be measured to exclude dysfunctional voiding as a cause of UTI as elevated PVR volume predicts recurrence of UTIs in toilet-trained children ⁽⁸⁾.

2. **Radionuclide scanning:**

Children younger than 3 years with atypical and/or recurrent urinary tract infection: do a DMSA (dimercaptosuccinic acid) scan 4-6 months after the acute infection to detect renal parenchymal defects (renal scars) while in the acute phase of a febrile UTI (up to 4-6 weeks), DMSA-scan can demonstrate pyelonephritis by perfusion defects.

3. **Micturating cystourethrography (MCUG):**

A micturating cystourethrogram (MCUG) is recommended after the first episode of febrile UTI in boys and girls depending on sex, age and clinical presentation also in atypical and recurrent infections in children below six months and in older children if there is poor urine flow, urinary tract dilatation on ultrasound, non-*Escherichia coli* infection or a family history of VUR.

The timing of VCUG does not influence the presence or severity of VUR ^(9, 10). Prophylactic antibiotics should be given orally for three days, with MCUG taking place on the second day. Another option is doing DMSA first, followed by VCUG if there is renal cortical uptake deficiency after UTI.

80.3 Acute Management:

- Infants and children with a high risk of serious illness should be referred urgently to the care of a pediatric specialist.
- Infants younger than 3 months with a possible UTI should be treated with parenteral antibiotics.
- Infants and children 3 months or older with acute pyelonephritis/upper urinary tract infection:
 - Oral antibiotics with low resistance patterns are recommended for 7–10 days, for example cephalosporin or amoxycillin/clavulonic acid.
 - If oral antibiotics cannot be used, Cephalosporins intravenous (IV) for 2–4 days followed by oral antibiotics for a total duration of 10 days.
- Infants and children 3 months or older with cystitis/lower urinary tract infection should be treated with oral antibiotics for 3 days. Trimethoprim, nitrofurantoin, cephalosporin or amoxicillin may be suitable.
- The parents or care givers should be advised to bring the infant or child for reassessment if the infant or child is still unwell after 24–48 hours. If an alternative diagnosis is not made, a urine sample should be sent for culture to identify the presence of bacteria and determine antibiotic sensitivity if urine culture has not already been carried out.
- Infants and children who receive aminoglycosides (gentamicin or amikacin), once daily dosing is recommended.
- Intramuscular treatment should be considered, if parenteral treatment is required and IV treatment is not possible.
- Infant or child who is on chemoprophylaxis and developed an infection, treatment should be with a different antibiotic, not a higher dose of the same antibiotic.
- Asymptomatic bacteriuria in infants and children should not be treated with antibiotics.

80.4 Long - term Management:

a) Prevention of recurrence:

- Children who have had a UTI should be encouraged to drink an adequate amount.
- Children who have had a UTI should have ready access to clean toilets when required and should not be expected to delay voiding.

- Dysfunctional elimination syndromes and constipation should be addressed in infants and children who have had a UTI.

b) Antibiotic Prophylaxis:

- Antibiotic prophylaxis should not be routinely recommended in infants and children following first-time UTI.
- Antibiotic prophylaxis may be considered in infants and children with recurrent UTI.
- Asymptomatic bacteriuria in infants and children should not be treated with
- Prophylactic antibiotics.

80.5 Follow-up:

- When results are normal, a follow-up outpatient appointment is not routinely required.
- Infants and children who have recurrent UTI or abnormal imaging results should be assessed by a pediatric urologists and nephrologists.
- Assessment of infants and children with renal parenchymal defects should include height, weight, blood pressure and routine testing for proteinuria.
- Infants and children with a minor, unilateral renal parenchymal defect do not need long-term follow-up unless they have recurrent UTI or family history or lifestyle risk factors for hypertension.
- Infants and children who have bilateral renal abnormalities, impaired kidney function, raised blood pressure and/or proteinuria should receive monitoring and appropriate management by a pediatric nephrologist to slow the progression of chronic kidney disease.

Table 92: Oral antibiotics used in Pediatric UTI

Oral Antibiotics	Dosing	Notes
Amoxicillin and clavulanic acid	20–40 mg/kg divided q8h	
Sulfamethoxazole and trimethoprim (SMZ-TMP)	30–60 mg/kg SMZ, 6–12 mg/kg TMP divided q12	
Cephalexin	50–100 mg/kg/day divided q6h	
Cefixime	8 mg/kg/day	
Cefpodoxime	10 mg/kg/day divided q12h	Use in mixed aerobic-anaerobic UTIs
Ciprofloxacin	Not recommended as a first choice in paediatrics, Can be used to treat MDR infections when there is no other safe and effective alternative. Limit to treat UTIs caused by <i>Pseudomonas aeruginosa</i> or other MDR gram-negative bacteria.	

MDR= multidrug resistant

Table 93: Parenteral Antibiotics used in pediatric UTI

Parenteral Antibiotics	Dosing	Notes
Ceftriaxone	50–75 mg/kg/day IV/IM single dose or divided q12h	Contra-indicated in < 6 weeks of age; bilirubin may be displaced from albumin
Ampicillin	100 mg/kg/day IV/IM divided q8h	< 2 weeks of age used in combo with gentamicin. Used in paediatrics allergic to cephalosporins. Initial therapy where either gram-positive cocci or no organism is found in urinary sediment
Cefotaxime	150 mg/kg/day IV/IM divided q6-8h	Safe in < 6 weeks of age Aged 2–8 weeks: Used in combo with ampicillin. Use in neonates and jaundiced paediatrics
Gentamicin	<7 days: 3.5–5 mg/kg/dose IV q24h < 5 years: 2.5 mg/kg/dose IV q8h or single daily dosing with normal renal function of 5–7.5 mg/kg/dose IV q24h ≥ 5 y: 2–2.5 mg/kg/dose IV q8h or single daily dosing with normal renal function; 5–7.5 mg/kg/dose IV q24h	Monitor blood levels and kidney function if therapy extends > 48 hours; Empirical therapy should not be used for > 3 days. If empirical therapy is still required, consider changing to ceftriaxone

Table 94: Recommendations for urinary tract infections in pediatric patients

Recommendation	Strength rating
1. Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	Strong

2. Exclude bladder and bowel dysfunction in any child with febrile and/or recurrent UTI and do not delay diagnosis and treatment of bladder-bowel-dysfunction.	Strong
3. The most effective way to collect an uncontaminated urine sample in an infant is through suprapubic bladder aspiration; bladder catheterisation is an alternative with a higher contamination rate.	Strong
4. Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results. Clean catch urine is an acceptable technique for toilet-trained children.	Strong
5. Urinalysis by dipstick yields rapid results, but it should be used with caution. Microscopic investigation is the standard method of assessing pyuria after centrifugation. Using flow imaging analysis, the numbers of white blood cells (WBCs), squamous epithelial cells and red cells correlate well with manual methods.	Weak
6. Local antimicrobial susceptibility patterns should be used when deciding on empiric treatment and should cover the most common uropathogens (Escherichia coli, Enterococcus, Proteus, and Klebsiella species).	Strong
7. The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; complicated pyelonephritis.	Strong
8. Complicated or uncomplicated UTIs should be treated for 7–10 days. However, short-courses of therapy may be used in adolescent girls with non-toxic UTIs.	Strong
9. Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms.	Weak
10. If during the use of prophylactic medication, a paediatric develops an infection: do not increase dose of current antibiotic, switch to a different agent.	Strong
11. Treat complicated UTI with broad-spectrum antibiotics (parenteral).	Weak
12. In infants with febrile UTI use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract.	Strong
13. In all infants, exclude vesicoureteral reflux (VUR) after the first episode of febrile UTI, using voiding cystourethography (VCUG) or a dimercaptosuccinic acid (DMSA) scan first (in case of a positive DMSA-	Strong

scan, follow-up with VCUG). In boys more than one year of age, exclude VUR after the second febrile UTI.	
14. Antibiotic treatment in the case of asymptomatic bacteriuria is not recommended	Strong

80.6 References:

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81 Congenital Upper Urinary Tract Obstruction (UPJ and UVJ obstruction):

81.1 Antenatal Hydronephrosis (ANH)

Congenital urinary tract obstruction is distinct from obstruction in the mature kidney. Obstruction in the developing kidney induces various degrees of renal dysplasia and hypoplasia with increasing usage of ultrasound (US) screening during pregnancy, most congenital obstructive uropathies are diagnosed prenatally and a rising number of patients are referred to the pediatric urologist for prenatal counseling. The vast majority of prenatally detected uropathies, however, does not require fetal interventions because of acceptable postnatal renal function and unacceptable high fetal morbidity and mortality secondary to the procedure. Consequently, prenatal counseling focuses on parental education and reassurance as well as on outlining a postnatal plan of management. Most cases of urinary tract obstruction that are discovered before birth will not produce clinical manifestations. Symptoms vary depending on age. The availability of only two treatment options for urinary tract obstruction, observation or surgery, has created a great deal of controversy when to intervene.

81.2 Epidemiology:

Dilation of the UUT is a significant clinical challenge in deciding which patient will benefit from surgery. Ureteropelvic junction (UPJ) obstruction is defined as impairment of urine flow from the pelvis into the proximal ureter with subsequent dilation of the collecting system and the potential to damage nephrons if left untreated. It is the most common pathological cause of neonatal hydronephrosis ⁽¹⁾. It has an overall incidence of 1:1,500 and a ratio of males to females of 2:1 in newborns. Ureterovesical junction (UVJ) obstruction is an obstructive condition of the distal ureter as it enters the bladder, commonly called a primary obstructive megaureter. Megaureters are the second most likely cause of neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side ^(2,3).

81.2.1 Diagnostic Evaluation:

The widespread use of antenatal ultrasound during pregnancy has resulted in a higher detection rate ⁽⁴⁾. The challenge in the management of dilated UUT is to decide which child should be observed, which should be managed medically, and which requires surgical intervention.

- Antenatal ultrasound:

Usually performed between the 16th and 18th weeks of pregnancy, the kidneys are visualized routinely, when almost all amniotic fluid consists of urine. The most sensitive time for fetal urinary tract evaluation is the 28th week. If dilatation is detected, US should focus on:

- Laterality, severity of dilatation, and echogenicity of the kidneys.

- Hydronephrosis or hydro-ureteronephrosis.
- Bladder volume and bladder emptying.
- Sex of the child.
- Amniotic fluid volume ⁽⁵⁾.

- Postnatal ultrasound:

Since transitory neonatal dehydration lasts about 48 hours after birth, imaging should be performed following this period of postnatal oliguria. However, in severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended ⁽⁶⁾. Ultrasound should assess the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine.

- Voiding cystourethrogram:

Conventional VCUG is the method of choice for primary diagnostic procedures. In newborns with identified UUT dilatation, it should exclude:

- Vesicoureteral reflux (found in up to 25% of affected children) ⁽⁷⁾.
- Urethral valves.
- Ureterocele.
- Diverticula.
- Neurogenic bladder.

- Diuretic renography:

Diuretic renography is the most used diagnostic tool to detect the severity and functional significance of problems with urine transport. Technetium-99m (99mTc) mercaptoacetyltriglycine (MAG3) is the radionuclide of choice yet due to its non-availability in Egypt, DTPA is used. It is important to perform the study under standardized circumstances (hydration, transurethral catheter) after the fourth and sixth weeks of life ⁽⁸⁾. Oral fluid intake is encouraged prior to the examination. At fifteen minutes before the injection of the radionuclide, it is mandatory to administer normal saline intravenous infusion at a rate of 15 mL/kg over 30 minutes, and furosemide is 1 mg/kg for infants during the first year of life ⁽⁹⁾.

81.2.2 Management:

- *Antibiotic prophylaxis for antenatal hydronephrosis:*

The benefits and harms of continuous antibiotic prophylaxis (CAP) vs. observation in patients with antenatal hydronephrosis are controversial. ⁽¹⁰⁾ Based on the currently available evidence, the benefits and harms of CAP in children with antenatal hydronephrosis remain unproven. Uncircumcised infants and infants with hydroureteronephrosis and high-grade hydronephrosis are more likely to develop a UTI. Continuous antibiotic prophylaxis should be reserved for this sub-group of children who are proven to be at high risk. ⁽¹¹⁾

- UPJ obstruction:

It is crucial that management decisions are made based on serial investigations that have used the same technique and have been under standardized circumstances. Indications for surgical intervention comprise impaired split renal function (< 40%), a decrease of split renal function of > 10% in subsequent studies, poor drainage function after the administration of furosemide, increased anteroposterior diameter on US, and grade III and IV dilatation as defined by the Society for Fetal Urology ⁽¹²⁾.

- Megaureter:

Non-operative management is the mainstay of treatment, provided adequate ureteral drainage is confirmed by a functional study such as a diuretic DTPA renal scan. Generally, low-dose prophylactic antibiotics within the first year of life are recommended for the prevention of UTIs ⁽¹³⁾. Spontaneous remission rates of up to 85% are reported in primary megaureter cases. Surgical management is reserved for megaureters with recurrent UTIs, deterioration of split renal function (20% difference or drop in function of 10% during follow up) and progressive obstruction. Data suggest that children with a ureteric diameter of > 10-15 mm are more likely to require intervention. Ureteral tailoring is usually required with ureteral diameter of more than 10 mm ⁽¹⁴⁾.

81.2.3 Conclusion:

The use of routine perinatal sonography has resulted in increased detection of hydronephrosis caused by UPJ or UVJ obstruction. Meticulous and repeat postnatal evaluation is mandatory to try to identify obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are quite standardized and have a good clinical outcome.

Table 95: Recommendations for Management of ANH

Recommendation	Strength rating
1. We recommend that ANH be diagnosed and its severity graded based on anteroposterior diameter (APD) of the fetal renal pelvis.	Strong
2. ANH is present if the APD is ≥ 4 mm in second trimester and ≥ 7 mm in the third trimester.	Weak
3. all newborns with history of ANH should have postnatal ultrasound examination within the first week of life	Strong
4. In neonates with suspected posterior urethral valves, oligohydramnios or severe bilateral hydronephrosis, ultrasonography should be performed within 24-48 h of birth	Strong
5. voiding cystourethrography in postnatal investigations is indicated in:	Strong

- patients with unilateral or bilateral hydronephrosis with renal pelvic APD > 10 mm, society of fetal urology(SFU) grade 3-4 or ureteric dilatation. - infants with antenatally detected hydronephrosis who develop a urinary tract infection.	
6. Infants with moderate to severe unilateral or bilateral hydronephrosis (APD >10 mm) who do not show VUR should undergo diuretic renography	Strong
7. Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection like uncircumcised infants, children diagnosed with hydroureteronephrosis and high-grade hydronephrosis, respectively.	Weak
8. Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	Weak
9. Offer surgical intervention in case of an impaired split renal function due to obstruction less than 35% or a decrease of split renal function in subsequent studies by 5-10%, or increased anteroposterior diameter on serial US examinations, and grade IV dilatation as defined by the Society for Fetal Urology.	Weak
10. Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies proving a substantially impaired or decrease in function.	Weak
11. Do not offer surgery as a standard for primary megaureters since the spontaneous remission rates are as high as 85%.	Strong

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82 Congenital Lower Urinary Tract Obstruction:

The term congenital lower urinary tract obstruction (CLUTO) is used for a foetus, which shows during intrauterine US screening a dilatation of the upper and lower urinary tract. At that time of life, the diagnosis is usually based only on US examinations. There is a broad spectrum of conditions, which could cause an intrauterine dilatation of the urinary tract. Postpartum diagnosis comprises PUV in 56-63%, urethral atresia/ dysplasia in 9%, urethral stenosis in 3-7%, anterior urethral valve in less than 1%, a prune belly syndrome in up to 25% and a dilating reflux in up to 13%. Cloacal malformation can be found in 5-15%, ureterocele in 1-2%, a Megacystis-Microcolon-intestinal hypoperistalsis syndrome in 1-3% and also a Megacystis-Megaureter Syndrome in 1%

a. Posterior Urethral valves:

82.1.1 Epidemiology and Etiology:

The incidence of posterior urethral valves (PUV) is 1 in 5,000–8,000 live births, which accounts for approximately 10% of all prenatally detected cases of urinary tract obstruction. PUV are classified as type I and type III valves (Young classification); however, presentation, diagnosis, treatment, and prognosis are similar. Type I valves comprise 95% of all PUVs and are leaflets, which extend from the verumontanum distally across the entire anterior circumference of the urethra leaving only a small channel along the posterior wall. Type II valves are no longer regarded as valves. Type III valves are diaphragmatic membranes distal to the verumontanum with a small central opening. The sequelae of congenital PUV are seen at all levels proximal to the obstruction secondary to high voiding pressure. The prostatic urethra is dilated and the bladder neck is hypertrophied and rigid. Detrusor muscle hypertrophy leads to bladder wall thickening and deterioration of bladder compliance. All PUV patients demonstrate hydroureteronephrosis and 50% have VUR. Various degrees of renal dysplasia (irreversible) and uropathy (reversible) are found.

82.1.2 Presentation and Diagnosis:

Sixty percent of patients present with tubular damage, which manifests as failure to concentrate and to eliminate urinary acids. Tubular damage worsens with age and high urine volumes contribute to the deterioration of renal and bladder function. Elevated voiding pressures cause pop-off mechanisms such as VUR, bladder diverticula, urinary ascites, and a patent urachus. Unilateral VUR that is associated with renal dysplasia is termed VURD syndrome (Valve Unilateral Reflux Dysplasia); its protective effect on renal function is controversial. Clinical manifestations of PUVs depend on the age of presentation. The most significant clinical problem of the neonate is pulmonary hypoplasia secondary to oligohydramnios accounting for most of the neonatal mortality. Urinary sepsis, renal insufficiency, and ascites are other common symptoms in the newborn period. The majority of older boys present with UTIs and/or voiding dysfunction.

Most of PUVs are diagnosed with prenatal US. Classic US findings include bilateral hydroureteronephrosis, distended bladder and dilated posterior urethra (“keyhole sign”), as well as a thickened bladder wall. VCUG confirms the diagnosis by demonstrating a trabeculated bladder, elevated bladder neck, and dilated posterior urethra. Radionuclide renal scans can provide valuable information regarding differential renal function and renal drainage.

82.1.3 Management:

PUV management begins with immediate bladder drainage. Five French (5Fr) feeding tubes and not Foley catheters are to be used for drainage because the latter have a smaller functional lumen and can induce significant bladder spasms with consecutive functional UVJ obstruction. The feeding tube is left for 5 to 7 days to facilitate the introduction of the endoscope in the miniature neonatal urethra and to reach the nadir serum creatinine. Once the patient is stabilized, within these 5 to 7 days, endoscopic valve incision is performed with a Bugbee electrode, resectoscope, laser, or cold knife at the 4 o’clock, 8 o’clock, and sometimes 12 o’clock position. Continued catheter drainage for 24 h reduces the risk for hematuria but is not imperative. If valve ablation cannot be performed (neonate too small for instrumentation or lack of a trained pediatric urologist), a vesicostomy is indicated.

Upper urinary tract diversion (ureterostomy, pyelostomy) is **strictly** reserved for patients who fail to respond to bladder drainage and continue to experience urosepsis, elevated creatinine (>2 mg/dl after 10 days of bladder drainage), and worsening hydroureteronephrosis. Only upper tract drainage that allows bladder cycling is recommended.

After valve ablation, a residual degree of dilatation is present in a good percentage of PUV patients, and should not push to ureteral reimplantation since the incidence of true stenosis at the ureterovesical junction is almost nil. Up to 30% of VUR will resolve spontaneously once the obstruction is relieved. Antibiotic prophylaxis is indicated for all cases of reflux. Antireflux procedures are very rarely indicated in valve patients. They should never be attempted in patients with high pressure bladders. Early administration of oxybutynin may improve bladder function. High-grade reflux is associated with a poor functioning kidney and is considered a poor prognostic factor. However, early removal of the renal unit seems to be unnecessary, as long as it causes no problems. A “valve bladder” describes a chronic condition in patients after adequate valve ablation that will lead to deterioration of the upper urinary tracts and to urinary incontinence. Polyuria, particularly at night, is another factor contributing to persistent dilatation of the upper tract, nocturnal overdistention of the bladder and eventually bladder dysfunction. Nocturnal catheter is beneficial in such cases. Patients with PUV commonly present with prolonged daytime and nighttime incontinence up to 20 years of age.

Table 96: Recommendations for PUVs managment

Recommendation	Strength Rating

1. Diagnose posterior urethral valves (PUV) initially by ultrasound but a voiding cystourethrogram (VCUG) is required to confirm the diagnosis.	Strong
2. Assess split renal function by dimercaptosuccinic acid scan or mercaptoacetyltriglycine (MAG3) clearance. Use serum creatinine as a prognostic marker.	Strong
3. Vesico-amniotic shunt antenatally is not recommended to improve renal outcome.	Weak
4. Offer endoscopic valve ablation after bladder drainage and stabilization of the child.	Strong
5. If primary ablation cannot be done due to nonavailability of appropriate instruments or due to technical reasons, the next preferred procedure is vesicostomy particularly in preterm infants in whom visualization or ablation of the valve is not possible.	Strong
6. if child is unstable (urosepsis) and the upper tracts are dilated and tortuous with deranged renal parameters despite 1 week of catheterization, higher diversion in the form of ureterostomy is indicated.	Strong
7. Monitor bladder and renal function life-long, in all patients.	Strong

82.2 Duplex Systems and Ureterocele:

82.2.1 Incidence and Embryology:

Duplication of the urinary tract has an incidence rate of 0.5% to 1.25% in postmortem series and is identified at prenatal US in 0.6% of pregnancies. Postnatal evaluation is only required if the duplex system is dilated or associated with a ureterocele. Duplex kidneys are seen approximately twice as frequently in female patients and are bilateral in one-fifth of cases. Duplex kidneys form because of premature branching, or duplication, of the ureteric bud before it interacts with the metanephros to form the kidney. The upper pole of the kidney ureter may insert ectopically into the prostatic urethra, ejaculatory duct, seminal vesicle, vas deferens, or epididymis in boys or the urethra or vagina in girls. In boys, all these structures lie above the external urethral sphincter; therefore, the ectopic insertion does not cause incontinence. This is not the case in girls, where an ectopic ureter might appear with persistent dribbling incontinence at presentation. Duplex systems may be associated with a cystic dilatation of the distal end of the upper moiety ureter as it inserts into the bladder, forming a cyst called a ureterocele. Prenatally diagnosed UTD in a duplex system may be caused by obstruction (of the upper moiety, usually by a ureterocele or an ectopic insertion, or of the lower moiety, usually due to UPJ obstruction) or VUR (more commonly into the lower moiety, it but could affect both moieties).

82.2.2 Diagnosis and Evaluation:

Postnatal renal tract US should be performed after 48 hours (if the UTD is unilateral) or more urgently if it is bilateral, as the ureterocele could cause bladder outlet obstruction (BOO), even if the baby appears to be voiding. Unilateral cases are subsequently investigated with VCUG to

look for VUR and bladder emptying and with renography to assess the split function of the upper and lower moieties. Upper moieties associated with an obstructing ureterocele or an ectopic ureter are often dysplastic and poorly functioning.

82.2.3 Treatment Options and Outcomes:

All neonates with prenatal UTD in a duplex system should be started on prophylactic antibiotics. If there is suspicion for bladder outlet obstruction, the neonate requires catheterization and urgent evaluation with VCUG. Further management will depend on the presence of symptoms, such as febrile UTIs or voiding difficulty and the function of the affected moiety. VUR in completely duplicated systems may initially be treated conservatively with observation and antibiotic prophylaxis, although the resolution rate is less than that for VUR in simplex systems. (20% vs 50%, respectively, at 5-year follow-up). Surgical intervention depends on the underlying cause for the UTD.

Ureterocele: Obstruction by a ureterocele may be initially treated endoscopically by puncturing the ureterocele, although this carries a risk of iatrogenic VUR. Failure of endoscopic management to relieve the obstruction may require a transurethral resection of the ureterocele. Alternatively, a more complex surgery may involve a heminephroureterectomy of the upper pole of the kidney, a ureteroureterostomy or excision of the ureterocele, and reimplantation. Small, asymptomatic, nonobstructive ureteroceles may not require any intervention.

Ectopic Ureter: kidneys in girls with dribbling incontinence may be notoriously difficult to identify and are not always apparent at US. Magnetic resonance urography may be helpful to clarify the anatomy and diagnose the ectopic ureter. Ectopic ureters may be surgically managed with a ureteroureterostomy (the ectopic ureter is disconnected and anastomosed to the lower moiety ureter), heminephroureterectomy of the nonfunctioning (often small) upper moiety, or reimplantation of the ectopic ureter into the bladder.

Table 97: Recommendationf of Diagnosis and Treatment Options for Ureterocele and Ectopic Ureter

Recommendations			Strength rating
Ureterocele	Diagnosis	Use ultrasound (US), radionuclide studies (mercaptoacetyltriglycine (MAG3)/dimercaptosuccinic acid (DMSA), voiding cystourethrography (VCUG), magnetic resonance urography, high-resolution magnetic resonance imaging (MRI), and cystoscopy to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	Weak
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial nephroureteretomy, complete primary reconstruction.	Weak

		Offer, early endoscopic decompression to patients with an obstructing ureterocele.	
Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	Weak
	Treatment	In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definitive solution. Ureteral reconstruction (ureteral re-implantation/ ureteroureterostomy/ureteropyelostomy and upper- pole ureterectomy) are other therapeutic option especially in cases in which the upper pole has function worth preserving.	Weak

83 Vesicoureteric Reflux:

Vesicoureteric reflux (VUR) is a very common urological anomaly in children, with an incidence of nearly 1%. Controversy persists over the optimal management of VUR, particularly the choice of diagnostic procedures, treatment (medical, endoscopic, or surgical), and the timing of treatment. The choice of management depends on the presence of renal scars, clinical course, grade of reflux, ipsilateral renal function, bilaterality, bladder and bowel dysfunction (BBD), associated anomalies and the age of the patient ^(1,2).

83.1 Initial Evaluation of the child with VUR:

83.1.1 General evaluation

Standard: VUR and urinary tract infections may detrimentally affect the overall health and renal function in affected children. Therefore, on initial presentation the child with VUR should undergo a careful general medical evaluation including measurement of height, weight, blood pressure and serum creatinine if bilateral renal abnormalities are found.

Recommendation: Urinalysis for proteinuria and bacteriuria is recommended. If the urinalysis indicates infection, a urine culture and sensitivity is recommended.

Option: A baseline serum creatinine may be obtained to establish an estimate of glomerular filtration rate (GFR) for future reference.

83.1.2 Imaging Procedures

Recommendation: Because VUR and urinary tract infection may affect renal structure and function, performing renal ultrasound to assess the upper urinary tract is recommended.

The use of VCUG is recommended in patients with US findings of high-grade hydronephrosis, duplex kidneys with hydronephrosis, cortical abnormalities (as cortical thinning and irregularity, as well as increased echogenicity) ureterocele, ureteric dilatation, and abnormal bladders (as keyhole sign).

Option: DMSA (technetium-99m-labeled dimercaptosuccinic acid) renal imaging can be obtained to assess the status of the kidneys for scarring and function.

The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of VUR. Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [10].

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83.1.3 Grading system for VUR on VCUG, according to the International Reflux Study Committee ⁽¹¹⁾:

Grade I: Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation.

Grade II: Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices.

Grade III: Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices.

Grade IV: Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible

Grade V: Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux.

- Dimercaptosuccinic acid (DMSA) is the best nuclear agent for visualizing the cortical tissue and differential function between both kidneys. DMSA scans are therefore used to detect and monitor renal scarring. Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive, need diuretic renogram to exclude obstruction.

83.1.4 Optional investigations:

- a) Video-urodynamic studies are only important in patients in whom secondary reflux is suspected, e.g. those with spina bifida or PUV.
- b) In the case of LUTS, diagnosis and follow-up can be limited to non-invasive tests (e.g. voiding charts, US, or uroflowmetry).
- c) Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies e.g. ectopic ureter that might influence therapy.

83.2 Initial Management of the Child with VUR

The goals of management of the child with VUR are to 1) prevent recurring febrile UTIs; 2) prevent renal injury; and 3) minimize the morbidity of treatment and follow-up.

83.3 Children with Febrile Urinary Tract Infections

Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections. A routine recommendation of VCUG at zero to two years of age after the first proven febrile UTI is the safest approach as the evidence for the criteria to selecting patients for reflux detection is weak. An alternative “top-down” approach is also an option; children with febrile infections and abnormal DMSA/renal US findings may have higher risk of developing renal scars and they should all be evaluated for reflux ⁽¹²⁾.

83.4 The child with VUR less than one year of age

Recommendation: Continuous antibiotic prophylaxis is recommended for the child less than one year of age with VUR with a history of a febrile urinary tract infection. This approach is based on the greater morbidity from recurrent urinary tract infections found in this population.

Recommendation: In the absence of a history of febrile urinary tract infections, continuous antibiotic prophylaxis is recommended for the child less than one year of age with VUR grades III–V who is identified through screening.

Option: In the absence of a history of febrile urinary tract infections, the child less than one year of age with VUR grades I–II who is identified through screening may be offered continuous antibiotic prophylaxis.

83.5 The child with UTI and VUR more than one year of age

Guidelines for management of VUR in the child more than one year of age are somewhat different from those for the child less than one year of age, reflecting several contributing elements that influence clinical outcomes. These include the greater likelihood of BBD, the lower probability of spontaneous resolution of VUR, lower risk of acute morbidity from febrile UTI and the greater ability of the child to verbally complain of symptoms to indicate acute infection. The management decision should be made with recognition of the clinical context, including the presence of BBD, patient age, VUR grade, the presence of scarring, and parental preferences. Given the individuality of each patient and their parental preferences, there can be no uniform guidelines of management.

Recommendation: If clinical evidence of bladder/bowel dysfunction is present (see "Initial evaluation of the child with VUR" above) treatment of bladder/bowel dysfunction is indicated, preferably before any surgical intervention for VUR is undertaken.

Recommendation: Continuous antibiotic prophylaxis is recommended for the child with bladder/bowel dysfunction and VUR due to the increased risk of urinary tract infection while bladder/bowel dysfunction is present and being treated.

Option: Continuous antibiotic prophylaxis may be considered for the child over one year of age with a history of urinary tract infections and VUR in the absence of bladder/bowel dysfunction.

Option: Observational management without continuous antibiotic prophylaxis, with prompt initiation of antibiotic therapy for urinary tract infections, may be considered for the child with VUR in the absence of bladder/bowel dysfunction, recurrent febrile urinary tract infections, or renal cortical abnormalities. While this approach is currently under investigation and therefore no firm recommendation can be made, preliminary data suggest that some groups of patients with VUR may do as well with this approach as with continuous antibiotic prophylaxis.

83.5.1 Disease Management

There are two main treatment approaches: non-surgical and surgical. The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation needs to be challenged, because the treatment should be tailored to different risk groups.

83.5.2 Non-surgical treatment:

It is based on the understanding that ⁽¹³⁾:

- Vesicoureteric reflux resolves spontaneously, mostly in young patients with low-grade reflux. Resolution is nearly 80% in VUR grades I and II and 30-50% in VUR grades III-V within four to five years of follow-up. Spontaneous resolution is low for bilateral high-grade reflux.
- Vesicoureteric reflux does not damage the kidney when patients are free of infection and have normal LUT function.
- There is no evidence that correction of persistent low-grade reflux (grades I-III) without symptoms and normal kidneys offers a significant benefit.
- There is no evidence that small scars can cause hypertension, renal insufficiency, or problems during pregnancy. Indeed, these are possible only in cases of severe bilateral renal damage.
- The initial treatment for all VUR patients diagnosed within the first year of life as corrective surgical intervention is not advised.
- It is strongly recommended to initially manage all VUR children presenting at age one to five years conservatively.

83.5.2.1 The conservative approach includes:

1. Watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with LUTD.
2. Circumcision during early infancy may be considered as part of the conservative approach because it is effective in reducing the risk of infection in normal children.
3. Regular follow-up with imaging studies (e.g. VCUG, nuclear cystography, or DMSA scan) to monitor spontaneous resolution and kidney status.
4. Should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered. ⁽¹⁴⁾

83.5.2.2 Continuous antibiotic prophylaxis (CAP)

CAP may not be needed in every reflux patient. Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms. CAP is

useful in patients with high-grade reflux in preventing recurrent infections by 50% but its use in preventing further renal scarring and its consequences (hypertension and renal failure) is not proven. Based on a risk classification system defines a high-risk group (uncircumcised males, infants / toilet-trained children, presence of BBD and high-grade reflux) who would benefit from an antibiotic prophylaxis significantly. It is recommended to use CAP until after children have been toilet-trained and ensuring that there is no LUTD. CAP has the cost of increased antimicrobial resistance ⁽¹⁵⁾.

Active surveillance of UTI is needed after CAP is discontinued. It is strongly advised that the advantages and disadvantages should be discussed in detail with the family.

83.5.3 Surgical treatment:

Surgical treatment can be endoscopic injection of bulking agents or ureteral re-implantation. Surgical correction should be considered in symptomatic patients with persistent high-grade reflux (grades IV/V) especially if associated with abnormal renal parenchyma, or in patients presented after toilet-training. Offer surgical correction if parents prefer definitive therapy to conservative management. There is no consensus about the timing (usually after age of one year) and type of surgical correction. The outcome of open surgical correction is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades and those with LUTD. In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.

83.5.3.1 Subureteric Injection of Bulking Materials

Endoscopic subureteric injection of biodegradable bulking agents has become an alternative to long-term antibiotic prophylaxis and open surgical intervention in the treatment of VUR in children. Using cystoscopy, a bulking material is injected beneath the intramural part of the ureter in a submucosal location. The injected bulking agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, which prevents reflux of urine into the ureter, while still allowing its antegrade flow.

Several bulking agents have been used over the past two decades. The most used agents nowadays are a solution of dextranomer/hyaluronic acid (Deflux™, Dexell®) and polyacrylatepolyalcohol copolymer hydrogel (Vantris®) ⁽¹⁶⁾.

In a meta-analysis of 5,527 patients and 8,101 renal units, the reflux resolution rate (by ureter) following one treatment for grades I and II reflux was 78.5%, 72% for grade III, 63% for grade IV, and 51% for grade V. If the first injection was unsuccessful, the second treatment had a success rate of 68% and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was significantly lower for duplicated (50%) vs. single (73%) systems, and neuropathic (62%) vs. normal (74%) bladders. Studies with long-term follow-up have shown that there is a high recurrence rate (up to 20%) in two years ⁽¹⁷⁾.

Obstruction at UVJ may happen in the long-term follow-up after endoscopic correction of reflux. Patients with high-grade reflux and dilated ureters are at risk of late obstruction ⁽¹⁸⁾.

83.5.3.2 Open Surgical Techniques

Various intra- and extravesical techniques have been described for the surgical correction of reflux. They all share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter in a tunnel of 5:1 ratio to ureteral diameter. All techniques have been shown to be safe with a low rate of complications and excellent success rates (92-98%) ⁽¹⁹⁾.

The most popular and reliable open procedure is cross trigonal re-implantation described by Cohen ⁽¹⁸⁾. The main concern with this procedure is the difficulty of accessing the ureters endoscopically, if needed, when the child is older. Alternatives are suprahialal re-implantation (Politano-Leadbetter technique) and extravesical procedure (Lich-Gregoir). In bilateral reflux, an intravesical anti-reflux procedure may be considered, because simultaneous bilateral extravesical reflux repair carries an increased risk of temporary post-operative urine retention ⁽²⁰⁾. Vesicostomy / ureterostomy may be indicated as shunting maneuver till the definitive surgery is safely done.

83.5.4 Laparoscopy and Robot-Assisted Techniques

Various anti-reflux surgeries have been performed with the robot and the extravesical approach is the most used. Operative times, costs and post-operative complications leading to secondary interventions are higher with laparoscopy, but post-operative pain and hospital stay is less compared to open surgery ⁽²¹⁾. Therefore, at present, a laparoscopic approach cannot be recommended as a routine procedure and should be limited to centers of excellence ⁽²²⁾.

Table 98: Recommendations for VUR managment

Recommendation	Strength rating
1. Initially treat all patients diagnosed within the first year of life with continuous antibiotic prophylaxis, regardless of the grade of reflux or presence of renal scars.	Weak
2. Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	Strong
3. Offer definitive surgical or endoscopic correction to patients with frequent breakthrough infections.	Weak
4. Offer open surgical correction to patients with persistent high-grade reflux and endoscopic correction for lower grades of reflux.	Strong
5. Initially manage all children presenting at age one to five years conservatively.	Strong
6. Offer surgical repair to children above the age of one presenting with high-grade reflux and abnormal renal parenchyma.	Weak

7. Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	Strong
8. Ensure that a detailed investigation for the presence of lower urinary tract dysfunction (LUTD) is done in all and especially in children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.	Strong
9. Offer surgical correction, if parents prefer definitive therapy to conservative management.	Strong
10. Select the most appropriate management option based on: • The presence of renal scars; • Clinical course; • The grade of reflux; • Ipsilateral renal function; • Bilaterality; • Bladder function; • Associated anomalies of the urinary tract; • Age and gender; • Compliance; • Parental preference.	Weak
11. In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.	Strong

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84 Disorders of Sex Development (DSD):

The term 'disorders of sex development (**DSD**)' is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex. This term replaced the former terms: 'intersex disorders', 'pseudohermaphroditism' and 'hermaphroditism' ⁽¹⁾. Overall, evidence-based literature on DSD is sparse. An exception is the risk of gonadal cancer, for which the level of evidence is higher ⁽²⁾.

DSD can present as prenatal diagnosis, neonatal diagnosis and late diagnosis. Prenatal diagnosis can be based on karyotype or US findings; neonatal diagnosis is based on genital ambiguity and late diagnosis is made on early or delayed puberty ⁽³⁾. *Dealing with neonates with DSD requires a multidisciplinary approach*, which should include specialized pediatric urologists, geneticists, neonatologists, endocrinologists, gynecologists, pediatric psychologists, ethicists, social workers and transition to adult care. **Refer the DSD newborn immediately to such tertiary pediatric centers.**

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84.1 Current classification of DSD conditions:

1- 46XX DSD group e.g. congenital adrenal hyperplasia (CAH) patients which represent approximately 80% of all DSD conditions. CAH are extremely important since they can be potentially life-threatening neonatal emergency because of salt loss phenomenon and immediate medical care is mandatory. ⁽⁴⁾

2- 46XY DSD group e.g. the partial androgen insensitivity syndrome (PAIS) as well as the complete androgen insensitivity syndrome (CAIS).

3- Sex chromosome mosaicism DSD group (45X, 45X/46XY, 47XXY) e.g. the mixed gonadal dysgenesis (MGD). Many have normal male phenotype and others asymmetric genitalia with one side is more a labia majora with usually no palpable gonad (most likely to be a streak gonad).

4- Ovotesticular DSD group because of the presence of ovarian and testicular tissue in the same individual (one ovary and one testis or one or two ovotestes) meaning that both – female and male structures – live together. There is great variability in phenotype with uni- or bilateral undescended gonads.

5- Non-hormonal/non-chromosomal DSD group including newborns with cloacal Exstrophy, aphallia, and severe micropenis.

84.2 Diagnostic evaluation:

84.2.1 Findings suggesting the possibility of DSD are:

- a) Apparent male: Severe hypospadias associated with bifid scrotum, undescended testis/testes with hypospadias and bilateral non-palpable testes in a full-term apparently male infant.
- b) Apparent female: Clitoral hypertrophy of any degree, non-palpable gonads, vulva with single opening, indeterminate and ambiguous genitalia.

84.2.2 Diagnostic work-up of neonates with DSD:

- a) History (family, maternal, neonatal): parental consanguinity, previous DSD or genital anomalies, previous neonatal deaths, primary amenorrhea or infertility in other family members, maternal exposure to androgens and failure to thrive, vomiting, diarrhea of the neonate.
- b) Physical examination: pigmentation of genital and areolar area, hypospadias or urogenital sinus, size of phallus, palpable and/or symmetrical gonads (mostly testis and virtually excludes 46XX DSD) and blood pressure. Medical photography can be useful but requires sensitivity and consent ⁽⁵⁾.
- c) Investigations: serum 17-hydroxyprogesterone - serum electrolytes, LH, FSH, TST, cortisol and ACTH - adrenal steroids in urine – Karyotype – Ultrasound – Genitogram - hCG stimulation test to confirm presence of testicular tissue and androgen-binding studies.
- d) Invasive diagnostics under general anesthesia: can be helpful in some cases.
 - i. Cystoscopy, to evaluate the urogenital sinus, the level of confluence, the vagina or utriculus, and the possible presence of a cervix at the top of the vagina.
 - ii. Laparoscopy allow a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed ⁽⁶⁾.

84.2.3 Gender assignment:

Nowadays it is obvious and clear that open and complete communications with caregivers and eventually the affected person are mandatory. The lack of outcome data and different preferences make it extremely difficult to determine whether and when to pursue gonadal or genital surgery. *Shared fully informed decision making is necessary, combining expert healthcare knowledge in a patient- and family-centered multidisciplinary setting.* The goal of all involved should be to individualize and prioritize each patient. Surgical interventions in children with DSD only being applied in emergency conditions and it is better to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent ⁽⁷⁾

84.3 Risk of tumor development:

Individuals with DSD have an increased risk of developing germ cell cancer in comparison with to the general population ⁽⁸⁾. *The highest risk prevalence (30-50%) is seen in patients with 46XY gonadal dysgenesis and in some patients with 45X/46XY DSDs.* Conversely, patients with testosterone biosynthesis disorders and androgen action disturbances show a much lower risk (1-15%) for carcinoma in situ (CIS) development during childhood and a limited tendency towards invasive progression of the lesions. Regarding clinical management a gonadal biopsy at the time of a possible orchidopexy, patients can be obtained for regular self-exams and annual ultrasound ⁽²⁾.

Table 99: Recommendations for DSD management

Recommendations	Strength rating
1. <i>Newborns with DSD conditions warrant a multidisciplinary team approach.</i>	Strong
2. <i>Refer children to experienced centers where neonatology, pediatric endocrinology, pediatric urology, child psychology and transition to adult care are guaranteed.</i>	Strong
3. <i>Do not delay diagnosis and treatment of any neonate presenting with ambiguous genitalia since salt-loss in a 46XX CAH girl can be fatal.</i>	Strong

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Committee X

Urinary Lithiasis



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EGYPTIAN UROLOGICAL GUIDELINES ON Urolithiasis

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85 Abbreviations

IVU	Intravenous Urography
NSAID	Non-Steroidal Anti-Inflammatory Drug
PDE-5	Phosphodiesterase type 5
URS	Ureteroscopy
RIRS	Retrograde and Antegrade,
URS	Ureteroscopy
ACOG	American College of Obstetrics and Gynecology
IVU	Intravenous Urography
RTA	Renal tubular acidosis
ALARA	As Low As Reasonably Achievable
FURS	Feasible Alternative For Renal Stones

86 Abstract

Urinary stone disease is a highly prevalent condition in Egypt. Management depends on stone site, size and composition and is based on an adequate grasp of endourologic techniques. The guidelines are grouped according to stone site in the urinary tract, with special sections for general recommendations and special conditions

86.1 Methods:

A comprehensive scoping effort covering all guidelines (American, European and Canadian) as regard to different patterns of urinary tract calculi was performed.

For each recommendation and advice in this overview, all of the following elements were highly considered:

- Quality of evidence for this recommendation.
- Impact of this practice on patient and oncological outcomes.
- The balance between this practice and the different aspects of health service in our locality.

86.2 Results.

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

86.3 Conclusions.

These guidelines provide practical evidence-based guidance on the clinical aspect of Urinary tract calculi. The main target is entirely focused on assessment and treatment, reflecting the recommended clinical practice. This can provide the basis for thinking through patient's management and also for planning and designing clinical services.

87 Introduction

Urinary stone disease is a highly prevalent disease worldwide, with significant variation in rates based on geography, climate, diet, fluid intake, genetics, sex, occupation and age. Egypt lies in a stone belt of increased incidence and the evolution of socioeconomic standards has led to a change in the pattern of stone disease in the country. ⁽¹⁻⁶⁾

Due to the significant impact of stone disease, a guidelines committee was developed to help Egyptian urologists incorporate recommendations into clinical practice based on current evidence based analysis. The aim being to establish a consensus on the treatment approach in keeping with our specific social environment and economic limitations.

The Guideline for Stone Diseases committee members meticulously reviewed the relevant references retrieved via the PubMed and MEDLINE databases. They also relied heavily on previous recommendations of esteemed international entities as:

- (i) EAU Guidelines on Urolithiasis 2017, published by the EAU;
- (ii) Surgical Management of Stones: AUA/Endourological Society Guidelines;
- (iii) NICE Guideline – Renal and ureteric stones: assessment and management; and,
- (iv) The Urological Association of Asia clinical guideline for urinary stone disease. ⁽⁷⁻¹⁰⁾

Information was incorporated into a modified set of Egyptian Guidelines suitable for incorporation based on our socioeconomic limitations while incorporating evidence based rationale. ⁽¹¹⁾ Having said this the best treatment also depends on the circumstances of each individual case and is not uniform so that the guidelines should be taken as an advisory not legally binding document that should be of benefit in case management.

88 General Recommendations and Precautions for Stone Removal

88.1 Antibiotic therapy:

Strong Recommendation:

- A. UTI should always be treated if stone removal is planned.
- B. Urine culture or urinary microscopy should be performed before treatment.
- C. Patients with clinically significant infection and obstruction, drainage should be performed for several days before starting stone removal.
- D. In absence of UTI SWL, does not require antimicrobial prophylaxis.
- E. In URS and PNL antimicrobial prophylaxis is strongly recommended.
- F. Patients undergoing PNL with sterile urine may still develop infectious complications including UTI and sepsis may be due to the presence of unsuspected bacteria within stones.
- G. Antimicrobial prophylaxis is based primarily on prior urine culture results.
 - 1. Administered prior to stone intervention within 60 minutes of the procedure and repeated during the procedure if the case length necessitates.
 - 2. A single oral or IV dose.
 - 3. An antibiotic that covers both gram positive and negative uropathogens.

88.2 Obesity

- A. Cohort studies concluded that individuals who are considered obese are more at risk of developing kidney stones.
- B. Obesity link with an increased risk of developing kidney stone disease and influence the composition of the stones. High BMI is associated with high urinary oxalate, calcium and uric acid levels. Whilst calcium oxalate still composed the majority of stones formed, as BMI increases, the proportion of uric acid stones increases.
- C. A high BMI can pose a higher anesthetic risk.
- D. The proposed management of kidney stones ranges from patient lifestyle modifications to pharmacological management and invasive intervention.
- E. Management plans should be tailored to individual patients and influenced by their BMI and the presence of metabolic syndrome.

F. The body habitus of an individual also influences the type of intervention that is most appropriate, with flexible URS/RIRS increasingly being the preferred option in obese patients.

G. Management of urolithiasis in patients with morbid obesity is usually associated with higher morbidity and mortality compared to non-obese patients.

H. SWL: The success rate is reduced, possible causes:

1. Patient weight.
2. Increase in skin to stone distance which leads to increased absorption of the shock wave.
3. Difficulty in stone localization and radiolucency of urate stones, and therefore inability to focus the shock wave beam effectively.
4. Increased likelihood of residual stone fragments.
5. A BMI > 30 kg/m² was also associated with an increased risk of renal haematoma, possibly due to inappropriately high energy usage, also, may be because many of these patients have concurrent hypertension and increased vascular vulnerability.

URS:

1. In severe obesity, it is a more promising therapeutic option than SWL.
2. Used as first-line therapy for ureteral and renal stones - Strong Recommendation.
3. A safe option in obese patients (BMI > 30 kg/m²) with comparable SFRs and complication rates. However, in morbidly obese patients (BMI > 35 kg/m²) the overall complication rates double.

Flexible URS/RIRS:

Is a safe and effective approach for renal stone treatment in obese individuals, except it requires long operation time depending on the size, number, and location of stones and on the experience of the surgeon.

Currently, seems to be the most appropriate intervention for small stones and PCNL for larger stones in the obese population

PCNL:

1. Is a particularly important therapeutic modality for obese individuals?
2. Studies have assessed the intra- and postoperative outcomes of PCNL in obese patients with renal stones > 2 cm but with longer operative times and the stone-free rate is inferior.

88.3 Stone composition

A. Consider the stone composition before deciding the method of removal - Strong Recommendation.

B. Stone composition is suspected based on:

1. Patient history.
2. Former stone analysis of the patient.
3. Hounsfield unit on NCCT.

C. Attempt to dissolve radiolucent stones - Strong Recommendation.

D. Hard stones for SWL:

1. Brushite, calcium oxalate monohydrate, and cystine.
2. Homogeneous stones with a high density on NCCT.

E. PNL, URS, and flexible URS/RIRS: alternatives to treat large SWL-resistant stones.

88.4 Contraindications of procedures

A. Contraindications of SWL:

1. Uncontrolled UTIs.
2. Bleeding diatheses: should be compensated for at least 24 hours before and 48 hours after treatment.
3. Pregnancy: potential effects on the fetus.
4. Severe skeletal malformations and severe obesity: prevent targeting of the stone.
5. Arterial aneurysm in the vicinity of the stone.
6. Anatomical obstruction distal to the stone.

B. Contraindications of URS:

1. Apart from general problems, for example with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

C. Contraindications of PNL:

1. Uncontrolled UTI.
2. Patients receiving anti-coagulant therapy: must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PNL.
3. Pregnancy.
4. Tumor in the presumptive access tract area.
5. Potential malignant kidney tumor.

88.5 Recommendations of preoperative work-up

KUB has low accuracy for the diagnosis of urinary stones (sensitivity and specificity of KUB is 44-77%). It can be used only for detection of radiopaque calculi and for comparison during follow-up.^(12,13)

US is radiation-free, cheap and readily available; but with low sensitivity/specificity (sensitivity 45% and specificity 94% for detecting ureteral stones)⁽¹⁴⁾

NCCT is highly sensitive and specific for the detection ureteric stones.^(8,9) Low-dose NCCT (<4 mSv) is recommended for diagnosis of ureteric stones in patients with BMI <30 kg/m⁽¹⁵⁾

During Pregnancy radiation exposure is a major concern. Low-dose CT has a high positive predictive value (95.8%), as opposed to MRI (80%) and US (77%) for detection of ureteric stones.⁽¹⁶⁾

Magnetic resonance urography cannot be used to detect urinary stones, it can detect the location of obstruction in the ureter, and renal parenchymal morphology.

Pain relief, should not be delayed by imaging assessments

88.5.1 Radionuclide renal scan

The least invasive method for determining differential function

Detection of baseline renal function can be useful in assessment of treatment outcomes for upper urinary tract stones⁽¹⁷⁾

Clinicians may obtain a functional imaging study (DTPA or MAG-3) if clinically significant loss of renal function in the involved kidney or kidneys is suspected.

In patients with ureteral stones causing obstruction the assessment of renal function by nuclear scan might not be accurate. Use of creatinine clearance from urine collected from PCN, compared with urine from contralateral percutaneous nephrostomy or self-voided urine can be used⁽¹³⁾

88.5.2 Re imaging

Can be performed for patients prior to surgery if:

- Passage of stones is suspected
- Stone movement will change management
- Reimaging should focus on the region of interest to limit radiation exposure.
- Repeat imaging can include KUB x-ray, renal/bladder US, or CT.

Table 100: Recommendations of preoperative work-up

Recommendations	Strength Rate
1. We recommend ultrasound (US) as a primary diagnostic imaging tool	Strong
2. We recommend non-contrast-enhanced CT to confirm stone diagnosis in patients with acute flank pain	Strong
3. We recommend KUB for follow up of radiopaque ureteric stones	weak
4. We recommend functional imaging study (DTPA or MAG - 3) if clinically significant loss of renal function in the involved kidney is suspected	weak
5. We recommend ultrasound as the preferred method of imaging during pregnancy	Strong
6. We recommend low dose non-contrast CT during pregnancy as a last line	weak
7. We do not recommend Magnetic resonance urography (MRU) for evaluation of ureteral calculi	strong

88.6 Diagnostic imaging in children

Radiation exposure is a major concern for children; therefore, US is the initial imaging modality for children

Plain films (KUB radiography) : Used to identify radiopaque stones, and for follow-up.

Intravenous urography (IVU) : The need for contrast medium injection is a major drawback.

Table 101: Diagnostic imaging in children

Recommendations	Strength Rate
1. Collect stone material for analysis to classify the stone type.	Strong
2. We recommend ultrasound as first-line imaging for children with suspected renal colic	Strong
3. We recommend kidney-ureter-bladder radiography (or low-dose non-contrast-enhanced computed tomography) if ultrasound will not provide the required information.	Strong

89 Ureteral Stones

89.1 Recommendations of treatment for ureteral stone pain management

NSAIDs are effective for acute stone colic, and have better analgesic effect compared to opioids. (18,19)

Patients with ureteral stones treated with alpha1-blockers can reduce the number of pain episodes, the need for analgesic medication (diclofenac) and hospitalization. (18)

- Offer intravenous paracetamol to adults, children and young people with suspected renal colic if NSAIDs are contraindicated or are not giving sufficient pain relief.
- Consider opioids for adults, children and young people with suspected renal colic if both NSAIDs and intravenous paracetamol are contraindicated or are not giving sufficient pain relief.

Table 102: Recommendations of treatment for ureteral stone pain management

Recommendations	Strength rating
1. We recommend non-steroidal anti-inflammatory drug (NSAID) as first-line treatment for patients with suspected renal colic.	Strong
2. We do not recommend antispasmodics to adults, children and young people with suspected renal colic	Strong
3. We recommend renal decompression or ureteroscopic stone removal in case of analgesic refractory colic pain.	Strong

89.2 Recommendations for use of medical expulsive therapy

α 1 receptor antagonists have the potential to inhibit ureteral spasm and uncontrolled contraction, theoretically reducing pain and promoting spontaneous stone passage. Tamsulosin significantly facilitated the passage of distal ureteral stones in patients with well-controlled pain, no infections, abnormal anatomy, renal insufficiency or high-grade obstruction. (16)

No improvement in stone passage rates was observed in patients with $\leq$ 5-mm distal ureteral stones. Stones of 5–10 mm showed a higher passage rate in the tamsulosin group. (20-22)

Experimental data on the effects of complete unilateral ureteral obstruction on renal function suggest the interval of conservative therapy should not exceed six weeks

α -blockers have been shown in multiple RCTs to have benefit for stent related discomfort. ⁽²³⁾

Patients treated with alpha blockers, calcium-channel inhibitors (nifedipine) and phosphodiesterase type 5 (PDE-5) inhibitors (tadalafil) are more likely to pass stones with fewer colic episodes than those not receiving such therapy. ^(24, 25)

Clinicians may offer antimuscarinic therapy to reduce stent discomfort.

PDE-5 Inhibitors or corticosteroids in combination with alpha blockers in MET can be made. ⁽²⁵⁾

Table 103: Recommendation for use of medical expulsive therapy

Recommendation	Strength Rating
1. We recommend alpha blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones less than 10 mm.	Strong
2. We recommend alpha blockers as an adjunct to SWL for adults with ureteric stones	weak
3. We recommend alpha blockers to reduce stent related discomfort.	weak

The Panel recommends a four to six-week interval for conservative treatment to reduce the potential for permanent damage. Furthermore, studies have indicated that most stones that pass do so within six weeks.

89.3 Role of medical chemolysis in uric acid stone

The role of medical chemolysis is to dissolve Uric acid stones.

Urinary pH is the most important factor in uric acid solubility. ⁽²²⁾

Oral alkaline citrate or sodium bicarbonate can be used for alkalinization of urine

The pH should be adjusted in the range of 7.0–7.2 to prevent formation of calcium phosphate calculi. ⁽²⁶⁾

No RCTs are available for this therapy.

Obstruction of the urinary tract by uric acid calculi can be treated by oral chemolysis in combination with urinary drainage. A combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones.

Table 104: Role of medical chemolysis in uric acid stone

Recommendation	Strength Rating
1. We recommend oral chemolysis to dissolve pure uric acid stones	Strong
2. We recommend monitoring patients during oral chemolysis of uric acid stones.	Strong
3. We recommend oral chemolysis with tamsulosin in case of ureteral stones (if active intervention is not indicated or refused by the patient.	Weak
4. We recommend treatment of obstructing uric acid calculi by oral chemolysis in combination with urinary drainage	Strong

89.4 Stenting before shockwave lithotripsy

Some urologists place ureteral stents prior to SWL with the intention of improving stone-free rates or preventing complications. Both the 1997 AUA Guideline and the 2007 EAU/AUA Guideline for the Management of Ureteral Calculi recommended against routine stenting with SWL. ^(8,9)

Table 105: Stenting before shockwave lithotripsy

Recommendation	Strength Rating
1. We do not recommend routine stenting to adults having shockwave lithotripsy for ureteric stones	Strong
2. We recommend pre-stenting in patients having SWL for ureteric stones with Solitary kidney either anatomical or functional	Strong

89.5 Guidelines for the management of sepsis and anuria

Ureteroscopy in presence of active, untreated infection can lead to life-threatening sepsis. The collecting system must be drained with a nephrostomy tube or a ureteral stent to allow drainage of infected urine and permit antibiotic penetration into the affected renal unit.

The mortality was higher in those not treated with surgical decompression compared to those who underwent drainage (19.2% vs 8.82%, $p < 0.001$). The choice of drainage modality, stent or nephrostomy tube, is left to the urologist, as both have been shown to be equally effective. ⁽²⁷⁾

Table 106: Guidelines for the management of sepsis and anuria

Recommendations	Strength rating
1. We recommend urgent drainage of the collecting system in case of sepsis with obstructing stones, using percutaneous drainage or ureteral stenting.	Strong
2. We recommend to delay definitive treatment of the stone until sepsis is resolved.	Strong
3. We recommend collecting urine again after decompression for antibiogram	Strong
4. We recommend to start antibiotics immediately	Strong
5. We recommend Re-evaluate antibiotic regimen following antibiogram findings.	Strong
6. We recommend in severely ill patients and massively dilated kidney PCN decompression rather than stent unless the patient has bleeding diathesis	Strong

89.6 Ureteroscopy (URS) (Retrograde and Antegrade, RIRS)

Endoscopic management is the standard approach for most stone removal. Surgery, open/laparoscopic/robotic-assisted may be required in selected situations

- Stones requiring complete removal within a single session (infection stones)
- Associated anatomical abnormalities requiring simultaneous reconstruction
- Failed endoscopic surgery

The current standard for rigid ureteroscopes is tip diameters of < 8 F. Rigid URS can be used for the whole ureter. ⁽²⁸⁾

Technical improvements and availability of disposable digital scopes, has increased the use of flexible URS in the ureter.

Clinicians should use normal saline irrigation for URS.

Percutaneous antegrade removal of ureteral stones is a consideration in:

- Large (>15mm), impacted proximal ureteral calculi in a dilated renal collecting system
- When the ureter is not amenable to retrograde manipulation. ⁽²⁹⁾

89.7 Anesthesia

Endoscopy for the upper urinary tract can be performed under general anesthesia, although local or spinal anesthesia is possible. Intravenous sedation is suitable for female patients with distal ureteral stones. ⁽³⁰⁾

89.8 Safety aspects

Fluoroscopic equipment must be available in the (OR).

We recommend placement of a safety wire.

Balloon and plastic dilators should be available.

Start with small diameter long semi-rigid URS for optical dilatation followed by flexible URS, if required.

If the URS does not pass due to tight ureter, insertion a JJ stent for seven to fourteen days then try again. ⁽³¹⁾

Bilateral URS during the same session is possible with minor increase in complications.

The limitations of semi-rigid URS are overcome by flexible URS. Flexible URS comes with higher success rates with low complications for < 2 cm proximal ureteral stones. ⁽³²⁾

Table 107: Recommendation on Safety Precautions during URS

Recommendations	Strength rating
1. We recommend using a safety GW in all ureteroscopic procedures	Strong
2. We recommend using small diameter URS at the start for optical dilation followed by flexible URS if required	Strong

89.9 Intracorporeal lithotripsy

89.9.1 The Holmium: Yttrium-Aluminium-garnet (Ho: YAG) laser:

The most effective lithotripsy system. The holmium laser can be activated 0.5 mm from the urothelial surface without risk of injury. It is considered the standard for URS and flexible nephroscopy. ⁽³³⁾

89.9.2 Pneumatic and US systems:

Used with high disintegration efficacy in rigid URS. ⁽³³⁾

Stone migration is a common problem that can be avoided by placement of special anti-migration device

Medical expulsion therapy following Ho: YAG laser lithotripsy increases SFRs and reduces colic episodes.

EHL can damage the ureteral mucosa, resulting in ureteral perforation. The expanding cavitation bubble generated by the spark may produce injury to the mucosa with reported rates of ureteral injury of 8.5%-17.6%. ⁽³⁴⁾

Table 108: Intracorporeal lithotripsy

Recommendations	Strength Rating
1. We recommend the pneumatic and US systems with rigid URS.	Strong
2. We recommend use of holmium: YAG laser lithotripsy for flexible ureteroscopy.	Strong
3. We recommend stone extraction only under direct endoscopic visualisation of the stone	Strong
4. We do not recommend EHL for intra-ureteral lithotripsy	Strong

89.10 Stenting before and after URS:

Pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces intra-operative complications.

Routine stenting after uncomplicated URS is not necessary. Stenting might be associated with higher post-operative morbidity and costs. A ureteral catheter for (one day) may be used. A number of randomized prospective trials have questioned stent placement for uncomplicated URS. ⁽³⁵⁻³⁷⁾

89.10.1 Post-operative Stents should be inserted in patients who are at increased risk of complications:

Ureteral trauma, Residual fragments, Bleeding, Perforation, UTIs, Pregnancy and Solitary kidney to avoid stressful emergencies.

The ideal duration of stenting is not known. The duration of ureteral stenting post-operatively should be minimized. Most urologists favor 1-2 weeks after URS. Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability. ⁽⁶⁰⁻⁶¹⁾

Table 109: Stenting before and after URS

Recommendations	Strength rating

1. Shorten the duration of post URS stent in uncomplicated cases.	Strong
2. Insert stent in all cases where you may need to insert it as emergency (Residual fragments, single kidney, ureteral trauma...)	Strong
3. We recommend pre-stenting in cases of tight ureter not admitting the small diameter URS.	Strong

89.11 Complications of ureteroscopy

The overall complication rate after URS is 9-25%. Most complications are minor and do not require intervention. Ureteral avulsion and strictures are rare (< 1%).^(28,38)

A safety guide wire should be used for most endoscopic procedures. It can provide access to the collecting system in cases of ureteric or collecting system injury, including perforation or avulsion. This will facilitate placement of an internalized stent in such cases.

89.11.1 There are situations where a safety guidewire cannot be placed (impacted ureteral stone)

- Try a hydrophilic guidewire
- Place the guide wire under vision using a small diameter URS
- Leave the wire below the stone, carefully fragment the stone until the proximal ureteral lumen is identified and a safety wire placed.
- Antegrade treatment using Flexible URS
- Place a nephrostomy tube or antegrade stent and performing stone removal at a different time.

89.12 Contraindications of URS

Apart from general problems, for example with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

Complications are minor and do not require intervention

The following complications are the most relevant sepsis; ureteral stricture; ureteral injury; and UTI.

Serious complications, including death and loss of kidney, are sufficiently rare

Table 110: Recommendation during ureteroscopy

Recommendations	Strength rating

1. We recommend having Fluoroscopic equipment available in the (OR).	Strong
2. We recommend placement of a safety wire in all ureteroscopic procedures	Strong

89.12.1 Indications for active removal of ureteral stones

Indications for active removal of ureteral stones are: ⁽²⁸⁾

- Stones with a low likelihood of spontaneous passage;
- Persistent pain despite adequate analgesic medication;
- Persistent obstruction
- Renal insufficiency (renal failure, bilateral obstruction, or single kidney).

89.13 Selection of procedure for active removal of ureteral stones

Large stones achieve earlier stone-free status with URS compared to SWL.

URS has greater potential for complications. The complication rate and morbidity of URS have now been significantly reduced. ⁽³⁸⁾ Ureteroscopy is a safe option in obese patients (BMI > 30 kg/m²) ⁽³⁹⁾

89.13.1 Bleeding disorder

Ureteroscopy can be performed in patients with bleeding disorders, with a moderate increase in complications ⁽⁴⁰⁾

Table 111: Recommendation for ureteric stones management in patients with bleeding tendency

Recommendations	Strength Rating
1. We recommend URS as having a better chance of achieving stone-free status with a single procedure.	Strong
2. Ureteroscopy has higher complication rates when compared to shock wave lithotripsy.	Strong
3. In cases of morbid obesity use URS as first-line therapy for ureteral stones.	Strong

89.14 Treatment algorithm for ureteral stones (if active stone removal is indicated)

Table 112: Treatment algorithm for ureteral stones (if active stone removal is indicated)

Proximal ureteral stones	
< 1cm	SWL or URS
1-2 cm	1-URS antegrade or retrograde 2-SWL
>2 cm	1-URS 2-open/laparoscopic/Antegrade PNL
Distal Ureteral stones	
<1 cm	SWL or URS
>1 cm	1-URS 2-open/laparoscopic surgery

89.14.1 Excerpts from AUA/Endourology Society Guidelines

1. Patients with uncomplicated ureteral stones <10 mm should be offered observation including MET with α -blockers. Stones of 5– 10 mm showed a higher passage rate using tamsulosin, by relaxing ureteral smooth muscle and decreasing the ureteral wall tone. ⁽²¹⁾
2. Offer surgical treatment (including SWL) to adults with ureteric stones and renal colic within 48 hours of diagnosis or readmission, if pain is ongoing and not tolerated or the stone is unlikely to pass.
3. In most patients, if observation with or without MET is not successful after four to six weeks and/or the patient/clinician decide to intervene sooner based on a shared decision making approach, clinicians should offer definitive stone treatment.
4. Clinicians should inform patients that SWL is the procedure with the least morbidity and lowest complication rate, but URS has a greater stone-free rate in a single procedure.
5. In patients with mid or distal ureteral stones who require intervention (who were not candidates for or who failed MET), clinicians should recommend URS as first-line therapy. For patients who decline URS, clinicians should offer SWL.
6. In patients who fail or are unlikely to have successful results with SWL and/or URS, clinicians may offer PCNL, laparoscopic, open, or robotic assisted stone removal.
7. If initial SWL fails, clinicians should offer endoscopic therapy as the next treatment option. Strong recommendation.

8. Clinicians should use URS as first-line therapy in most patients who require stone intervention in the setting of uncorrected bleeding diatheses or who require continuous anticoagulation/antiplatelet therapy Strong Recommendation.

Furthermore, Clinicians performing URS for proximal ureteral stones should have a flexible ureteroscope available, or be ready for stenting and SWL in case of migration.

Performing semi-rigid URS in the proximal ureter may not be possible, and carries a higher risk of ureteral injury

The semi-rigid ureteroscope may be unable to pass the angulation of the ureter associated with a large prostate or the iliac vessels.

Semi-rigid URS above the level of the iliac vessels can cause additional torque on the ureteroscope, with a risk for damage. These limitations are overcome by flexible URS.

Flexible URS has been shown in both prospective and retrospective studies to have high overall success rates with low morbidity/complications for < 2 cm proximal ureteral stones. Failure and retreatment rates are higher in the proximal ureter for semi-rigid URS compared to flexible URS.
(38)

89.14.2 Laparoscopy and open surgery

Open/ laparoscopic /robotic surgery should not be offered as first-line therapy to most patients with stones. When expertise is available, laparoscopic ureterolithotomy can be performed for large proximal ureteral stones as an alternative to URS or SWL ⁽⁴¹⁾

These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates

Open surgery should be considered as the last treatment option, after other possibilities have been explored.

Table 113: Recommendation on Laparoscopy and/or open surgery for ureteric stones

Recommendation	Strength Rating
We recommend laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, retrograde or antegrade ureteroscopy and percutaneous nephrolithotomy fail, or are unlikely to be successful.	Strong

89.15 Ureteroscopy in Pregnancy

MET appears safe in the pregnant population. ⁽⁴²⁾

In pregnant patients with ureteral stones, clinicians may offer URS to patients who fail observation.

Ureteroscopy is best performed by an experienced urologist and at an institution that has obstetric support for both maternal and fetal care. Ureteral stent and nephrostomy tube are alternative options. Frequent stent or tube changes are usually necessary. ⁽⁴³⁾

Non-urgent ureteroscopy in pregnant women should be best performed during the second trimester. ⁽⁴³⁾

Table 114: Recommendation for ureteric stone management during pregnancy

Recommendation	Strength Rating
1. Treat ureteral calculi during pregnancy conservatively (except when there are clinical indications for intervention).	Strong
2. Ureteroscopy can be done safely during pregnancy to avoid long term stenting and drainage	Strong

89.16 Treatment for pediatric patients with ureteral calculi:

In children, the indications for SWL, URS and PNL are similar to those in adults.

In pediatric patients with uncomplicated ureteral stones ≤10 mm, clinicians should offer observation with or without MET using α-blockers.

Clinicians should offer URS or SWL for pediatric patients with ureteral stones who are unlikely to pass the stones or who failed observation and/or MET, based on patient-specific anatomy and body habitus.

89.17 Rigid/semi-rigid ureteroscopy in children:

In recent years ureteroscopy is increasingly used in children with ureteral stones. Ureteroscopy proved to be effective with SFR of 81-98%, retreatment rates of 6.3%-10% and minor complications. Preliminary stenting has not proven necessary. ⁽⁴⁴⁻⁴⁶⁾

Table 115: Recommendation on management of ureteric stones in children

Recommendations	Strength rating
1. Offer children with single ureteral stones less than 10 mm shock wave lithotripsy (SWL) if localisation is possible as first line option.	Strong

2. Ureteroscopy is a feasible alternative for ureteral stones not amenable to SWL.	Strong

URS requires particularly skilled and **experienced endo-urologists** in the following conditions

- Morbidly obese patients
- Pregnancy
- Children
- Patients with bleeding diathesis
- Previous open surgery at the same level
- Huge prostate size
- Patients with skeletal deformities

90 Renal Stones

90.1 Diagnosis

A complete urinalysis is essential, and if clinical or laboratory signs of infection are present, urine culture is additionally required. Serum creatinine is particularly appropriate in presence of infection and bilateral affection or associated medical disease, and a complete blood count is essential prior to intervention.

Non-contrast CT of the urinary tract has become the standard evaluation for renal calculi. It has proven superior to a combination of Ultrasound and plain x-ray. It defines stone burden and distribution, gives an idea about stone composition as well as collecting system anatomy and so guides management decisions. In case of complex stones or anatomy, additional contrast imaging may be necessary. ⁽⁴⁷⁻⁴⁹⁾

A radioisotope renal study is the standard to assess renal function if significant renal loss is suspected. IV, CT and MR Urography are adequate alternatives and parenchymal thickness can also give a rough guide to renal function. ⁵⁰

Sepsis with an obstructing stone is an indication for urgent drainage and antibiotic therapy prior to definitive stone management.

90.2 Treatment of Renal Stones

90.2.1 Conservative Options

There is still no consensus on the optimal management of small, non-obstructing, asymptomatic calculi. Active surveillance appears to be the best option for asymptomatic renal stones less than 5 mm, and some renal stones in the 5-10 mm range, with active intervention in case of stone growth or development of symptoms. ^(51,52)

Chemolysis by alkalinisation is the best management for uric acid calculi in the absence of infection or marked back pressure. ⁵³

Table 116: Recommendations for Conservative management of renal stones

Recommendations	Strength rating
1. Asymptomatic calyceal calculi <1cm may be followed up	weak
2. On active follow-up stone growth, de novo obstruction, associated infection, and acute and/or chronic pain are indications for treatment.	strong

90.2.2 Active Stone Removal

According to the EAU Guidelines,⁸ indications for the removal of renal stones, include:

- Stone growth;
- Stones in high-risk patients for stone formation;
- Obstruction caused by stones;
- Infection;
- Symptomatic stones (e.g., pain or haematuria);
- stones > 15 mm;
- Stones < 15 mm if observation is not the option of choice;
- Patient preference;
- Comorbidity;
- Social situation of the patient (e.g., profession or travelling)

Choices for active intervention include ESWL, PCNL and open surgery/laparoscopy.

90.2.3 Selection of procedure for active removal of renal stones

90.2.3.1 Stones in renal pelvis or upper/middle calices

It is the consensus that in patients with a total renal stone burden >20 mm, clinicians should offer PCNL as first-line therapy. If this is not feasible then RIRS may be considered with the knowledge that it may take several sessions. Open surgery/laparoscopy should be kept as a last option, and ESWL is not a suitable choice in this situation. ⁽⁸⁻¹⁰⁾

For stones ≤ 20 mm, ESWL and RIRS are acceptable alternatives to PCNL. ⁽⁸⁻¹⁰⁾

90.2.3.2 Stones in the lower renal pole

Clearance of fragments from the lower pole is lower than other sites. Consequently, ESWL is only indicated if stone size is < 10mm although it can be chosen if factors affecting clearance are considered particularly favorable. If available, RIRS might be a more suitable option for such calculi. PCNL is also an option, and it is the primary choice for all larger calculi. ⁽⁸⁻¹⁰⁾

90.2.4 ESWL

Successful lithotripsy depends on fragmentation and clearance and this is directly affected by stone composition, site and size. ^(54,55)

If the stone density is greater than 1000HU it is resistant to fragmentation. Calculi > 20mm require multiple treatments, and their clearance is associated with a higher incidence of ureteral obstruction (colic or steinstrasse) often requiring adjunctive procedures. For the lower pole, calculi > 10mm are associated with an unacceptable stone free rate. ^(54,55)

ESWL is best suited for renal calculi < 20mm. In the lower pole it is best reserved for calculi < 10mm. ^(54,55) and it is markedly affected by calyceal anatomy. ⁽⁵⁶⁻⁵⁷⁾ Otherwise, it should not be offered as first-line therapy.

The EAU guidelines summarised factors adversely affect SWL as follows ⁸

- Steep infundibular-pelvic angle;
- Long calyx;
- Long skin-to-stone distance;
- Narrow infundibulum;
- Shock wave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).

SWL should not be considered if there is obstruction distal to the stone.

α-blocker therapy may be offered to facilitate passage of fragments, and stone material is best collected for analysis.

Table 117: Recommendations for management of lower pole calculi

Recommendations	Strength rating
1. PCNL and RIRS are better options for lower pole calculi unless factors are particularly favorable for clearance	Strong

90.2.5 Retrograde Infrarenal Surgery

RIRS is an acceptable option for renal calculi < 20mm. It provides an attractive alternative to SWL but it’s use is limited by the high cost of the necessary equipment. This is accentuated by the fragility of the flexible instruments. The introduction of disposable flexible ureteroscopes has somewhat mitigated this issue. ^(54,55)

90.2.6 PCNL

Percutaneous nephrolithotomy is the primary option in renal stones > 2 cm.

It should be done under antimicrobial coverage, and the procedure should be aborted by placement of a percutaneous nephrostomy if purulent urine is encountered. On the other hand, placement of a nephrostomy tube is optional in an incident free PCNL, if the patient is considered stone free.

Mini-PCNL with 14–20-Fr tracts have proven as effective as standard PCNL in a variety of situations with a higher safety profile. ⁵⁸

Table 118: Recommendation for renal stone management

Recommendations	Strength rating
1. PCNL is the primary treatment option for renal calculi > 2cm	Strong

90.2.7 Open/Laparoscopic Surgery

Open/Laparoscopic surgery is not the first option for stone management. It is only indicated with especially large/complex stones and in case of certain anatomic considerations.

90.2.8 Special Situations

Staghorn calculi are not suitable for observation and should be actively managed if possible. The best option is PCNL but anatomy and stone configuration might necessitate open surgery. Both options are technically demanding and are best left to tertiary referral centres that are adequately equipped and have a high-volume practice.

Stones in calyceal diverticulum are a similar situation that are best managed endoscopically in a high volume centre.

In patients with calculi that necessitate intervention in a kidney with negligible function, nephrectomy is an acceptable option. This is often a difficult procedure with high complication rates that exceed that for radical nephrectomy.⁵⁹

Table 119: Recommendation for staghorn stone

Recommendations	Strength rating
1. Staghorn calculi should be actively managed whenever possible.	Strong

91 Management of Specific Patients' Groups

91.1 Stones in pregnant patients:

- A. Urolithiasis is the most common cause of non-obstetrical abdominal pain that requires hospitalization in pregnant women.
- B. Stones during pregnancy is often a diagnostic and therapeutic challenge:
 - 1. Many signs and symptoms of urolithiasis can be found in a normal pregnancy or may be associated with broad differential diagnoses of other sources of abdominal pathology including appendicitis, diverticulitis, or placental abruption.
 - 2. Investigations are complicated by the normal changes during pregnancy that can resemble obstructing calculi.
 - 3. Standard imaging and treatment algorithms can pose undue risk to the developing fetus.
 - 4. The risks to the fetus of ionizing radiation, analgesics, antibiotics, and anesthesia must also be considered.
 - 5. Most stones pass spontaneously with conservative treatment. However, if the calculus does not pass, ureteral obstruction, upper urinary tract infection, urosepsis, or perinephric abscess may occur.
 - 6. May precipitate premature labor or interfere with the progression of normal labor, which poses a significant health risk to the fetus.
 - 7. These factors can cause a delay or inappropriate diagnosis difficult decisions.
- C. Evaluation and management is complex and must be multidisciplinary:
 - 1. It demands close collaboration between patient, radiologist, obstetrician and urologist.
 - 2. The obstetrician or maternal fetal medicine physician, anesthesiologist, and urologist must work together to develop a safe and effective plan for the patient.
 - 3. Coordinate pharmacological and surgical intervention with the obstetrician.
 - 4. Should medication be given, the obstetrician or maternal fetal medicine physician along with the pharmacist can insure medications prescribed are safe to the developing fetus based on gestational age at time of presentation.
 - 5. Should ionizing radiation is necessary for diagnostic or treatment purposes, the radiation physicist along with the obstetrician can estimate radiation exposure so the

total pregnancy exposure does not exceed the American College of Obstetrics and Gynecology (ACOG) recommended maximum of 50 mGy.

6. Although obstetric complications at time of surgical intervention are rare (<5%), the patient should only be undertaken by clinicians facile with the treatment approach and at an institution that has both the equipment required for URS and obstetric support for managing maternal and fetal emergencies should complications ensue intra or post operatively.
- D. Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except when there are clinical indications for intervention) - Strong Recommendation.
- E. Conservative treatment and MET: pregnant patients with ureteral stone(s) and well controlled symptoms:
1. Offer observation as first-line therapy - Strong recommendation.
 2. Spontaneous passage rates are not different than in non-pregnant patients.
 3. Be aware that a stone event in pregnancy carry an increased risk of maternal and fetal morbidity.
 4. Close follow-up for recurrent or persistent symptoms.
 5. The patient should be counseled that MET has not been investigated in the pregnant population, and the pharmacologic agents are being used for an "off-label" remain debatable.
 6. For analgesia:
 - a) NSAIDs: are contraindicated, not recommended during the first 20 weeks of pregnancy. Associated with an 80% increased risk of miscarriage, also linked to renal congenital abnormalities and fetal pulmonary hypertension and may cause premature closure of the ductus arteriosus.
 - b) Acetaminophen for mild analgesia.
 - c) Morphine: frequent small doses used safely in severe pain.
- F. Should surgical intervention be warranted, the multidisciplinary team is imperative, utilizing an anesthesiologist who specializes in obstetrics to perform fetal monitoring, if indicated, and to keep drug exposure to the minimum.
- G. Ureteral stent or percutaneous nephrostomy tube placement:
1. Indication:
 - a) Patient who fail observation.

- b) If complications develop (e.g., infection, intractable symptoms), severe hydronephrosis, large or bilateral stones, abnormal anatomy, or obstetric complications (induction of premature labour).
 - c) When definitive surgical treatment is not advisable or available.
 - d) When there is insufficient multidisciplinary support and/or scant endourological or anesthetic resources available.
- 2. Ureteral stent and nephrostomy tube are options with frequent stent or tube changes usually being necessary - Strong Recommendation
- 3. Both, double-J catheter and nephrostomy tube are equally effective in draining an infected collecting system and it is up to the urologist to choose which one is the most appropriate for each situation.
- 4. Effectively decompress obstructed collecting system and bring symptom relief.
- 5. Associated with poor tolerance and require multiple exchanges due to the potential for encrustation.
- H. SWL: Pregnancy is an absolute contraindication for SWL.
- I. If intervention becomes necessary, place a ureteral stent or a percutaneous nephrostomy tube as readily available primary options - Strong Recommendation.
- J. URS:
 - 1. For patients who fail observation
 - 2. A definitive treatment as it accomplishes stone clearance.
 - 3. Reasonable alternative to avoid long-term stenting / drainage (until delivery). It results in fewer needs for stent exchange, less irritative LUTS and better patient satisfaction by obviating prolonged drainage.
 - 4. Can be done with limited X-ray emission, using shield protection at the patient's pelvis, or completely US-guided only.
 - 5. Non-urgent ureteroscopy in pregnant women should be best performed during the second trimester, by an experienced urologist.
 - 6. Counselling should include access to neonatal and obstetric services.
- K. PNL:
 - 1. Feasible but remain an individual decision.
 - 2. Should be generally avoided.

3. Should be performed only in experienced centres.

L. Diagnosis:

1. Ideally, no ionizing radiation should be used in the first or second trimesters, if at all possible. Radiation exposure in the third trimester is less of a risk to the fetus.
2. Guidelines available from the American College of Obstetricians and Gynecologists stress the need to weigh the risks of exposure to radiation and contrast agents with the risk of non-diagnosis and worsening of disease. Fetal risk of anomalies, growth restriction, or abortion have not been reported with radiation exposure of less than 50 mGy, a level above the range of exposure for most diagnostic procedures.
3. The EAU guidelines recommend US for the diagnosis of urolithiasis during pregnancy. However, the guidelines note that normal physiologic changes in pregnancy can mimic ureteral obstruction and the role of US is limited in acute obstruction because it cannot properly differentiate causes of dilation. MRI is recommended as a second-line imaging study, but use of low-dose CT is restricted to selected cases.
4. Ultrasound:
 - a) Renal with or without Doppler studies and bladder US has become the first line option for imaging pregnant women with renal colic.
 - b) Transvaginal US can add important information as it better evaluates the distal ureter and ureteral-vesical-junction.
 - c) Although less specific and sensitive compared to CT scans, it is harmless to the patient and fetus.
5. Intravenous urography (IVU or IVP) :
 - a) Is reserved for more complex cases.
 - b) If US findings are equivocal and clinical symptoms strongly suggest renal calculi.
 - c) Limited IVP with reduced films and radiation exposure: has been shown to successfully reveal calculi without the high radiation dose of full IVP.
 - d) If the US and limited IVP test findings are unclear, additional tests or procedures may be indicated, depending on the clinical scenario. However, many experts suggest proceeding directly to URS for diagnosis and treatment when this procedure is indicated, especially in the first and second trimesters.
6. CT scans:
 - a) Limited CT scanning.

- b) Reserved for more complex cases.
- c) Used if US and limited IVP test findings are unclear.
- d) Avoided due to the high X-ray emission and its potential teratogenic effects (particularly in the first trimester).
- e) Nevertheless, it has been shown that radiation doses of less than 50 mGY during pregnancy are not associated with higher risk of malformation or pregnancy loss.
- f) The judicious use of low dose CT scan protocols that expose the fetus to lower radiation doses and maintain diagnostic accuracy, can be an option.

7. MRI/MRU:

- a) Recently, non-contrast MRU has been used with a better accuracy than US and is used by some as second line to US.
- b) Has limited utility in urinary stone disease and during pregnancy.
- c) Visualizes stones poorly; it cannot demonstrate the actual stone, only the point of obstruction.
- d) Provide a benefit in its ability to reveal non-urinary-tract pathology that may manifest with similar symptoms (ie, ovarian torsion, appendicitis).
- e) MRU can be used to differentiate a physiological upper tract dilatation from a pathologic ureterohydronephrosis during pregnancy and to ascertain whether the obstruction is intrinsic or extrinsic.
- f) Does not use ionizing radiation or iodinated contrast, but its use during the first trimester is not recommended because its effect on fetal development is not clear.
- g) Other disadvantages include expense, discomfort for the pregnant patient, and a lack of availability.

8. Nuclear renography is reserved for functional studies to direct treatment, of limited value during pregnancy

91.1.1 Stones in patients with urinary diversion:

- A. These patients are at high risk for stone formation. One study has shown that the risk for recurrent upper tract stones in patients with urinary diversion subjected to PNL was 63% at five years.
- B. Site: renal collecting system, ureter, the conduit, or continent reservoir.
- C. Causes:

1. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia).
2. Infection with urease-producing bacteria.
3. Foreign bodies.
4. Mucus secretion.
5. Urinary stasis.

D. Management

1. Smaller upper-tract stones: SWL is an effective treatment.
2. In majority of cases, endourological techniques are necessary to achieve stone-free status.
3. The choice of access depends on the feasibility of ureteric orifice identification in the conduit or bowel reservoir.
4. Stones in a conduit:
 - a) Perform a Trans-stomal approach.
 - b) Remove all stone material (along with the foreign body).
 - c) Use standard techniques, including intracorporeal lithotripsy and flexible endoscopes.
 - d) Manipulations must be performed carefully to avoid disturbance of the continence mechanism.
5. Patients with long, tortuous conduits or with invisible ureter orifices: retrograde endoscopic approach might be difficult or impossible.
6. PNL is indicated in - Strong Recommendation:
 - a) Large renal stones.
 - b) Antegrade URS for stones that cannot be accessed via retrograde approach.
 - c) Ureteral stones that are not amenable to SWL.
7. Before considering PNL:
 - a) CT should be done to assess the presence of an overlying bowel which could make this approach unsafe.
 - b) If overlying bowel, an open surgical approach should be considered.

E. Prevention :

1. Recurrence risk is high.
2. Metabolic evaluation and close follow-up are necessary.
3. Measures:

- a) Medical management of metabolic abnormalities.
- b) Appropriate therapy of urinary infections.
- c) Hyperdiuresis or regular irrigation of continent reservoirs.

91.2 Stones in patients with neurogenic bladder:

- A. Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.
- B. Risk factors:
 - Bacteriuria.
 - Hydronephrosis.
 - VUR.
 - Renal scarring.
 - Lower urinary tract reconstruction.
 - Thoracic spinal defect.
- C. Site:
 - 1. At any level of the urinary tract.
 - 2. Bladder: more frequently especially if augmentation has been performed.
- D. Causes:
 - 1. Urinary stasis.
 - 2. Infection.
 - 3. Indwelling catheters (facilitate UTI).
 - 4. Surgical interposition of bowel segments (facilitate UTI).
- E. Diagnosis:
 - 1. May be difficult and delayed, causes:
 - a) Absence of clinical symptoms due to sensory impairment.
 - b) Vesico-urethral dysfunction.
 - 2. Difficulties in self-catheterisation should lead to suspicion of bladder calculi.
 - 3. Imaging studies are needed (US, CT) to confirm diagnosis prior to intervention.
- F. Management

1. Take appropriate measures regardless of the treatment provided since in myelomeningocele patients latex allergy is common - Strong Recommendation.
2. Surgery must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia.
3. Bone deformities often complicate positioning on the operating table.

G. Prevention:

1. Appropriate infection control.
2. Restoration of normal storing/voiding function of the bladder if available.
3. Correction of the metabolic disorder.
4. After augmentation cystoplasty in immobile patients with sensory impairment, irrigation protocols significantly reduce the risk of stone formation.

91.3 Management of stones in patients with transplanted kidneys

A. Incidence 1%.

B. Stones can either be transplanted or present de novo.

C. Risk factors for de novo stone formation: multifactorial

1. Dependency on a solitary kidney.
2. Immunosuppression: increases the risk of recurrent UTIs.
3. Biochemical and metabolic causes:
 - a) Hyperfiltration.
 - b) Excessively alkaline urine.
 - c) Renal tubular acidosis (RTA).
 - d) Increased serum calcium due to persistent tertiary hyperparathyroidism.

D. Diagnosis:

1. Usually detected by routine US examination.
2. NCCT indicated in unclear cases.
3. Perform US or NCCT to rule out calculi in transplanted patients with unexplained fever, or unexplained failure to thrive (particularly in children) -Weak Recommendation.

E. Management

1. Being a solitary kidney that maintain the patients renal function, any impairment in urinary stasis/obstruction require immediate intervention or drainage.

2. Selecting the appropriate technique is difficult.
3. Principles are similar to those applied in other single renal units.
4. Factors influencing the surgical strategy:
 - a) Transplant function.
 - b) Coagulative status.
 - c) Anatomical obstacles due to the abnormal iliacal position of the transplanted kidney.
5. Complete metabolic evaluation after stone removal - Strong Recommendation.
6. Small asymptomatic stones - Conservative but:
 - a) Close surveillance.
 - Absolutely compliant patients.
 - b) Offer patients with transplanted kidneys, any of the contemporary management options, including SWL, flexible URS/RIRS and PNL - Weak Recommendation.
 - c) SWL:
 - For small calyceal stones - option.
 - Minimal risk of complication.
 - Stone localisation can be challenging:
 - Position of the graft close to the iliac bone.
 - Might potentially lessen the effectiveness of the shock waves.
 - Might preclude fluoroscopic stone localisation.
 - Repeated sessions might be required for complete disintegration representing further burden to the patient.
 - SFRs are poor (combining with RIRS might clear residuals).
 - Close follow-up is mandatory: the graft is eventually left with stone debris that while passing through the ureter might induce silent ureteral obstruction.
7. Large or ureteral stones:
 - a) Careful percutaneous access and antegrade endoscopy using flexible URS/RIRS or nephroscope: favorable.
 - b) Percutaneous access performed in the supine position.
 - c) Be aware of potential injury to adjacent organs (bowel), consequently extreme care is required and a more lateral puncture should be performed cautiously.

- d) Extreme caution should be taken as the fibrosis around the graft renders the procedure considerably difficult.
- e) Access to the pelvicalyceal system is commonly performed through an anterior calyx in the upper pole (alternatively a middle calyx) facilitated by US guidance preferably combined with fluoroscopic guidance.
- f) Antegrade Double-J stent is routinely fixed at the end of the procedure.
- g) Mini-PNL has recently been suggested with small track size inducing less parenchymal injury.
- h) Retrograde access: difficult because of
 - Anterior location of the ureteral anastomosis.
 - Ureteral tortuosity.
- i) Flexible URS/RIRS:
 - A valid treatment option.
 - Outperforming conventional semirigid URS with minimal morbidity.
 - Unusual location of the ureteral orifice could be overcome by:
 - Applying suprapubic pressure.
 - Evaluating the bladder at different levels of filling.
 - Use 70° lens.
- j) Open surgery - Reserved for:
 - More complex cases resulting from ureteral stenosis.
 - Transplant in context of urinary diversion.
 - Stones formed around missed stents.
- k) Complete metabolic evaluation after stone removal - Strong Recommendation.

91.4 Management of stones in children

91.4.1 General considerations:

1. Stone disease in the children has been reported to be increasing.
2. At present, our understanding of stone management is somewhat rudimentary, as the published literature is sparse.
3. Future efforts to better define the effects of surgical stone treatment in this population will also be important.

4. In children, the indications for SWL, URS and PNL are similar to those in adults.

91.4.2 Incidence:

1. The true incidence is unclear due to the global lack of large epidemiological studies.
2. Data derived from nation-wide epidemiological studies performed in different countries worldwide, and large-scale databases indicate that the incidence and prevalence of pediatric urinary stone disease has increased over the last decades.
3. Although boys are most commonly affected in the first decade of life, the greatest increase in incidence has been seen in older female adolescences.

91.4.3 Stone composition:

1. Similar as in adults with predominance of calcium oxalate stones.
2. Metabolic abnormalities are less commonly identified in children.
3. Age may affect the predominant metabolic abnormality:
 - a) Hypocitraturia most common disorder in children >10 years old.
 - b) Hypercalciuria most common disorder in children <10 years old.
4. Genetic or systemic diseases:
 - a) Example: cystinuria or nephrocalcinosis.
 - b) Rare, <17% of the identifying causes.
5. The role of diet: Unclear. Some evidence:
 - a) Low urine volume.
 - b) Children are drinking less water.
 - c) Children are taking greater daily amounts of sodium than is recommended.

91.4.4 Clinical presentation:

1. Symptoms are age-dependent in the form of pain, hematuria or UTI.
2. Can be asymptomatic or present with non-specific symptoms that necessitate a high index of suspicion for proper diagnosis.
3. Infants: present with crying, irritability and vomiting (40% of cases).
4. Older children: flank pain, micro or gross- haematuria and recurrent UTIs.

91.4.5 Diagnostic imaging:

1. Children with urinary stones have a high risk of recurrence; therefore, standard diagnostic procedures for high-risk patients apply, including a valid stone analysis.

2. Complete a metabolic evaluation based on stone analysis - Strong Recommendation.
3. Collect stone material for analysis to classify the stone type - Strong Recommendation.
4. The most common non- metabolic disorders facilitating stone formation:
 - a) VUR.
 - b) UPJO.
 - c) Neurogenic bladder.
 - d) Other voiding difficulties.
5. The principle of ALARA (As Low As Reasonably Achievable) should be observed.
6. When selecting diagnostic procedures, it should be remembered that these patients might be:
 - a) Uncooperative.
 - b) Require anaesthesia.
 - c) May be sensitive to ionizing radiation.
7. Increased awareness of the potential adverse effects of ionizing radiation in children has led to efforts to reduce radiation exposure in this population.
8. Children may be more susceptible to radiation-induced injury due to their rapidly developing tissues, and they have a longer potential lifespan during which radiation-induced illness may manifest.
9. US:
 - a) The first-line imaging modality when a stone is suspected (it should include the kidney, fluid-filled bladder and the ureter next to the kidney and the bladder) - Strong Recommendation.
 - b) Colour Doppler US shows differences in the ureteral jet and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction.
 - c) Advantages:
 - Absence of radiation.
 - No need for anaesthesia.
 - d) Disadvantages:
 - Fails to identify stones in >40% of children.
 - Provides limited information on renal function.
10. KUB radiography:

- a) Can help to identify stones and their radiopacity.
- b) Can facilitate follow-up.
- c) An alternative investigation (together with low-dose NCCT) if US will not provide the required information - Strong Recommendation.

11. IVU:

- a) The radiation dose is comparable to that for VCUG (0.33 mSV).
- b) The need for contrast medium injection is a major drawback.

12. NCCT:

- a) An alternative investigation (together with KUB) if US will not provide the required information - Strong Recommendation.
- b) Recent low-dose protocols significantly reduce radiation exposure.
- c) Only 5% of stones escape detection by NCCT.
- d) Sedation or anaesthesia is rarely needed with modern high-speed equipment.

13. MRU:

- a) Cannot be used to detect urinary stones.
- b) Advantage: might provide anatomical information about
 - Collecting system.
 - Renal parenchymal morphology.
 - Site of obstruction / stenosis in the ureter.

91.5 Ureteral Stones:

1. Uncomplicated ureteral stones ≤ 10 mm:

- a) Significant proportion of children will pass their stones spontaneously, thus avoiding the need for surgical intervention.
- b) Observation can be carried out under carefully controlled conditions, assuming no evidence of infection, the patient is able to hydrate orally, and pain can be adequately controlled.
- c) Offer observation with or without MET using α -blockers - weak Recommendation.
- d) Families should be aware that the probability of spontaneous passage is lower for children with stone approaching 1 cm in size.
- e) The role of MET with α -blockers in middle and proximal ureteral stones, similar to adults, is not well-defined.

- f) As in adults, the maximum time duration for a trial of MET is undefined, but it seems prudent to limit the interval to a maximum of 6 weeks from initial clinical presentation in order to avoid irreversible kidney injury.
2. Ureteral stones unlikely to pass or stones that failed observation and/or MET:
- a) The benefits of treating the stone include alleviating symptoms, minimizing risk of infection, and preserving renal function by eliminating obstruction.
 - b) Offer URS or SWL based on patient- specific anatomy and body habitus - Strong Recommendation.
 - c) SFRs:
 - Higher for stones <10mm (87% for SWL and 95% for URS).
 - Lower for stones >10mm (73% for SWL and 78% for URS).
 - d) While SWL is an acceptable option for ureteral stones, the poor visualization of the ureter (particularly the mid -ureter) with US-based lithotriptors may limit use of SWL in this setting.
 - e) SWL may be preferable in certain pediatric populations, such as very small children, or other patients in whom ureteroscopic access may be challenging due to their anatomy (e.g., severe scoliosis, history of ureteral re-implantation).
3. Except in cases of coexisting anatomic abnormalities, clinicians should not routinely perform open/ laparoscopic / robotic surgery for upper tract stones – weak recommendation.
- a) These approaches should be considered secondary or tertiary options for treatment of renal or ureteral stones since more conventional procedures, including SWL, URS, and PCNL, have high rates of success and lower risks of serious complications.
 - b) There is very little evidence directly comparing the use of laparoscopic surgery or robotic-assisted laparoscopic surgery with more conventional treatments for stone disease in children.
 - c) The primary exception is the presence of an anomaly associated with stones that may be treated at the time of reconstructive surgery. In such cases, open, laparoscopic, or robotic-assisted laparoscopic surgery is indicated to remove the stone(s) and repair the primary anatomic defect (UPJO with one or more renal or ureteral stones, others as ureterovesical junction obstruction and duplication anomalies with an obstructed ectopic ureter).
4. SWL:

- a) Offer children with single ureteral stones <10 mm SWL if localisation is possible as first line option - Strong Recommendation.
- b) Well tolerated by children.
- c) Complication rates rising up to 15% in modern series, mostly in the form of ureteral obstruction secondary to steinstrasse formation.
- d) Improvements in modern (second and third generation) lithotripters, successful treatment using intravenous sedation, patient-controlled analgesia or no medication at all has been increasingly performed in a select population of older, co-operative children.
- e) Less likely to be successful for:
 - Stones >10 mm in diameter.
 - Impacted stones.
 - Calcium oxalate monohydrate or cystine stones.
 - Unfavourable anatomy.
 - In whom localisation is difficult.
- f) Overall SFR: 70-90% (higher for stones <10 mm than for stones >10 mm).
- g) Re-treatment rate: 4-50% (higher as the stone size increase).
- h) Auxiliary procedures: needed in 4-12.5% of cases.

5. Rigid / semi-rigid URS:

- a) Recently is increasingly used in children with ureteral stones.
- b) A feasible alternative for stones not amenable to SWL - Strong Recommendation.
- c) Effective.
- d) SFR: 81-98%.
- e) Complication rate: 1.9-23%.
- f) Re-treatment rate: 6.3%-10%.
- g) Stenting before URS: similar to adults, clinicians should not routinely place a stent prior to URS – weak recommendation.
 - Access to the upper tract is readily possible in the majority of children.
 - If stone access is difficult or impossible, placement of a ureteral stent results in passive dilation of the ureter thus permitting access at the time of the next attempted URS.

- h) Stenting after URS: a strong predictor of re-treatment requiring anaesthesia in children.

91.6 Renal Stones:

1. In asymptomatic and non-obstructing renal stones, clinicians may utilize active surveillance with periodic US – Weak recommendation.
 - a) Monitor: increase in size of stone, number of stones, or silent obstruction.
 - b) Families should be counseled about the need for regular follow-up.
 - c) Evaluate the patient for underlying abnormalities that may predispose to further stone formation.
 - d) Metabolic evaluation as the incidence of metabolic abnormalities is high in pediatric stone formers.
 - Toilet-trained children and adolescents: 24-hour urine collections are appropriate to assess urinary stone risk parameters.
 - Infants and non-toilet trained children: “spot” urine sample is used to screen for hypercalciuria (diagnostic limitations).
 - Infants and young children with hyperoxaluria should be screened for primary hyperoxaluria.
2. Obtain a low-dose NCCT prior to performing PCNL - Strong Recommendation.
3. In total renal stone burden ≤ 20 mm:
 - e) Offer SWL - Strong Recommendation.
 - f) Very few high-quality comparative studies for SWL and URS or other modalities for treatment of renal stones in the pediatric population.
 - g) SWL:
 - Success rate: high.
 - Stone-free rates: are high, 80-85% (overall) and 80% (lower pole stones).
 - Complication rates: low (8%-10%).
 - Serious complications are rare.
 - Little evidence of long-term sequelae.
 - SWL compared to mini-PCNL for lower pole renal stones 1-2 cm in size:
 - SWL has lower SFRs.
 - SWL has higher rates of secondary procedures.

- SWL has less severe adverse events.

h) FURS/RIRS:

- A feasible alternative for renal stones ≤ 20 mm in all locations - Weak Recommendation.
- Success rate: high.
- Recent studies:
 - SFRs: 76-100%.
 - Re-treatment rate: 0-19%.
 - Complication rate: 0-28%.
- Causes of failure:
 - Younger age.
 - Cystine composition.
 - Large stone diameter.
 - Lack of pre-stenting.
- Lower calyx stones in the presence of unfavorable factors for SWL: may be an effective option but lacking high level of evidence to support strong recommendation.
- Compared to PCNL in large and complex kidney stones:
 - Disadvantage: significantly lower SFR vs. PCNL (71% vs. 95%).
 - Advantage:
 - ❖ Less radiation exposure.
 - ❖ Lower complication rates.
 - ❖ Shorter hospital stay.
- Compared to mini- or micro-PCNL:
 - Disadvantage: lower SFRs compared to mini- or micro- PCNL.
 - Advantage:
 - ❖ Shorter operative time.
 - ❖ Shorter fluoroscopy time.
 - ❖ Less hospitalisation time.

4. In total renal stone burden >20 mm:

- a) Offer children with renal pelvic or calyceal stones with a diameter >20 mm PCNL
- Strong Recommendation.
- b) Both PCNL and SWL are acceptable treatment options – Weak Recommendation.
SFR: high with both:
 - SWL: 73-83%. Placement of a ureteral stent or nephrostomy tube is recommended to prevent postoperative renal obstruction.
 - PCNL: vary by site. Recent large series approached 90% success rates.
- c) Factors taken into consideration when selecting which of these procedures:
 - Stone composition and attenuation.
 - Stone location.
 - Body habitus.
 - Collecting system anatomy.
 - Relation of the kidney to surrounding viscera.
 - Medical co-morbidity.
 - Parental preference.
- d) The utilization of smaller instruments for PCNL (mini-PCNL, micro-PCNL) may limit the risk of hemorrhage in this population.
- e) PCNL:
 - Indications:
 - Similar to those in adults.
 - Renal stones >2 cm.
 - Smaller stones resistant to SWL and URS.
 - SFRs: 71.4 - 95% after a single session.
 - Overall complication rate: 20%.
 - Increased blood loss if:
 - High degree of hydronephrosis.
 - Increased number of tracts.
 - Increased operative time.
 - Large tract size.
 - ❖ Child age and stone burden predispose to the use of larger instruments.

- ❖ Miniaturisation of equipment increases the opportunity to perform tubeless PCNL in appropriately selected children, which can reduce the length of hospital stay and post-operative pain.
- ❖ Studies showed that blood transfusion requirement is significantly less in all age groups when <20FG sheath is used.
- Concerns have been raised regarding possible adverse effects of PCNL on the renal parenchyma of the developing child. However, focal damage is only reported in 5% of cases. Using pre- and post-PCNL DMSA scans, Cicekbilek et al. demonstrated that PCNL tracts between 12-24 Charrière in size did not cause significant harm to pediatric kidneys.

91.6.1 Open surgery:

1. With the advances in ESWL, PCNL and RIRS, very few cases require open surgery.

91.6.2 Laparoscopic / robot-assisted stone surgery:

1. Laparoscopy and robotic-assisted laparoscopy have been utilized successfully in adults for treatment of calculi during the concomitant treatment of UPJO and in the primary treatment of staghorn calculi. Small series have only recently been described to be use these techniques in children.
2. Laparoscopy for the management of pediatric renal and ureteric stones is a safe and effective procedure when specific indications are followed.
3. SFRs of 100% were reported when:
 - a) Laparoscopic pyelolithotomy if applied for:
 - A single stone, ≥ 1 cm in size, located in an extra-renal pelvis.
 - b) Laparoscopic ureterolithotomy if applied for:
 - Impacted ureteric stone ≥ 1.5 cm or ureteric stones refractory to SWL or URS.
4. The available early experiences demonstrate that laparoscopic pyelolithotomy is feasible, safe, and efficacious as an alternative to open pyelolithotomy in children but needs further study.
5. Because of their demanding technical nature, these procedures most likely be limited to cases who failed endourologic management in academic centers with abundant expertise in laparoscopy.

91.6.3 Special considerations on recurrence prevention:

1. All pediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type.

2. Children are in the high-risk group for stone recurrence.

92 Special problems in stone removal

92.1 Calyceal diverticulum stones

1. SWL:
 - a) SFR is low, well-disintegrated stone material remains in the original position due to narrow calyceal neck.
 - b) Although some patients experience a reduction or elimination of symptoms, they are at risk for:
 - Recurrence of symptoms.
 - New or residual stone growth.
2. Endoscopic therapy:
 - a) Flexible URS/RIRS, PNL, laparoscopic, robotic.
 - b) Should be preferentially used - Strong Recommendation.
 - c) SFR are higher.
 - d) The chance for eradication of symptoms is greater.
 - e) The approach also permits correction of the anatomic abnormality, with the chance for successful obliteration being highest with PCNL, laparoscopic, or robotic assisted surgery.
 - f) The approach depend on:
 - Stone location.
 - Stone size.
 - Relation to surrounding structures.
 - Patient preference.

92.2 Horseshoe kidneys

1. Can be treated in line with the options described above.
2. Passage of fragments after SWL might be poor.
3. Acceptable SFRs can be achieved with flexible URS/RIRS.

92.3 Stones in pelvic kidneys

1. SWL, flexible URS/RIRS, PNL or laparoscopic surgery.
2. Obese patients: flexible URS/RIRS, PNL or open surgery.

92.4 Stones formed in a continent reservoir:

1. Each stone must be considered and treated individually.

92.5 Patients with UPJO:

1. When outflow abnormality requires correction.
2. Stone removal with open pyeloplasty.
3. Stone removal with laparoscopic reconstructive surgery.
4. PNL and percutaneous endopyelotomy (iatrogenic / recurrent UPJO).
5. Flexible URS/RIRS and endopyelotomy:
 - In iatrogenic / recurrent UPJO.
 - Considered if falling of stone into pelvi-ureteral incision can be prevented
 - Using Ho:YAG laser for incision and lithotripsy or Acucise balloon catheter.

92.6 Non-obstructing calyceal stones:

1. Asymptomatic patients:
 - a) Offer active surveillance - Conditional Recommendation.
 - b) Detection has increased due to the increased utilization of CT imaging.
 - c) Follow-up imaging: to assess stone growth or new stone formation.
 - d) Dietary modification may be considered.
 - e) Medical therapy may be considered.
 - f) Observation: appropriate.
 - Council the patient about risk of stone growth, passage, and pain.
 - Intervention if:
 - Associated infection.
 - Vocational reasons (e.g. airline pilots, military).
 - Poor access to contemporary medical care.
2. Symptomatic patients: flank pain without another obvious etiology for pain.

- a) Offer stone treatment – Weak Recommendation.
 - b) Inform patient of the possibility that the pain may not improve or resolve after the procedure.
3. Symptomatic patients, stone < 10 mm.
- a) Offer SWL or flexible URS/RIRS - Strong Recommendation.
 - b) SWL and flexible URS/RIRS: No statistically significant difference in SFRs.
 - c) NCCT imaging parameters should be used for patient selection.
 - d) SWL:
 - Patient-derived QoL measures are somewhat better.
 - Less successful results if:
 - Skin-to-stone distance > 9-10 cm.
 - Stone attenuation > 900-1000 HU.
 - e) Flexible URS/RIRS:
 - Higher intraoperative complications.
 - Certain techniques employed to improve results:
 - Repositioning of stones into the upper pole before fragmentation.
 - Utilization of a ureteral access sheath.
 - Extraction of the generated fragments.
4. Symptomatic patients, stone > 10 mm:
- a) Do not offer SWL as first-line therapy and use endoscopic approach]- Strong Recommendation.
 - b) Endoscopic approaches: benefit over SWL
 - Better SFR with a moderate associated increase in risk.
 - Less affected by stone burden.
 - c) PNL: superior single-treatment stone-free rate.
 - Should be considered the primary treatment for most cases.
 - Inform the patient:
 - It has the higher SFR but greater morbidity - Strong Recommendation.
 - Nature of the procedure.
 - Expected morbidity.

- Potential complications.
- PNL with smaller access sheaths (mini-PNL or micro-PNL) may allow similar outcomes with lower complication rates.
- d) Flexible URS/RIRS: inform the patient
 - Re-treatment rate is higher.
 - SFR is significantly lower.
 - Higher likelihood of clinical stone recurrence due to retained fragments.
 - Difficulties:
 - ❖ Stone may not be accessible:
 - ✓ Narrow lower pole infundibulum.
 - ✓ Acutely angled lower pole infundibulum.
 - ✓ Severe hydronephrosis.
 - ✓ Renal anomalies (horseshoe kidney).
 - ❖ Stone may not be possible to grasp and relocate necessitating laser treatment in the lower calyx with the ureteroscope maximally deflected with potential increasing the risk of laser fiber failure and ureteroscope damage.

5. Symptomatic patients with non-lower pole renal stone burden < 20 mm

- a) Treatment options: SWL, flexible URS/RIRS, and PNL.
- b) Offer SWL or flexible URS/RIRS - Strong Recommendation.
- c) Treatment selection process must include a shared decision- making approach.
- d) SFR:
 - PNL: the least affected by stone size.
 - SWL:
 - Acceptable SFR.
 - SFR decline with increasing stone burden.
 - Less morbidity compared to PNL
 - Flexible URS/RIRS:
 - Acceptable SFR.
 - SFR decline with increasing stone burden.

- Less morbidity compared to PNL.
- Lower likelihood of repeat procedure compared to SWL.
- The patient will become stone-free quicker than with SWL.

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Urinary Tract Infections



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94 List of Abbreviations

ABP	Acute bacterialprostatitis
ABU	Asymptomatic bacteriuria
AFB	Acid fast bacilli
AUA	American urological association
AUC	Acute Uncomplicated Cystitis
BPS	Best Practice statement
CAA	circulating anodic antigen
CA-uti	Catheter associated urinary tract infection
CBP	Chronic bacterial prostatitis
CDC	The Centers for Disease Control and Prevention
CFU	colony forming unit
CLED	cysteine-lactose- electrolyte- deficient media
CMV	cytomegalovirus
CT	Computed tomography
cUTI	Complicated urinary tract infections
EAU	European association of urology
ESBL	extended spectrum beta lactamase
FAST-ELISA	Falcon assay screening test – enzyme linked immunosorbent assay
GCS	Glasgow coma scale
HPF	high power field
LUTS	Lower urinary tract symptoms
MDR	Multiple drug resistance
ml	Milliliter
μl	Microliter
MRSA	Methicillin Resistant Staph Aureus
NAAT	nucleic acid amplification tests
NG	Neisseria gonorrhoeae
NICE	National institute for health and care excellence

NIDDK	National Institute of Diabetes, Digestive and Kidney Diseases
NIH	National Institutes of Health
PCR	Polymerase chain reaction
PMNL	polymorphonuclear leukocytes
PNL	Percutaneous nephrolithotomy
PUT	Plain x-ray urinary tract
PZQ	Praziquantel
QSOFA	Quick Sequential [Sepsis-related] Organ Failure Assessment
RCT	Randomized controlled trials
SWL	Shock wave lithotripsy
rUTI	Recurrent urinary tract infections
TMP-SMX	Trimethoprim- sulphamethoxazole
TRUS	Trans rectal ultrasound
TURP	Transurethral resection of prostate
UTI	Urinary tract infection
WHO	World health organization
XGP	Xanthogranulomatous pyelonephritis

95 Introduction

These guidelines provide essential summarized updated information for diagnosis, treatment and prevention of urinary tract Infections with emphasizing on judicious use of antimicrobials based on culture and sensitivity to reduce bacterial resistance which is a serious issue especially with malpractice and misuse of antibiotics in Egypt. Moreover, the recommendations included in these guidelines are not representing absolute mandates but provisional protocols respecting environmental and socioeconomic conditions of Egypt, considering our religious and traditional background.

95.1 Methodology

Our recommendations are the outcome of integrating 3 resource categories:

1. Four guidelines (including their latest updates), namely American Urological Association [AUA], European Urological Association [EUA], Canadian Urological Association [CUA] and National Institute for Health and care excellence [NICE].
2. Good quality relevant international and Egyptian publications.
3. A panel of 7 urologists and a microbiologist working in several Governorates in Egypt dealing with several types of urological infections.

All statements were graded according to 2 parameters:

Strength of clinical practice recommendation, expressed as strong and weak. This reflects the consensus of the authors and guided by other guideline recommendations, it is modified to suit the Egyptian environment

Guidelines

96 Asymptomatic Bacteruria (ABU):

96.1 Definition:

Asymptomatic bacteriuria (ABU) is the presence of bacteria in the properly collected urine of a patient that has no symptoms or signs of urinary tract infection. Escherichia coli (E-coli) is the most common bacteria identified. ⁽¹⁾

96.2 Incidence:

ABU is more common in females than males because of short wide urethra with easy access of the bacteria from the urethral meatus and perineum to the bladder. ⁽²⁾

96.3 Recommendations for diagnosis:

- Diagnosis of ABU is made by urine culture is strongly recommended, either properly collected clean-catch specimen or a catheterized specimen is acceptable.
- The combination between urine dipstick for leucocyte esterase and nitrites is recommended.
- Urinalysis with microscopic examination for bacteria is suggested but non-quantitative way to identify bacteriuria.

96.4 Recommendations for management:

Most patients with ABU will not develop symptomatic UTI and will have no adverse consequences without treatment. Treatment of these patients does not improve survival, does not decrease the incidence of symptomatic UTI, increase antibiotic resistance and development of antibiotic resistant strains. ⁽³⁾

96.5 Recommendation for Management of UTI

Table 120: Recommendation for Management of UTI

Recommendations	Strength Rating
1. Do not screen or treat asymptomatic bacteriuria in the following conditions: • Women without risk factors • Patients with well-regulated diabetes mellitus; However poorly regulated diabetes is a risk factor for symptomatic UTI and infectious complications and ABU should be treated • Post-menopausal women;	Strong

• Patients with spinal cord injury, dysfunctional and/or reconstructed lower urinary tracts, and indwelling catheter in the urinary tract and/or catheter exchange. • Elderly institutionalized patients; • Patients with dysfunctional and/or reconstructed lower urinary tracts; • Patients with renal transplant. Except in patients who are in the first three months following renal transplantation should be treated as treatment of these patients decrease the risk of symptomatic UTI. • Patients prior to arthroplasty surgeries; • Patients with recurrent urinary tract infections.	
2. Treatment of UTI prior to urologic procedure breaching the mucosa	Strong
3. Treatment of UTI in pregnancy	Strong

96.5.1 Treatment of ABU is strongly recommended in pregnancy

The incidence of ABU in pregnant Egyptian ladies is 10% and increase with frequent sexual intercourse which increase the probability of transfer of uropathogens into the urethra. Washing the genitalia after urination or defecation from back to front which leads to spread of anal or vaginal flora into the urethra, ⁽⁴⁾

The most common organism isolated in ABU during pregnancy is E-coli, followed by klebsiella ⁽⁵⁾

Periodic screening each trimester especially at 9-17 gestational weeks by quantitative urine culture is recommended. ⁽⁴⁾

Antibiotic treatment of ABU during pregnancy significantly reduced the number of symptomatic UTI, and associated with low rate of low birthweight and low rate of preterm delivery. The treatment duration varies between single dose, short course (2-7 days), long course (8-14 days), and continuous (until delivery). And we recommend short course treatment as it is associated with significant decrease in the rate of low birthweight and preterm deliveries as compared to single dose which is characterized by significant low rate of side effects.

An Egyptian study showed that the most common antibiotic used according to culture and sensitivity are nitrofurantoin, imipenem and amikacin demonstrated 100% sensitivity, followed by ceftriaxone, ceftazidime, sulphamethoxazole-trimethoprim, ciprofloxacin and norfloxacin. ⁽⁴⁾

97 Acute uncomplicated cystitis (AUC):

97.1 Definition:

Acute uncomplicated cystitis (AUC) refers to a bladder infection that occurs in women who have normal structure and function of the genitourinary tract. ⁽⁶⁾

97.2 Incidence:

- 10% of women experience at least one episode of AUC in a year.
- 60% have at least one episode during their lifetime. ⁽⁷⁾
- The peak incidence of infection occurs in young, sexually active women aged 18 to 24 years. ⁽⁸⁾

97.3 Causative organisms:

In Egypt, the most common organisms are eight species, the common organism is E. coli (74%), the next most common is Pseudomonas (13.1%), other organisms include; MRSA (6.1%), Klebsiella (2.2%), enterococcus (1.9%), proteus (1.3%), Acinetobacter and staph. aureus (0.6%). ⁽⁸⁾

Table 121: Recommendations for diagnosis:

Recommendations	Strength Rating
1. Diagnose uncomplicated cystitis in women who have no risk factors for complicated urinary tract infections based on: • A focused history of lower urinary tract symptoms (dysuria, frequency and urgency) is strongly recommended. • The absence of vaginal discharge or irritation.	Strong
2. Use urine dipstick testing for diagnosis of acute uncomplicated cystitis is suggested	Weak
3. Urine cultures is strongly recommended in the following situations: • Suspected acute pyelonephritis; • Symptoms that do not resolve or recur within four • Weeks after the completion of treatment; • Women who present with atypical symptoms;	Strong

• Pregnant women.	

97.4 Recommendations for management:

Women with uncomplicated cystitis should be treated by antimicrobial therapy with or without symptomatic treatment e.g. ibuprofen. The choice of antimicrobial therapy should be guided by spectrum and susceptibility patterns of the aetiological pathogens, tolerability and adverse reactions, costs, and availability. ⁽¹⁰⁾

According to the previously mentioned principles and available susceptibility patterns in Egypt, an Egyptian study determined the most common uropathogens and their pattern of sensitivity to the commonly used antimicrobials ⁽⁹⁾

97.4.1 In mild cases:

We strongly recommend empirical treatment by one of the following antimicrobial therapy:

- Nitrofurantoin has sensitivity 52.9% (100 mg twice daily for 5 days)
- Levofloxacin has sensitivity 39.4% (500 mg once /day for 5 days)
- Ciprofloxacin has sensitivity 35.9% (500mg twice /day for 5 days)
- Norfloxacin has sensitivity 33% (400 mg twice /day for 5 days)
- Trimethoprim- sulphamethoxazole (TMP-SMZ) has sensitivity 12.2% (160-800 mg twice daily for 3 days)

E. coli strains showed the least rate of resistance to Nitrofurantoin and the highest rate of resistance to TMP/SMZ. No organism were absolutely resistant to Nitrofurantoin while Klebsiella, Enterococcus, Proteus, Staph. aureus and Acinetobacter were absolutely resistant to TMP/SMZ. ⁽⁹⁾

It is strongly recommended to not use Aminopenicillins for empirical therapy because of worldwide high E. coli resistance. But Aminopenicillins in combination with a beta-lactamase inhibitor such as ampicillin/sulbactam or amoxicillin/clavulanic acid and oral cephalosporins may be suggested in selected cases.

97.4.2 In severe cases:

It is strongly recommended to send a sample of urine for culture and sensitivity and start empirical treatment as before till the result of culture and sensitivity appear. If the symptoms persist, change the antibiotic according the culture and sensitivity, but if the symptoms improved and the result of culture is different from the current antibiotic use, you should not change the antibiotic, because of differences between the in vitro and in vivo effectiveness so an additional course of antibiotics may be unnecessary treatment.

97.5 Recommendations for follow-up:

- It is strongly recommended to do urine culture and sensitivity in patients with persistent symptoms or recurrent symptoms within 2 weeks post treatment and antimicrobial therapy should be given at least 7 days.
- It is recommend not doing urine culture and sensitivity in asymptomatic patients post treatment

98 Recurrent urinary tract infections (rUTIs):

98.1 Definition:

Recurrent UTIs (rUTIs) are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months. Although rUTIs include both lower tract infection (cystitis) and upper tract infection (pyelonephritis), repeated pyelonephritis should prompt consideration of a complicated etiology: ⁽¹¹⁾

Recurrent UTIs occur due to bacterial reinfection or bacterial persistence. Persistence involves the same bacteria not being eradicated in the urine 2 weeks after sensitivity-adjusted treatment. A reinfection is a recurrence with a different organism, the same organism in more than 2 weeks, or a sterile intervening culture ⁽¹²⁾

Table 122: Risk factors associated with recurrent UTIs in women:

Young and pre-menopausal women ⁽¹¹⁾	Post-menopausal and elderly women
• Sexual intercourse • Use of spermicide • A new sexual partner • A mother with a history of UTI • History of UTI during childhood • Blood group antigen secretory status	• History of UTI before menopause • Urinary incontinence • Atrophic vaginitis due to oestrogen deficiency • Cystocele • Increased post-void urine volume • Blood group antigen secretory status

Table 123: Host factors that classify a urinary tract infection as complicated

Complication ⁽¹²⁾	Examples
Anatomic abnormality	Cystocele, diverticulum, fistula
Iatrogenic	Indwelling catheter, nosocomial infection, surgery
Voiding dysfunction	Vesicoureteric reflux, neurologic disease, pelvic floor dysfunction, high post void residual, incontinence
Urinary tract obstruction	Bladder outlet obstruction, ureteral stricture, ureteropelvic junction obstruction
Others	Pregnancy, urolithiasis, diabetes or other immunosuppression

98.2 Recommendations for diagnosis:

- a. It is strongly recommended to diagnose each UTI episode clinically and is supported by symptoms of dysuria, frequency, urgency, hematuria, back pain, costovertebral tenderness and the absence of vaginal discharge or irritation.
- b. Complicated causes of UTI may also be ruled out on history and physical examination. Uroflowmetry and determining post void residual are suggested tests in postmenopausal women to exclude complicated causes of UTI.
- c. Culture and sensitivity analysis is strongly recommended when symptomatic and in 2 weeks from sensitivity-adjusted treatment to confirm UTI, guide further treatment and exclude persistence.
- d. Further investigations e.g. (pelviabdominal US, PUT, CT abdomen and pelvis with or without contrast or cystoscopy) are not routinely recommended except in atypical cases as in table 2.

98.3 Recommendations for disease management and follow-up:

98.3.1 Avoidance of risk factors:

behavioral modifications is suggested e.g. reduced fluid intake, habitual and post-coital delayed urination, wiping from front to back after defecation, douching and wearing occlusive underwear.

98.3.2 Non-antimicrobial measures:

1. Hormonal replacement: it is suggested to use vaginal oestrogen cream in post-menopausal women to prevent recurrent UTIs (3C) and we recommend not to use oral oestrogen for fear of cancer.
2. Immunoactive prophylaxis: it is strongly recommended to use OM-89(Uro-vaxom) as an immunoprophylaxis in females with recurrent UTIs (1C)
3. Prophylaxis with cranberry: it is recommended not to use cranberry as a prophylaxis against recurrent UTIs.

98.3.3 Antimicrobial prophylaxis:

It is strongly recommended to use antimicrobial prophylaxis either continuously for long period (3-6 months) or shortly within 2 hours post coital.

Table 124: Antimicrobial prophylaxis

Continuous	Postictal (within 2 hours of coitus)
Trimethoprim/sulfamethoxazole (TMP/SMX) (40 mg/200 mg daily or thrice weekly)	TMP/SMX (40 mg/200 mg to 80 mg/400 mg)

Ciprofloxacin (125 mg daily)	Ciprofloxacin (125 mg)
Cephalexin (125 mg to 250 mg daily)	Cephalexin (250 mg)
Cefaclor (250 mg daily)	
Nitrofurantoin (50 mg–100 mg daily)	Nitrofurantoin (50 mg–100 mg)
Norfloxacin (200 mg daily)	Norfloxacin (200 mg)
Fosfomycin (3 g every 10 days)	Ofloxacin (100 mg)

Table 125: Recommendations for the diagnostic evaluation and treatment of rUTIs

Recommendation	Strength Rating
1. Diagnose recurrent UTI by urine culture	Strong
2. Advise patients on behavioural modifications which might reduce the risk of recurrent UTI.	Weak
3. Use immunoactive prophylaxis to reduce recurrent UTI in all age groups.	Strong
4. Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when non-antimicrobial interventions have failed. Counsel patients regarding possible side effects. For patients with good compliance self-administered short term antimicrobial is advised	Strong

99 Uncomplicated pyelonephritis

Uncomplicated pyelonephritis is defined as pyelonephritis with no known relevant urological abnormalities or comorbidities⁽¹¹⁾

99.1 Recommendations for diagnosis and management:

- Urinalysis is strongly recommended including the assessment of white and red blood cells and nitrite, for routine diagnosis
- It is strongly recommended to perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis
- Imaging of the urinary tract (US) is strongly recommended to exclude urgent urological disorders
- It is strongly recommended to treat patients who will be managed as outpatients by single-drug oral therapy with a fluoroquinolone or cephalosporines.
- It is strongly recommended for patients requiring hospitalization should be treated initially with an intravenous antimicrobial regimen e.g. a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin.
- Carbapenem is strongly recommended only in patients with early culture results indicating the presence of multi-drug resistance organisms.⁽¹³⁾

Table 126: Treatment Regimens for empirical oral antimicrobial therapy in Uncomplicated Pyelonephritis

Antimicrobial	Daily dose	Duration of therapy
Ciprofloxacin	500-750 mg b.i.d	7 days
Levofloxacin	500-750 mg q.d	5-7 days
Cefexime	400mg dq	5-10 days

b.i.d = twice daily; q.d = every day.

Table 127: Treatment Regimens for empirical parenteral antimicrobial therapy in Uncomplicated Pyelonephritis

Antimicrobial	Daily dose	Duration of therapy
Ampicillin and gentamicin or Ampicillin and Amikacin	1 gm and 5mg/kg or 15mg/kg qd	7-14 days
Ciprofloxacin	400 mg bid	7-14 days
Levofloxacin	500 mg qd	7-14 days
ceftriaxone	1-2 gm qd	7-14 days
Imipenem	0.5 g t.i.d	7-14 days
Meropenem	1 g t.i.d	7-14 days

b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

- The antimicrobial agents should be modified according to local resistance patterns and drug susceptibility results⁽¹⁴⁾

- The higher rate of sensitivity among uropathogen was towards amikacin (77.55%), imipenem (76.53%), nitrofurantoin (75.5%) and gentamicin (71.43%). So, these antimicrobial agents should be used. ⁽¹³⁾
- When Extended Spectrum β -Lactamase Producing *Escherichia coli* and *Klebsiella pneumoniae* were suspected imipenem and fosfomycin should be considered ⁽¹⁴⁾
- It is strongly recommended to repeat urine analysis on the fifth to the seventh day of therapy and 10 to 14 days after discontinuing antimicrobial therapy to ensure that the urinary tract remains free of infections.

Table 128: Recommendations for the diagnostic evaluation of uncomplicated pyelonephritis

Recommendations	Strength Rating
1. Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	Strong
2. Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis	Strong
3. Perform imaging of the urinary tract to exclude urgent urological disorders.	Strong
4. Treat patients with uncomplicated pyelonephritis not requiring hospitalisation with short course fluoroquinolones as first line treatment.	Strong
5. Treat patients with uncomplicated pyelonephritis requiring hospitalization with an intravenous antimicrobial regimen initially.	Strong
6. Switch patients initially treated with parenteral therapy, who improve clinically and can tolerate oral fluids, to oral antimicrobial therapy.	Strong
7. Do not use nitrofurantoin, oral fosfomycin, and pivmecillinam to treat uncomplicated pyelonephritis.	Strong

100 Complicated UTIs (cUTI):

A complicated UTI (cUTI) occurs in an individual with predisposing factors (e.g. diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction), pregnancy or recent instrumentations are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection ⁽¹¹⁾.

100.1 Recommendations for diagnosis and management:

- Urinalysis is strongly recommended including the assessment of white and red blood cells and nitrite, for routine diagnosis
- Performing urine culture and antimicrobial susceptibility testing is also strongly recommended in patients with complicated UTI
- Imaging of the urinary tract with US to exclude urgent urological disorders is strongly recommended. Additional investigations, such as an unenhanced helical computed tomography (CT) are strongly recommended if the patient remains febrile after 72 hours of treatment. For diagnosis of complicating factors in pregnant women, US or magnetic resonance imaging (MRI) is strongly recommended to avoid radiation risk to the foetus.
- It is strongly recommended appropriate management of the urological abnormality or the underlying complicating factor.
- Patients with UTI with systemic symptoms requiring hospitalization strongly recommended to be initially treated with an intravenous antimicrobial regimen, such as an aminoglycoside with or without amoxicillin, or a second or third generation cephalosporin.
- Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from the urology department or when patients have used fluoroquinolones in the last six months.
- Treatment for seven to fourteen days is strongly recommended, but the duration should be closely related to the treatment of the underlying abnormality.
- The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results. These recommendations are not only suitable for pyelonephritis but for all other cUTIs.

101 Special Types of Renal Infections:

101.1 Renal abscess:

They can rupture into the urinary tract or penetrate through the renal capsule to become a perinephric abscess. ⁽¹⁵⁾ Use of IV combined antibiotics and careful observation of a small abscess less than 3 cm or even 5 cm in a clinically stable patient is strongly recommended. Percutaneous drainage, however, remains the first line procedure of choice for most renal abscesses greater than 5 cm in diameter or open surgical drainage if percutaneous failed.

101.2 Perinephric abscess:

The clinical symptoms are chills, fever, back or abdominal pain, CVA tenderness, flank mass and redness ⁽¹⁵⁾ Broad spectrum antimicrobial agents are strongly recommended to be started immediately upon diagnosis of perinephric abscess. For larger collections or those not responsive to initial antibiotic therapy, intervention is the next step in treatment. Surgical drainage or nephrectomy if the kidney is nonfunctioning or severely infected, was the classic treatment for perinephric abscesses. However, with the advent of the field of interventional radiology and improvements in percutaneous drainage techniques, renal ultrasonography and CT- or ultrasound-guided percutaneous aspiration and drainage of perirenal collections is now a good option for therapy.

101.3 Emphysematous pyelonephritis:

This is caused by gas-forming *E. coli*, *K. pneumoniae*, *E. cloacae* fermenting glucose. The contralateral kidney is often also affected. ⁽¹⁵⁾ Emphysematous pyelonephritis is a surgical emergency. Most patients are septic, and fluid resuscitation and broad-spectrum antimicrobial therapy are strongly recommended. If the kidney is functioning, medical therapy can be considered. If a kidney is obstructed, catheter drainage is strongly recommended. If the affected kidney is nonfunctioning and not obstructed, nephrectomy should be performed because medical treatment alone is usually lethal. Nephrectomy is recommended for patients who do not improve after a few days of therapy.

101.4 Xanthogranulomatous pyelonephritis (XGP):

This is characterized by a chronic purulent, fatty inflammation of the renal parenchyma, the pelvis and the hilar tissue. ⁽¹⁵⁾ The primary obstacle to the correct treatment of XGP is incorrect diagnosis. Broad-spectrum antimicrobial therapy is strongly recommended to stabilize the patient preoperatively, and, occasionally, long-term antimicrobial therapy will eradicate the infection and restore renal function. Because the renal abnormality may be diagnosed preoperatively as a renal tumor and/ or is diffuse, nephrectomy is usually performed. If localized XGP is diagnosed preoperatively or at exploration, it is amenable to partial nephrectomy.

102 Catheter Associated Urinary Tract Infection

Catheter-associated UTI refers to presence of symptoms or signs compatible with UTI in a person whose urinary tract is currently catheterized within the past 48 hours with no other identified source of infection.^(11,16) The most common isolated organisms among Egyptian patients in cross sectional prospective study in medical wards and intensive care unit's patients ;Candida yeasts (18%) ,E.coli (3%) ,Pseudomonas (1%), Isolated MDR organisms consisted about 10% of the total isolated organisms and the most common isolated MDR organism is Vancomycin resistant enterococci (50%)and no organism isolated in 70.5%.⁽¹⁷⁾.

102.1 Recommendations for Diagnosis:

- It is strongly recommended to do routine urinary culture only in symptomatic patients, take the sample from the catheter using an aseptic technique, if the catheter has been removed obtain a midstream urine sample.
- It is strongly recommended not to use pyuria as indicator for catheter associated UTI, the longer the catheter in place, the most likely bacteria will be found. After one month nearly all patients have bacteriuria.
- It is strongly recommended not to use the presence or absence of odorous or cloudy urine alone differentiates CA-UTI from CA- asymptomatic bacteriuria.

102.2 Recommendations for Management:

- It is strongly recommended to treat symptomatic catheter CA-UTI according to recommendations for complicated UTI.
- When prescribing an antibiotic for catheter-associated UTI, take account of local antimicrobial resistance.
- Give oral antibiotics as a first line if the person can take oral medications, and the severity of their condition does not require intravenous antibiotics.
- Choice of intravenous antibiotics (if vomiting, unable to take oral antibiotics or severely unwell). Antibiotics may be combined if susceptibility of sepsis is a concern.
- It is strongly recommended to consider removing or, changing the catheter as soon as possible in people with a catheter-associated UTI if it has been in place for more than 7 days. Do not allow catheter removal or change to delay antibiotic treatment.
- It is strongly recommended not to treat CA-UTI asymptomatic bacteriuria in general except:
- Prior to traumatic urinary tract intervention
- Pregnant woman as of increase risk of pyelonephritis and preterm labor.

102.3 Recommendations for Prevention and Self-care:

- It is strongly recommended not to routinely offer antibiotic prophylaxis to prevent catheter-associated UTIs in people with a short-term or a long-term (indwelling or intermittent) catheter.
- It is strongly recommended to give advice about seeking medical help if symptoms of an acute UTI develop.
- It is strongly recommended to use paracetamol for pain associated with CA-UTI.
- It is recommended to advise people with CA-UTI about drinking enough fluids to avoid dehydration.

Table 129: Recommendations for the diagnostic evaluation of uncomplicated pyelonephritis

Recommendations	Strength Rating
1. Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	Strong
2. Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis	Strong
3. Perform imaging of the urinary tract to exclude urgent urological disorders.	Strong
4. Treat patients with uncomplicated pyelonephritis not requiring hospitalization 5. With short course fluoroquinolones as first line treatment.	Strong
6. Treat patients with uncomplicated pyelonephritis requiring hospitalization with an intravenous antimicrobial regimen initially.	Strong
7. Switch patients initially treated with parenteral therapy, which improve clinically and can tolerate oral fluids, to oral antimicrobial therapy.	Strong
8. Do not use nitrofurantoin, oral fosfomycin, and pivmecillinam to treat uncomplicated pyelonephritis.	Strong

Table 130: Recommendations for diagnostic evaluation of CA-UTI

Recommendations	Strength Rating
1. Do not use prophylactic antimicrobials to prevent catheter-associated UTIs.	Strong

2. Do not apply topical antiseptics or antimicrobials to the catheter, urethra or meatus.	Strong
3. Do not carry out routine urine culture in asymptomatic catheterised patients.	Strong
4. Do not use pyuria as sole indicator for catheter-associated (CA-UTI).	Strong
5. Do not use the presence or absence of odorous or cloudy urine alone to differentiate catheter-associated asymptomatic bacteriuria from CA-UTI.	Strong
6. Do not treat catheter-associated asymptomatic bacteriuria in general.	Strong
7. Treat symptomatic CA-UTI according to the recommendations for complicated UTI.	Strong
8. Take a urine culture prior to initiating antimicrobial therapy in catheterised patients	Strong
9. Replace or remove the indwelling catheter before starting antimicrobial therapy.	Strong
10. Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate).	Strong

103 Urosepsis

Sepsis in urology remains a severe situation with a considerable mortality rate. Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis, although the rate of sepsis due to Gram-positive and fungal organisms has increased, Gram-negative bacteria remain predominant in urosepsis ^(11, 18, 19)

Table 131: Definition and criteria of sepsis and septic shock

Disorder	Definition ^(20,21,22)
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical application, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. For rapid identification, a quick SOFA (qSOFA) score was developed: respiratory rate of 22/min or greater, any altered mentation" instead of requiring a GCS <15, or systolic blood pressure of 100 mmHg or less. The score ranges from 0 to 3 points. The presence of 2 or more qSOFA points near the onset of infection was associated with a greater risk of death or prolonged intensive care unit.
Septic shock	Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

103.1 Recommendations for diagnosis:

- It is strongly recommended to perform the quick SOFA score to identify patients with potential sepsis.
- It is strongly recommended to take a urine culture and two sets of blood cultures before starting antimicrobial treatment.
- It is suggested using biomarkers for diagnosis however; urosepsis cannot be diagnosed from biomarkers alone.
- Procalcitonin in monitoring may be useful in patients likely to develop sepsis and to differentiate from a severe inflammatory status not due to bacterial infection,
- Serum lactate is a marker of organ dysfunction and is associated with mortality in sepsis.

103.2 Recommendations for treatment of urosepsis:

- It is strongly recommended that urosepsis treatment requires a combination of appropriate antimicrobial therapy, source control (obstruction of the urinary tract) and adequate life-support care.
- In such a situation, it is suggested that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

103.2.1 Antimicrobial therapy:

- It is strongly recommended to administer parenteral high dose broad spectrum antimicrobials within the first hour after clinical assumption of sepsis.
- It is strongly recommended to provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available.
- It is strongly recommended to use high dosage of the antimicrobial substances in patients with sepsis syndrome with appropriate adjustment for renal function.

Table 132: Suggested regimens for antimicrobial therapy for urosepsis.(11)

Antimicrobials	Daily dose	Duration of therapy
Cefotaxime	2 g t.i.d	7-10 days Longer courses are appropriate in patients who have a slow clinical response
Ceftazidime	1-2 g t.i.d	
Ceftriaxone	1-2 g q.d	
Cefepime	2 g b.i.d	
Piperacillin/tazobactam	4.5 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Gentamicin*	5 mg/kg q.d	
Amikacin*	15mg/kg q.d	
Ertapenem	1 g q.d	
Imipenem/cilastatin	0.5 g t.i.d	
Meropenem	1 g t.i.d	

b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

103.2.2 Source control:

- It is strongly recommended to initiate as soon as possible source control including removal of foreign bodies, decompression of obstruction and drainage of abscesses in the urinary tract.
- It is recommended to use of least-invasive methods to release urinary tract obstruction until the patient is stabilized
- It is strongly recommended to urgently decompress the collecting system in case of sepsis with obstructing stones, using percutaneous drainage or ureteral stenting.
- It is strongly recommended to collect (again) urine for antibiogram test following decompression
- It is strongly recommended to delay definitive treatment of the stone until sepsis is resolved.

103.2.3 Adjunctive measures:

- It is strongly recommended to provide immediate adequate life-support measures including fluid therapy with crystalloids, or albumin, if crystalloids are not adequately increasing blood pressure: as vasopressors norepinephrine should be used primarily, dobutamine in myocardial dysfunction.
- It is strongly recommended to give hydrocortisone only if fluid and vasopressors do not achieve a mean arterial pressure of ≥ 65 mmHg.
- It is strongly recommended to give blood products target a hemoglobin level of 7-9 g/dL.
- It is strongly recommended to apply mechanical ventilation with a tidal volume 6 mL/kg and plateau pressure ≤ 30 cm H₂O and a high positive end-expiratory pressure.
- It is strongly recommended to use sedation minimally; neuromuscular blocking agents should be avoided
- It is strongly recommended that glucose levels to be targeted at ≤ 180 mg/dL.
- It is strongly recommended to use low-molecular weight heparin subcutaneously for deep vein thrombosis prevention.
- It is strongly recommended to use proton pump inhibitors for stress ulcer prophylaxis in patients at risk.
- It is strongly recommended to start parenteral nutrition early (< 48 hours).

103.3 Recommendations for prevention of urosepsis:

- It is recommended to reduce hospital stay as possible.
- It is recommended to remove indwelling urinary catheters early.

- It is recommended to avoid unnecessary urethral catheterization, correct use of closed catheter systems, and to pay attention to simple daily aseptic techniques to avoid cross-infection.
- It is recommended to routine use of disposable gloves. Frequent hand disinfection and infectious disease control measures to prevent cross-infections.

Table 133: Recommendations for the diagnosis and treatment of urosepsis

Recommendations	Strength Rating
1. Take urine and blood cultures before starting antimicrobial treatment.	Strong
2. Administer parenteral high dose broad spectrum antimicrobials within the first hour after clinical assumption of sepsis, and then shift according to culture results.	Strong
3. Initiate source control including removal of foreign bodies, decompression of obstruction and drainage of abscesses in the urinary tract.	Strong
4. Provide immediate adequate life-support measures.	Strong

104 Urethritis:

Urethritis is the most common genitourinary syndrome in sexually active men. Urethritis is associated with several etiological agents including *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis*, and *Mycoplasma genitalium* and causes a wide variety of symptoms, which include discharge, dysuria, localized pruritus, and penile tingling. ⁽²³⁾

104.1 Recommendation for diagnosis:

- Detailed history taking including age, sexual activities, and presence of urethral discharge is strongly recommended.
- It is strongly recommended to do urine analysis (first voided urine) and leukocyte esterase testing five or more polymorphonuclear leukocytes (PMNL) per high power field (HPF) is diagnostic of urethritis.
- It is recommended to do Gram or methylene-blue stain of urethral secretions, to diagnose gonococcal urethritis.
- Nucleic acid amplification tests are suggested (NAAT) especially in cases of urethritis with negative Gram stain test as it is more sensitive and specific in diagnosis of chlamydial and gonococcal infections.
- Urethral swab culture is suggested before initiation of treatment, in patients with a positive NAAT for gonorrhea to assess the antimicrobial resistance profile of the infective strain.
- Urethral swab culture for *N. gonorrhoeae* and *C. trachomatis* is recommended in treatment failure or persistence of symptoms more than 4 weeks of treatment.

104.2 Recommendation for disease management:

- It is strongly recommended to assess all sexual partners at risk with maintaining patient confidentiality. Empirical treatment is strongly recommended following diagnosis especially in severe cases even before Gram stain test result.

104.3 Gonococcal urethritis:

- Combination treatment using two antimicrobials with different mechanisms of action is strongly recommended to improve treatment efficacy
- It is strongly recommended to start with Ceftriaxone 1 g intramuscularly or intravenously with azithromycin 1 g single oral dose as first-line treatment

104.4 Non-gonococcal urethritis:

- Oral doxycycline 100 mg twice daily for seven days as first-line treatment is strongly recommended.
- It is also recommended, single dose oral azithromycin 500 mg day one and 250 mg day's two to four.

- Fluoroquinolones, such as ofloxacin or levofloxacin is recommended as second-line treatment only in selected cases when the use of other agents is not possible, such as hypersensitivity to avoid bacterial resistance to quinolones.
- Oral metronidazole or tinidazole 2 g single dose as first-line treatment for urethritis caused by *T. vaginalis* is strongly recommended.
- It is strongly recommended to instruct Patients to abstain from sexual intercourse for seven days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated.

Table 134: Suggested regimens for antimicrobial therapy for urethritis

Pathogen	Antimicrobial	Dosage&Duration of therapy	Alternative regimen ⁽²⁴⁾ :
Gonococcal Infection	Ceftriaxone Azithromycin	1g i.m or i.v, SD 1g p.o., SD	• Ceftriaxone 400 mg p.o., SD pluse Azithromycin 19 p.o., SD In case of cephalosporin allergy: • Genatamicin 240 mg i.m SD plus Azithromycin 2 g p.o., SD • Genatamicin 320 mg p.o., SD plus Azithromycin 2 g p.o., SD • Spectinomycin 2g i.m., SD • Fosfomycin trometamol 3g p.o., on days 1, 3 and 5 • In case of azithromycin allergy in combination with ceftriaxone or cefixime: • Doxycycline 100 mg b.i.d. p.o., 7 days
Non-gonococcal Infection (non-identified pathogen)	Doxycycline	100 mg b.i.d, p.o., 7-10 days	Azithromycin 500 mg p.o., day1 250 mg p.o., 4 days
Chlamydia trachomatis	Azithromycin Or Doxycycline	1.0 - 1.5g p.o., SD 100 mg b.i.d, p.o., for 7 days	• Levofloxacin 500 mg p.o., q.d., 7 days • Ofloxacin 200 mg p.o., b.i.d., 7 days

Mycoplasma genitalium	Azithromycin	500 mg p.o., day1 250 mg p.o., 4 days	In case of macrolide resistance: • Moxifloxacin 400 mg q.d., 7-14 days
Ureaplasma Urealyticum	Doxycycline	100 mg b.i.d, p.o., for 7 days	Azithromycin 1.0 - 1.5g p.o., SD
Trichomonas vaginalis	Metronidazole Tinidazole	2 g p.o., SD 2 g p.o., SD	Metronidazole 500 mg p.o., b.i.d., 7 days
Persistent non-gonococcal urethritis			
After first-line doxycycline	Azithromycin Plus Metronidazole	500 mg p.o., day1 250 mg p.o., 4 days 400 mg p.o., b.i.d., 5 days	If macrolide resistant M. genitalium is detected moxifloxacin should be substituted for azithromycin
After first-line azithromycin	Moxifloxacin Plus Metronidazole	400 mg q.d., 7-14 days 400 mg p.o., b.i.d., 5 days	

SD = single dose; b.i.d = twice daily; q.d = every day; p.o. = orally; i.m. = intramuscular.

105 Bacterial Prostatitis:

Table 135: Classification of prostatitis and CPPS according to NIDDK/NIH

Type ⁽²⁴⁾ :	Name and description
I	Acute bacterial prostatitis (ABP)
II	Chronic bacterial prostatitis (CBP)
III	Chronic non-bacterial prostatitis - CPPS
IIIA	Inflammatory CPPS (white cells in semen/EPS/VB3)
IIIB	Non-Inflammatory CPPS (no white cells in semen/EPS/VB3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

CPPS = chronic pelvic pain syndrome; EPS=expressed prostatic secretion;

VB3 = voided bladder urine specimen 3 (urine following prostatic massage)

105.1 Acute Bacterial Prostatitis (ABP):

105.1.1 Recommendation for diagnosis:

- Detailed history taking is strongly recommended as ABP usually presents abruptly with fever and voiding symptoms and distressing poorly localized pain ⁽²³⁾. It is often associated with malaise and fever.
- Mid-stream urine analysis, testing for nitrite and leukocytes is strongly recommended.
- Mid-stream urine culture and sensitivity for proper antimicrobial treatment is recommended.
- Prostatic massage is not recommended in acute bacterial prostatitis (ABP) as it can induce bacteremia and sepsis.
- Transrectal ultrasound is recommended if prostatic abscess is highly suggested.
- PSA testing is not recommended for patients with ABP as it has no clinical or practical significance.

105.1.2 Recommendation for management:

- Empirical high doses bactericidal antimicrobials, such as broad spectrum penicillins, a third-generation cephalosporin or fluoroquinolones are strongly recommended. ⁽²⁶⁾
- It is strongly recommended to continue oral treatment after improvement of general condition for two to four weeks.

- In case of prostatic abscess, both surgical drainage or conservative treatment according to abscess size and general condition is recommended

Table 136: Recommendations for the diagnosis and treatment of bacterial prostatitis

Recommendations	Strength Rating
1. Do not perform prostatic massage in acute bacterial prostatitis (ABP).	Strong
2. Take a mid-stream urine culture in patients with ABP symptoms to guide diagnosis and tailor antibiotic treatment.	Weak
3. Treat acute bacterial prostatitis according to the recommendations for complicated UTI.	Strong

105.2 Chronic Bacterial Prostatitis:

Chronic bacterial prostatitis is defined by symptoms (pain or/ and LUTS) that persist for at least three months.⁽²⁷⁾

105.2.1 Recommendations for diagnosis:

- Detailed history taking is strongly recommended including the character, site and duration of symptoms, Prostatitis symptom questionnaires have a weak clinical importance.
- Detailed history of sexual activities, marital status and age of marriage is recommended as the delayed marriage and absence of sexual activities due to religious and traditional conditions are important causes of prostatic congestion and chronic prostatitis in Egypt.
- The Meares and Stamey 2- or 4-glass test is strongly recommended in patients with CBP.
- Prostatic biopsy is not recommended to avoid sepsis in case of untreated chronic bacterial prostatitis.
- Transrectal ultrasound is suggested in selected cases to rule out chronic prostatic abscess and prostatic calcification.
- Semen culture is suggested as a part of evaluation of chronic bacterial prostatitis
- PSA testing is not recommended for patients with CBP as it has no clinical or practical significance.

105.2.2 Recommendations for management:

- Fluoroquinolone (e.g. ciprofloxacin, levofloxacin) is strongly recommended as a first-line treatment for CBP.
- Tetracycline or macrolides is strongly recommended if intracellular bacteria have been identified as the causative agent of CBP.
- Metronidazole is strongly recommended in patients with *Trichomonas vaginalis* CBP.

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Table 137: Suggested regimens for antimicrobial therapy for chronic bacterial prostatitis

Antimicrobial (24):	Daily dose	Duration of therapy	Comment
Floroquinolone	Optimal oral daily dose	4-6 week	
Doxycycline	100 mg b.i.d.	10 days	Only for C. trachomatis or mycoplasma infection
Azithromycin	500 mg once daily	3 weeks	Only for C. trachomatis infection
Metronidazole	500 mg t.i.d.	14 days	Only for T. vaginalis infection

b.i.d = twice daily; t.i.d = three times daily.

106 Acute Infective Epididymitis

106.1 Recommendations for the diagnosis and treatment of acute infective epididymitis

- It is strongly recommended to obtain first voided urine and mid-stream urine for pathogen identification by culture and nucleic acid amplification test.
- It is strongly recommended to initially prescribe a single antibiotic or a combination of two antibiotics active against *Chlamydia trachomatis* and Enterobacteriaceae in young sexually active men; in older men without sexual risk factors only Enterobacteriaceae have to be considered.
- It is strongly recommended that if gonorrhoeal infection is likely to give single dose ceftriaxone 500 mg intramuscularly in addition to a course of an antibiotic active against *Chlamydia trachomatis*.
- It is strongly recommended to follow national policies on reporting and tracing/treatment of contacts for sexually transmitted infections.
- Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis in boys and young men.⁽²⁸⁾
- The predominant pathogens isolated are *C. trachomatis*, Enterobacteriaceae (typically *E. coli*) and *N. gonorrhoeae*.⁽²⁸⁾
- If tuberculous epididymitis is suspected, three sequential early morning urine samples should be cultured for acid-fast bacilli (AFB) and sent for screening by NAAT for *M. tuberculosis* DNA.⁽²⁸⁾

106.2 Empiric antibiotic regimens for acute infective epididymitis⁽²⁸⁾

106.2.1 For men with acute epididymitis at low risk of gonorrhoea (e.g. no discharge)

A single agent or combination of two agents of sufficient dose and duration to eradicate *C. trachomatis* and Enterobacteriaceae should be used. Appropriate options are:

- A. fluoroquinolone active against *C. trachomatis* orally once daily for ten to fourteen days*
- OR
- B. Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days plus an antibiotic active against Enterobacteriaceae for ten to fourteen days

106.2.2 For men with likely gonorrhoeal acute epididymitis

A combination regimen active against *Gonococcus* and *C. trachomatis* must be used such as:

Ceftriaxone 500 mg intramuscularly single dose plus Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days

106.2.3 For non-sexually active men with acute epididymitis

A single agent of sufficient dose and duration to eradicate Enterobacteriaceae should be used. Appropriate option is a fluoroquinolone by mouth once daily for ten to fourteen days.

Table 138: Surgical exploration may be required to drain abscesses or debride tissue.

Recommendation ⁽²⁸⁾ .	Strength Rating
1. Obtain mid-stream urine and first voided urine for pathogen identification by culture.	Strong
2. Initially prescribe a single antibiotic or a combination of two antibiotics active against <i>Chlamydia trachomatis</i> and Enterobacteriaceae in young sexually active men; in older men without sexual risk factors only Enterobacteriaceae have to be considered.	Strong
3. If gonorrhoeal infection is likely give single dose ceftriaxone 500 mg intramuscularly in addition to a course of an antibiotic active against <i>C. trachomatis</i> .	Strong
4. Adjust antibiotic agent when pathogen has been identified and adjust duration according to clinical response.	Strong

107 Fournier's gangrene

Fournier's gangrene is an aggressive and fulminant infection affecting soft tissue of external genitalia and perineum with high mortality rate 21.6 % ⁽²⁹⁾.

Typically, there is painful swelling of the scrotum or perineum with sepsis ⁽²⁸⁾.

Patient risk factors for occurrence and mortality include immune compromise, most commonly diabetes or malnutrition, recent urethral or perineal surgery, and high body mass index (BMI). ⁽²⁸⁾

Examination shows small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease ⁽²⁸⁾

107.1 Recommendations for the disease management of Fournier's Gangrene

It is strongly recommended to start treatment for Fournier's gangrene with broad-spectrum antibiotics on presentation, with subsequent refinement according to culture and clinical response.

It is strongly recommended to commence repeated surgical debridement for Fournier's gangrene within 24 hours of presentation.

It is suggested to perform primary or secondary wound closure for scrotal defects $\leq 50\%$ with the use of flaps or skin grafts for defects involving $> 50\%$ of the scrotum or with extension outside the scrotum.

Table 139: Suggested regimens for antimicrobial therapy for Fournier's Gangrene of mixed microbiological aetiology

Antimicrobial ⁽²⁸⁾	Daily dose
Piperacillin-tazobactam plus vancomycin	3.37 g every 6-8 h IV 15 mg/kg every 12 h
Imipenem-cilastain	1 g every 6-8 h IV
Meropenem	1 g every 8 h IV
Eryapenem	1 g once daily
Cefotaxime plus Metronidazole clindamycin	2 g every 6 h IV 500 mg every 6 h IV 600-900 mg every 8 h IV

Table 140: Recommendations for the disease management of Fournier's Gangrene

Recommendations	Strength Rating
1. Start treatment for Fourniers gangrene with broad-spectrum antibiotics on presentation, with subsequent refinement according to culture and clinical response	Strong
2. Commence repeated surgical debridement for Fournier's gangrene within 24 hours of presentation.	Strong

107.2 Antibiotic prophylaxis in urologic surgery

107.2.1 Antibiotic prophylaxis

Antibiotic prophylaxis entails the treatment with antimicrobial agent(s) before or shortly after (for limited time) certain surgical procedure to prevent local surgical site infection or systemic postprocedural infection. The 2019 Best Practice statement (BPS) from the American urological association (AUA) education and research recommended perioperative antibiotic for any urological procedures that will break the normal tissue barrier, and antibiotic should be administrated within 60 minutes of the procedure^(30,31)

107.2.2 Ability of the host to respond to bacteruria or bacteremia

Ability of the host to respond to bacteruria or bacteremia is affected by many factors that increased risk of infection as

Advanced age, and poor nutritional status

Anatomic anomalies and smoking

Chronic corticosteroid use and, immunodeficiency

Chronic indwelling hardware and Infected endogenous/exogenous material

Distant coexistent infection/Prolonged hospitalization⁽³²⁾

107.2.3 Timing and dose of prophylactic antibiotic:

Infusion of the first dose should begin within 60 minutes of the surgical incision (with the exception of 120 minutes for intravenous fluoroquinolones and vancomycin). As with timing, correct dosing is equally important. Some drugs should be adjusted to the patient's body weight (or corrected dosing weight) or body mass index. Additional doses are required intraoperatively if the procedure extends beyond two half-lives of the initial dose^(30,33,34)

107.2.4 Asymptomatic bacteriuria and prophylactic antibiotic

Generally, asymptomatic bacteriuria is not considered as risk factor indicating antibiotic prophylaxis, in diagnostic and therapeutic procedures not entering the urinary tract.

It is a definite risk factor if the procedures entering the urinary tract and breaching the mucosa, especially in endoscopic urologic surgery, so it is recommended to do urine culture before such procedures and preoperative antibiotic is given accordingly. ⁽³⁵⁾

- Antimicrobial prophylaxis in different urologic procedures

1. Urodynamic study and cystography:(Prophylaxis is indicated if risk factors)

Antimicrobial prophylaxis are not recommended before cystography and urodynamic study ^(30,36).

Our panel recommend prophylactic antibiotic in case of bacteruria (Fluoroquinolone, or trimethoprim sulfamethoxazole)

2. Urethral Catheterization and removal:(Prophylaxis is indicated if risk factors)

Prophylactic antimicrobials are not recommended for patients with risk factors for infection antibiotic prophylaxes with an oral agent such as TMP-SMX should decrease the risk of postprocedural infection ^(30,37).

3. Shock-Wave Lithotripsy (Prophylaxis is indicated if risk factors)

Antimicrobial prophylaxis is not recommended before shock-wave lithotripsy Antimicrobial prophylaxis is recommended if there is recent documented UTI or infected stone is present. (Fluoroquinolone, or trimethoprim sulfamethoxazole) ^(38,39).

4. TRUS guided prostatic biopsy (Prophylaxis indicated in all patients)

Antimicrobial prophylaxis is moderately recommended before TRUS prostatic biopsy, in the form of fluoroquinolone that should be given orally the day of the procedure and two days after ⁽⁴⁰⁾.

5. Simple Cystoscopy (Without Manipulation) (Prophylaxis is indicated if risk factors)

Antimicrobial prophylaxis is not necessary for the majority of either flexible or rigid diagnostic urethracystoscopy with absence of any manipulations and in good surgical sterile condition ⁽³⁵⁾.

6. Transurethral Resection of the Prostate and Bladder (Cystourethroscopy With Manipulation): (Prophylaxis indicated in all patients)

Large numbers of RCTs showed that antimicrobial prophylaxis reduce the rate of infectious complications after TURP ⁽⁴¹⁾. It is strongly recommended to give either fluoroquinolone or 3rd generation cephalosporin before the procedure.

7. Ureteroscopy: (Prophylaxis indicated in all patients)

The rate of bacteruria is up to 30 % after ureteroscopy if done without prophylactic antibiotic, with febrile UTI in 4-25% of cases. It is strongly recommended to give fluoroquinolone, trimethoprim sulfamethoxazole or 3rd generation cephalosporin before ureteroscopy⁽³⁵⁾

8. Percutaneous Renal Surgery (Prophylaxis indicated in all patients)

Antibiotic prophylaxis in the form of fluoroquinolone, aminoglycosides or 3rd generation cephalosporin is strongly recommended before surgery ⁽⁴²⁾.

In a recent randomized Egyptian study, the use of single dose of ciprofloxacin infusion before PNL showed higher efficacy than 3rd generation cephalosporin in protection against postoperative febrile UTI ⁽⁴³⁾.

9. Open or laparoscopic surgery without entering the urinary tract (Prophylaxis indicated in all patients)

Antibiotic prophylaxis in the form of first, 2nd, or 3rd generation cephalosporin is strongly recommended before surgery, especially if there are risk factors ⁽⁴⁴⁾

10. Open or laparoscopic surgery entering the urinary tract (Prophylaxis indicated in all patients)

It is strongly recommended to give antibiotic prophylaxis in the form of fluoroquinolone, aminoglycosides or 3rd generation cephalosporin before such procedure, as the expected rate of febrile UTI is 5% to 10% without prophylaxis ⁽⁴²⁾.

11. Open or laparoscopic surgery involving implanted prosthesis (Prophylaxis indicated in all patients)

It is strongly recommended to give aminoglycosides plus 1st or 2nd generation cephalosporin or vancomycin before penile prosthesis surgery ⁽³⁰⁾

108 Urinary Schistosomiasis

Schistosomiasis is a chronic parasitic disease affecting about 207 million individuals worldwide. It is still a major health problem in many tropical and subtropical countries, as well as for travelers from developed countries ⁽⁴⁶⁾.

108.1 Prevalence:

In Egypt, between 1989 and 1996, about 2.5 million schistosomiasis cases were diagnosed and treated, mentioning that the prevalence of schistosomiasis was close to 40% in 1983 at the national level. The Ministry of Health and Population in Egypt has announced the start of a campaign to confirm the final elimination of schistosomiasis by 2020, and the ministry has achieved success in reducing the prevalence of schistosomiasis to about 0.2% by the end of 2016. ⁽⁴⁷⁾

108.2 Recommendations for diagnosis

Clinical picture is not specific for the disease, especially in endemic areas like Egypt.

- **Acute schistosomiasis** has either non-specific symptoms or passed silent and so all persons exposed to potentially infested water are considered infected and strongly recommended to start laboratory diagnostic procedure and treatment. ⁽⁴⁸⁾
- **Chronic schistosomiasis:** Chronic active stage characterized by increased eggs in the urothelium and irritative LUTS and hematuria. Urinary tract obstruction due to vesical sclerosis or ureteral stenosis, renal insufficiency, and genital lesions are seen at a later stage of the infection. Urethralgia is also a typical symptom in the late ulcerative stage ⁽⁴⁹⁾

Investigations:

108.2.1 Urine analysis:

It is the gold standard and strongly recommended when infection is suspected. Urine should be collected between 9 AM and 3 PM. Degree of infection is according to the egg count (number of eggs / 10ml of urine)

Light infection <100,

Moderate infection (100-400)

Severe infection > 400(50)

108.2.2 Serologic tests:

It is strongly recommended when the diagnosis of urinary schistosomiasis is suspected and urine is negative for eggs. (1C)

- FAST-ELISA followed by Western blot analysis.

Patients become antibody positive after 4-6 months from infection

The assays are more than 90% sensitive and specific, but did not distinguish between active and chronic infection

- PCR for antigen detection:

Detection of circulating anodic antigen (CAA) and circulating cathodic schistosome antigens (CCA) in serum and urine are specific for active infection and quantitative measurements useful for determining infection severity ⁽⁵¹⁾

108.2.3 Radiological investigations:

Ultrasonography on the abdomen and pelvis: is strongly recommended as a screening tool for upper urinary tract obstruction in all patients diagnosed or suspected to have the diseases ^(50,52).

Intravenous urography or CT urography: is strongly recommended for all patients proved to have positive findings in ultrasound.

- Detect calcifications in the urinary bladder wall and intramural ureteral wall calcifications in plain films
- Ureter stenosis with hydronephrosis
- Filling defects in the bladder and ureters (polyps or tumor)
- Large post voiding residual urine due to bladder neck contracture.
- Combining intravenous urography with fluoroscopy can differentiate between tonic and atonic ureters and identify nonstenotic immobile ureters ^(50,52)

108.2.4 Voiding cystography:

Recommended when vesico-ureteral reflux is suspected as it occurs in 25% of the affected ureters ^(50,52).

108.3 Recommendations for treatment:

108.3.1 Medical treatment

- Praziquantel is the recommended oral treatment now
- It is currently recommended by the WHO and has replaced metrifonate and oxamniquine as a main drug of treatment.
- Dose: Two 20-mg/kg oral doses of PZQ are given on the same day, 6 to 8 hours apart (or alternatively, one 40-mg/kg dose)
- The drug has lower effect against schistosomulae than adult worms, so another course should be repeated after several weeks to ensure eradication of infection ⁽⁵²⁾

108.3.2 Cystoscopy:

It is highly recommended if LUTS is persisting after adequate medical treatment or radiological findings of bladder lesions.

- Bladder proliferative inflammatory lesions are resected for histopathology.
- Sandy patches are biopsied
- Ulcer are multiple biopsied and coagulated or resected
- Tumor should be resected deeply.
- Bladder neck contracture is incised or resected especially if augmentation cystoplasty is encountered to ensure low pressure augmented bladder⁽⁵⁰⁾.

108.3.3 Surgical intervention:

It is recommended according to the long-term sequelae of the disease.

108.3.3.1 Stenotic lower end ureter:

- Minimal invasive procedures like endodilatation or incision usually fail unless the lesion is minimal
- Uterteral re-implantation has high failure rate as the lower end of the ureter has to be excised more proximally and the bladder is not healthy for mobilization or Boar flap technique
- Ileal replacement: although it is more complicated technique, it is recommended in such situation with high success rate.⁽⁵⁰⁾

108.3.3.2 Contracted bladder:

- Many surgical procedures like, bladder denervation, urinary diversion, ileacystoplasty, or hydrodistension according to the bladder and patient conditions.
- Partial cystectomy indicated for chronic deep bladder ulcer that does not respond to endoscopic surgery.⁽⁵²⁾

108.4 Effect of control of schistosomiasis in Egypt on the pattern of cancer bladder:

In a study in the national cancer institute of Egypt between 1970 and 2007, there is reduction in the proportion of patient with cancer bladder from 27.6% to 11.7%, reduction in the percent of presence of schistosomal ova in the pathological specimen from 82.4% to 55.3%, increase in the age of presentation from 47.7 to 60.5, decrease in the male to female ratio from 5.4 to 3.3 and decrease in proportion of squamous carcinoma from 75.9% to 33%. Another study showed that in 2005 there is 6-fold increases in the risk of urethelial carcinoma of the bladder versus squamous carcinoma in comparison to 1980⁽⁵⁴⁾

108.5 Urinary tract infection: Causes, Culture, Susceptibility test and Antibiotic resistance

108.5.1 Urine culture: (technique and interpretations)

108.5.1.1 Specimen collection

- It is the responsibility of the laboratory to provide the physician with sterile, wide-mouthed, glass or plastic jars, other suitable receptacles.
- The laboratory must insist on a clean-catch midstream urine specimen, particularly in females and children. Since urine itself is a good culture medium, all specimens should be processed by the laboratory within 2 hours of collection, or be kept refrigerated at 4°C until delivery to the laboratory and processed no longer than 18 hours after collection.
- Whenever possible, urine specimens for culture should be collected in the morning. It is advisable to ask the patient the night before to refrain from urinating until the specimen is to be collected.
- Urine specimens may have to be collected by a surgical procedure, e.g. suprapubic aspiration, cystoscopy, or catheterization. ⁽⁵⁵⁾

108.5.2 A female or male outpatient should:

1. Wash her hands thoroughly with soap and water and dry them with a Clean towel.
2. Spread the labia, and cleanse the vulva and labia (or wash the glans) thoroughly using sterile cotton gauze pads and warm soapy water, disinfectants should not be used.
3. Rinse the vulva and labia (or the glans) thoroughly with warm water and dry with a sterile gauze pad. During the entire process the patient should keep the labia separated and should not touch the cleansed area with the fingers.
4. Pass a small amount of urine. The patient should collect most of the remaining urine in a sterile container, closing the lid as soon as the urine has been collected. This is a midstream urine specimen.
5. Hand the closed container to the nursing personnel for prompt delivery to the laboratory.

108.5.3 Culture and interpretation

All urine specimens brought to the microbiology laboratory should be examined at once, or placed in a refrigerator at 4°C until they can be examined.

108.5.3.1 The examination procedure includes the following steps:

1. Examination of a Gram-stained smear.
2. A screening test for significant bacteriuria.
3. A definitive culture for urine specimens found to be positive in the screening test, and for all specimens obtained by cystoscopy, suprapubic bladder puncture, or catheterization.
4. Susceptibility tests on clinically significant bacterial isolates.

108.5.3.2 Preparation and examination of a Gram-stained smear is a necessary part of the laboratory process:

1. One or more bacterial cells per oil-immersion field usually imply that there are 100,000 or more bacteria per milliliter in the specimen.
2. The presence of one or more leukocytes per oil-immersion field is a further indication of UTI.
3. Non-infected urine samples will usually show few or no bacteria or leukocytes in the entire preparation.

N.B: In specimens from females, the presence of many squamous epithelial cells, with or without a mixture of bacteria, is strong presumptive evidence that the specimen is contaminated with vaginal flora and a repeat specimen is necessary, regardless of the number of bacteria per oil-immersion field.

108.5.3.3 Screening method:

1. The absence of leukocytes and bacteria in a Gram-stained smear of a clean- catch urine sample prepared as described above is good evidence that the urine is not infected and does not need to be cultured
2. The strip is dipped into the urine specimen as instructed in the package literature. Any pink color is a positive reaction indicating the presence of leukocyte esterase and/or bacteria in excess of 100,000 per ml.
3. Urine samples that are positive in the screening test should be cultured as soon as possible to prevent possible overgrowth by non-significant bacteria.
4. If the strip does not develop a pink color it is interpreted as a negative screening test, is so reported, and no culture is indicated.

N.B: The test strip may not be sensitive enough to detect bacterial counts of less than 100,000 per ml of urine.

108.5.3.4 Quantitative culture and presumptive identification by Calibrated loop technique:

The recommended procedure uses a calibrated plastic or metal loop to transfer 1µl of urine to the culture medium (MacConkey agar with crystal violet and non-selective blood agar, they can also be replaced by another non-selective medium (e.g. CLED agar).

108.5.3.5 Interpretation of quantitative urine culture results

For many years, only the presence of at least 100,000 colony-forming units (CFU) per ml in a clean-catch midstream urine specimen was considered clinically relevant for a diagnosis of urinary tract infection. This assumption has been challenged; some experts feel that 10,000 CFU or even fewer may indicate infection. Others believe that the presence of polymorph nuclear leukocytes plays an important role in the pathology and clinical manifestations of UTI. It is not possible to define precisely the minimum number of bacteria per milliliter of urine that is definitely associated with UTI. General recommendations for reporting are given below.

Category 1:(Fewer than 10,000 CFU per ml.)

Report as probable absence of UTI. (Exceptions: if fewer than 10,000 CFU per ml are present in urine taken directly from the bladder by suprapubic puncture or cystoscopy, in; symptomatic women, or in the presence of leukocyturia, report the identification and the result of the susceptibility test.

Category 2: (10,000 – 100,000 CFU per ml.)

- If the patient is asymptomatic, request a second urine specimen and repeat the count.
- If the patient has symptoms of UTI, precede with both identification and susceptibility tests if one or two different colony types of bacteria are present. Bacterial counts in this range strongly suggest UTI in symptomatic patients, or in the presence of leukocyturia.
- If the count, the quality of the urine specimen, or the significance of the patient's symptoms is in doubt, a second urine specimen should be obtained for retesting. Report the number of CFU.

Category 3: (More than 100,000 CFU per ml.)

Report the count to the physician and proceed with identification and susceptibility tests if one or two different colony types of bacteria are present. These bacterial counts are strongly suggestive of UTI in all patients, including asymptomatic females.

If more than two species of bacteria are present in urine samples in categories 2 and 3, report as "Probably contaminated; please submit a fresh, clean-catch specimen".

108.5.3.6 Susceptibility tests:

Susceptibility tests should only be performed on well-isolated colonies of similar appearance that are considered significant according to the guidelines presented above. The standardized disc-diffusion test (Kirby–Bauer) should be used. Only antimicrobials currently being used by the requesting physicians should be tested. New and expensive antimicrobials should only be tested (or reported) on special request, or when the isolate is resistant to other drugs

108.5.3.6.1 General principles of antimicrobial susceptibility

Testing Antimicrobial susceptibility tests measure the ability of an antimicrobial agent to inhibit bacterial growth in vitro. This ability may be estimated by either the dilution method or the diffusion method.

It is important that both the clinician and the laboratory worker understand the exact definitions and the clinical significance of these categories.

- **Susceptible:** An organism is called "susceptible" to an antimicrobial when the infection caused by it is likely to respond to treatment with this antimicrobial, at the recommended dosage.
- **Intermediate susceptibility:** covers two situations. It is applicable to strains that are "moderately susceptible" to an antimicrobial that can be used for treatment at a higher dosage (e.g. b-lactams) because of its low toxicity or because the antimicrobial is concentrated in the focus of infection (e.g. urine).

- The classification also applies to strains that show “intermediate susceptibility” to a more toxic antimicrobial (e.g. aminoglycoside) that cannot be used at a higher dosage. In this situation, the intermediate category serves as a buffer zone between susceptible and resistant.
- **Resistant:** This term implies that the organism is expected not to respond to a given antimicrobial, irrespective of the dosage and the location of the infection ⁽⁵⁵⁾

108.6 Antibiotic resistance

108.6.1 Causes of antibiotic resistance:

Antibiotic overuse leads to antibiotic resistance. Some strains of bacteria are now resistant to all of the most commonly used antibiotics. When UTIs recur or don't go away with treatment, urine samples are usually tested at a microbiology lab, and if resistant organisms are discovered they are often found to be Extended Spectrum Beta Lactamase ESBL E. coli or (ESBL) and Klebsiella⁽⁵⁶⁾ or other non-bacterial causes as infection with Candida which usually occurs in patients with urinary catheters, typically after antibiotic therapy.⁽⁵⁷⁾ Also chlamydia infection is other cause of resistance ⁽⁵⁸⁾

108.6.2 Diagnosis:

1. New and expensive antimicrobials should be tested (or reported) on special request, or when the isolate is resistant to other drugs. ⁽¹⁾
2. Diagnosis of candida infection by Gram stain, Germ tube test and culture on Sabouraud agar.
3. Diagnosis of chlamydia infection by either through culture or identification of the genetic material of the bacteria referred to as nucleic acid amplification tests (NAATs). ⁽⁵⁸⁾

108.6.3 Treatment recommendations:

1. Fosfomycin is an oral broad-spectrum antibiotic that acts against many multidrug-resistant pathogens in the urinary tract. ⁽⁵⁹⁾
2. For ESBL E. coli or ESBL Klebsiella: intravenous drip of carbapenem antibiotic ⁽⁵⁶⁾
3. For candida infection:
 - Symptomatic cystitis, treatment is with fluconazole 200 mg orally once a day for 2 weeks (2 doses).
 - For pyelonephritis, fluconazole 200 to 400 mg orally once a day is preferred for 2 weeks (2 doses).
 - For fungi resistant to fluconazole, amphotericin B is recommended at a dose of 0.3 to 0.6 mg/kg IV once a day for 2 weeks for cystitis and 0.5 to 0.7 mg/kg IV once a day for 2 weeks for pyelonephritis ⁽⁵⁷⁾
4. for chlamydia infection:
 - The Centers for Disease Control and Prevention (CDC) recommends azithromycin and doxycycline as first-line drugs for the treatment of chlamydial infection.

- Alternative agents include erythromycin, levofloxacin, and ofloxacin⁽⁵⁸⁾

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Committee XII

Renal Transplantation



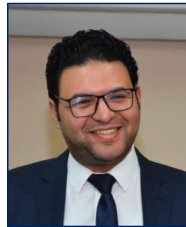
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110 Abbreviations

ACR	Acute cellular rejection
ADPKD	Autosomal dominant polycystic kidney disease
AMR	Antibody-mediated rejection
ASB	Asymptomatic bacteriuria
BK	Polyoma (BK) virus
CDC	Chronic kidney disease
CDC	Complement-dependent cytotoxicity
CMV	Cytomegalovirus
CT	Computerized Tomography
DSA	donor-specific antibodies
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GN	Glomerulonephritis
HLA	Human leucocyte antigen
HSV	Herpes Simplex Virus
HTLV	Human T-cell lymphotropic virus
LLDN	Laparoscopic living-donor nephrectomy
MMR	Measles/Mumps/Rubella
MRA	Magnetic resonance angiography
PRA	Panel of reactive antibodies
RAT	Renal artery thrombosis
RCT	Randomized controlled trial
TB	Tuberculosis
UTI	Urinary tract infection
VCUG	Voiding cystourethrogram
VUR	Vesicoureteric reflux
VZV	Varicella-Zoster Virus

111 Abstract

111.1 Objective:

Our Objective is to provide evidence-based data to surgeons performing kidney transplantation essential to improve both the safety and the outcome of the procedure. Our goal is to transform available evidence in literature and clinical practice into recommendations for best practice use by all kidney transplant surgeons.

111.2 Methods:

Our specialized panel reviewed available literature on kidney transplantation, including all published urological associations guidelines, review articles, meta-analysis and large prospective multicentric studies. Recommendations were stated in accordance with the Egyptian guidelines grading system (Strong and weak).

111.3 Results:

In this guideline, we classified kidney transplantation into three main categories: pre-transplant assessment, transplant surgery (donor and recipient), and post-transplant management and complications. Despite the importance of the medical aspects in managing transplant patients, we opted to emphasize on the surgical aspects that concerns all transplant surgeons, the targeted group of this guidelines. Medical preparation, immunosuppression and medical complications will be discussed in brief, as they are beyond the scope of this guidelines.

111.4 Conclusion:

Our guidelines provide important recommendations to all Egyptian transplant surgeons to ensure safe clinical practice and better outcome when performing kidney transplantation.

112 Introduction:

Guidelines are summaries of the highest level of evidence in literature, according to published data from experts in the field. Following the guidelines does not necessarily guarantee the outcome but will assist urologists in providing patients with safe clinical practice, that has been reproducibly reported to achieve best and safest results. The goal of our guidelines is to provide urologists and transplant surgeons, performing kidney transplantation, with an updated evidence-based review of literature on renal transplant, hence the guidelines will emphasize on the surgical aspects of kidney transplantation. Published data from meta-analysis, large prospective multicentric studies, review articles and Egyptian literature, as well as guidelines from known associations were thoroughly reviewed ⁽¹⁻⁵⁾. Recommendations in the guidelines are in accordance with the Egyptian Guidelines Grading System (Strong and weak).

113 Patients' selection

- We recommend that all patients with chronic kidney disease (CKD) G4-5 (glomerular filtration rate [GFR] $< 30\text{ml/min/1.73 m}^2$) are to be considered for kidney transplantation regardless of sex, gender, race or socioeconomic status, except in CKD patients with metastatic untreatable malignancies, severe irreversible restrictive or obstructive lung disease, un-supported patients with serious mental retardation, non-compliance, unstable psychiatric disorder, active substance abuse, severe decompensated liver or cardiac failure (unless liver and cardiac transplantation are considered; respectively).
- We recommend pre-emptive kidney transplantation with kidneys from living donors as the treatment of choice in CKD patients.
- We encourage using living related donors as the main source of kidney donation followed by un-related donors.
- We recommend that the following conditions exclude any potential donor from kidney donation:
 - Age < 21 yrs
 - 50 yrs (living-unrelated) or > 60 yrs (living-related)
 - Hypertension
 - Diabetes Mellitus or abnormal glucose tolerance test
 - History of thrombosis or embolism
 - Severe peripheral vascular disease
 - Chronic lung disease with impaired oxygenation
 - Recent malignancy with long time to possible recurrence
 - Urological abnormalities, bilateral recurrent renal stones, or severe vascular anomalies
 - Impaired renal function ($\text{GFR} < 80 \text{ ml/min/1.73m}^2$)
 - Proteinuria $> 300 \text{ mg}$ in 24 hrs
 - Active HIV, Hepatitis B or C infection

114 Legal considerations in kidney transplantation

- Kidney transplantation in Egypt must be only done in licensed transplant centers, after obtaining an official approval from the higher supreme committee for organ transplantation, Ministry of Health.
- We recommend that an informed consent must be taken from both recipients and donors prior to kidney transplantation.
- We recommend that donor's decision to withdraw at any stage prior to surgery should be respected and supported in a manner that protects confidentiality.

115 Pre-Transplant Assessment

115.1 Patients' Education and counselling

Table 141: Recommendations for Patients' education and counseling

Recommendation	Strength Rating
1. Counselling and education represent an integral part of preoperative preparation of renal transplant recipients.	Strong

Patient education may improve patients' recovery after surgery, reduce the postoperative psychological stress, and allow early recovery of healthy lifestyle. ^(6,7) All potential transplant candidates and their primary care givers are encouraged to attend a "patient education" session before the formal evaluation process. Patients are educated on the benefits and risks of renal transplantation, the necessity for frequent outpatient visits in the early postoperative period, the potential adverse effects of immunosuppression, lifestyle adjustments (cessation of cigarette smoking, weight loss...etc), stress coping strategies, the effect of transplantation on existing medical conditions, and the importance of compliance with immunosuppressive therapy. ^(7,8)

115.2 Transplant Workup

The purpose of the evaluation is to identify contraindications to kidney transplantation and correct medical and psychological conditions that may affect the transplant outcome.

Table 142: . Recommendations for Donor assessment

Recommendations	Strength Rating
History taking	
A comprehensive and detailed history taking is strongly recommended and it should cover the following aspects: 1- Age, smoking, alcohol, or drug dependence 2- Medical conditions (such as history of peripheral edema, gout, nephrolithiasis, diabetes mellitus, cardiovascular disease, and current or previous malignancy) 3- Transmissible infection (such as TB, HIV, and hepatitis)	Strong
Clinical Examination	
Full clinical examination of the donor is recommended, and it should include but not limited to:	Strong

1- Cardiovascular examination (blood pressure, ECG, chest X-ray) 2- Calculation of BMI 3- Examination for abnormal masses or swelling 4- Surgical scars 5- Mental health	
Laboratory & Radiological investigations	
Laboratory investigations should include at least: 1- Urinalysis for detection of hematuria, proteinuria, and glucose and urine culture (at least two times are recommended). 2- General laboratory examination (complete blood count, liver function test, coagulation profile, lipid profile, thyroid function, blood electrolyte, fasting blood sugar.... etc) 3- Assessment of renal function (urea, creatinine, eGFR) 4- Evaluation of infection (HBV, HCV, HIV, CMV, EBV) 5. Blood group/HLA typing	Strong
Renal imaging (e.g., computed tomographic angiography, renal scan,,,,, etc) should be performed in all donor candidates to assess renal anatomy and function before nephrectomy.	Strong

T.B: Tuberculosis, HIV: Human immunodeficiency virus, CMV: cytomegalovirus, HLA: Human leucocytic antigens, ECG: electrocardiogram

Table 143: Recommendations for Recipient assessment

Recommendations	Strength Rating
History taking	
A comprehensive and detailed history taking is strongly recommended for renal transplant recipients and it should cover the following aspects: 1- Age, smoking, alcohol, or drug dependence 2- Medical conditions (such as history of peripheral edema, gout, nephrolithiasis, diabetes mellitus, cardiovascular disease, and current or previous malignancy) 3- Transmissible infection (such as TB, HIV, and hepatitis) 4- Renal disease assessment (etiology, assessment of the native renal biopsy if possible, history of previous transplant, and previous graft loss)	Strong
Clinical Examination	

Full clinical examination of the recipient is recommended, and it should include but not limited to: 1- Cardiovascular examination (blood pressure, ECG, chest X-ray, echocardiogram) 2- Calculation of BMI 3- Examination for abnormal masses or swelling 4- Surgical scars 5- Psychological and mental assessment 6- Conditions that may require pre-transplant surgical treatment (inguinal hernia, and peripheral vascular disease)	Strong
Examination for malignancy (as per local guidelines)	Strong
Laboratory & Radiological investigations	
1. Laboratory investigations should include at least: 1. Urinalysis and culture (at least two times are recommended). 2. General laboratory examination (complete blood count, liver function test, coagulation profile, lipid profile, thyroid function, blood electrolyte, fasting blood sugar, and renal function tests) 3. Evaluation of infection (HBV, HCV, HIV, CMV, EBV)	Strong
2. Imaging studies should include abdominal US and abdominopelvic CT	Strong
3. Native renal biopsy is indicated to identify the underlying cause of renal failure (if unknown) as it may help predicting the risk of recurrence	Weak
Immunological tests	
1. ABO grouping and HLA typing (class I and II) must be done to all recipients	Strong
2. DSA assessment must be done to all recipients prior to transplantation	Strong
3. Cross match must be done prior to all kidney transplantations	Strong

DSA: donor-specific antibodies

115.2.1 General Assessment

General assessment starts with a detailed history and physical examination. The history should focus on the etiology of the renal disease with a review of the native kidney biopsy if available. It may help to assess the risk of recurrence in the transplanted kidney. A detailed history of any prior transplant courses including the causes of graft loss, medication compliance, and previous transplant complications should be obtained in re-transplant candidates. For candidates with ESRD secondary to congenital and urological abnormalities, appropriate urological evaluation is required.

Issues of specific importance to the surgeon include the patient’s previous surgical history, vascular examination, overall risk for anesthetic complications, and the presence of any pathologic process that might require pretransplant surgical treatment (i.e., inguinal hernia, peripheral vascular disease, symptomatic polycystic kidney disease). Candidates’ BMI should be measured as obesity is associated with adverse outcome and poses technical challenges with surgery.

115.2.2 Informed consent

Table 144: Recommendations of informed consent

Recommendations	Strength Rating
For renal transplantation surgery in Egypt, it is mandatory to obtain an informed written consent from both the donor and the recipient and to obtain an approval from the Egyptian Supreme Committee of Organ Transplantation	Strong

Like other surgeries, an informed consent should be obtained from both the donor and the recipient. However, it should be noted that the informed consent for donation should ensure precise understanding of the related risks and benefits of donation and it should be obtained from the donor candidate; in the absence of any of the concerned personnel such as the intended recipient, family members and other persons who could influence the donation decision. ⁽⁹⁾

Substitute decision makers should not be used on behalf of a donor candidate who lacks the capacity to provide informed consent (e.g., children or those who are mentally challenged), except under extraordinary circumstances and only after ethical and legal review. Donor’s decision to withdraw at any stage of transplantation prior to surgery must be respected and protected. ⁽¹⁰⁾

115.2.3 Laboratory Assessment

Laboratory investigations for both recipients and donors must include complete blood picture, urine analysis and culture, ABO group, renal and liver function tests, fasting glucose level, coagulation profile, 24 hrs urine protein, serum electrolytes, lipid profile and HLA typing. Serum PSA level must be assessed in all male recipients above the age of 45 yrs. Recent PAP smear (within 6 months) should be done in all adult female recipients and mammography in females >50 yrs. Screening for tuberculosis (TB) using PCR for TB in urine is encouraged in suspicious cases, including recipients from endemic areas. Occult blood in stool is to be tested in recipients >60 yrs., patients with lower GI symptoms, diverticular disease, or positive family history of lower GI malignancy. (Strong)

Virology workup of recipients and donors must include Hepatitis B, Hepatis C, Human immunodeficiency Virus (HIV), Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV).

(Strong) Screening for Herpes Simplex Virus (HSV), Varicella-Zoster Virus (VZV), Polyoma (BK) virus and Human T-cell lymphotropic virus (HTLV) is encouraged (weak).

115.2.4 Radiological Assessment

Radiological imaging of recipients includes echocardiography, chest X ray and an ultrasound for the abdomen and pelvis. Additional imaging modalities are required according to individual cases. Plain Computerized Tomography (CT) for the abdomen and pelvis is frequently required to accurately assess the abdomen, exclude any pathology, evaluate the vascular anatomy such as the presence of atherosclerosis with calcification, assess Autosomal dominant polycystic kidney disease (ADPKD) patients and the potential need for native nephrectomy....etc. Imaging studies on the lower urinary tract are required in specific cases. Urodynamic evaluation is required in recipients with suspected bladder storage or emptying dysfunction.

Radiological assessment of potential donor includes echocardiography, chest x-ray, abdominal sonography, triphasic multi-slice CT abdomen and pelvis, CT angiography, and diuretic renal scan. Further imaging modalities can be required for selected cases. (Strong)

115.2.5 Vascular Assessment

Vascular Assessment is suggested in all transplant recipients; nevertheless, it is recommended to be done in all candidates with symptoms of ischemic leg disease, femoral bruits, claudication, or absent pedal pulses. Selective iliac angiography, abdominal CT angiography, or Magnetic resonance angiography (MRA) are among the additional imaging studies that can be used in such cases.

115.2.6 Cardiac Assessment

- We recommend that all transplant donors and recipients undergo cardiac assessment prior to kidney transplantation. Cardiovascular disease is the leading cause of death in recipients after kidney transplantation. Cardiac assessment is essential to optimize the cardiac condition prior to surgery, as well as to exclude recipients with decompensated cardiac failure.
- We recommend electrocardiogram (ECG) and echocardiography to be done to all transplant donors and recipients prior to surgery. Additional tests are to be done, accordingly, for specific or symptomatic cases.

115.2.7 Vaccination

- We recommend that all potential transplant recipients should be fully immunized before transplantation.
- We recommend live vaccines to be administered at least 6 weeks before kidney transplantation.
- We recommend that transplant recipients should receive the following vaccinations prior to transplant: Diphtheria, Pertussis, Hepatitis B, Haemophilus Influenza-B,

Meningococcal (conjugate), Pneumococcal (conjugate and/or polysaccharide), Influenza and Measles/Mumps/Rubella (MMR).

- We recommend post-transplant vaccination to be resumed one year after kidney transplantation, except for seasonal flu vaccine which can be given 4 weeks after transplantation.
- We recommend no live vaccines to be given after kidney transplantation.
- We recommend yearly influenza immunization to all transplant recipients post transplantation.

115.2.8 Specific Assessment

- We recommend performing cystoscopy to assess the lower urinary tract, upper and lower GI endoscopy to selected kidney transplant recipients. (strong)
- We recommend urodynamic evaluation only in suspected cases of bladder filling or emptying dysfunction. (weak)

115.2.9 Immunological considerations

- We recommend a negative crossmatch preferably using flowcytometry before kidney transplantation.
- We suggest performing crossmatch using complement-dependent cytotoxicity (CDC) as a less favorable alternative.
- We recommend assessing anti-HLA and donor-specific antibodies (DSA) in all transplant recipients prior to transplantation. According to which immunological risk can be assessed. We recommend highly sensitized recipients to be desensitized prior to transplantation.
- We recommend classifying transplant recipients according to history of previous transplantation, multiple pregnancies, repeated blood transfusion, high panel of reactive antibodies (PRA), HLA mismatching, and the presence of HLA antibodies to; low, intermediate or high immunological risk groups.
- We recommend using induction immunosuppression in all high-risk recipients, preferably using a T-cell depleting antibodies (anti-thymocyte globulin) induction therapy. We recommend using any induction therapy in intermediate-risk group whether with monoclonal or polyclonal antibodies, while the use of induction in low-risk group is preferred.
- We recommend the use of multi-drug regimen immunosuppressive therapy to all recipients post transplantation.
- We recommend to routinely assess the blood levels of measurable immunosuppressive drugs in all recipients after transplantation.

116 Transplant procedure

116.1 Donor Nephrectomy:

116.1.1 Choice of kidney

Table 145: Recommendations for Choice of donor kidney

Recommendations	Strength Rating
Generally, the better functioning kidney should stay in the donor; but if all the factors (including the quality and function) are equivalent, it may be recommended to remove the left kidney as it has a longer vein.	Strong

Generally, the best kidney should stay with the donor. Differential function of $50\% \pm 2$ is the cutoff for considering equality of the function of both kidneys. Factors influencing which kidney to harvest include split function, arterial, venous and ureteral anatomy, and any other renal abnormalities (i.e. cysts). Extrarenal findings such as previous operations and scars or perceived difficulty in positioning on one side may also play a role. While in case all factors, including function and quality, are equivalent, the kidney with the lowest risk for surgical complications in the recipient is selected. It is then generally preferable to remove the left kidney since it has a longer renal vein that makes the recipient operation easier. ^(11,12)

116.1.2 Surgical approach

Table 146: Recommendations of Donor nephrectomy

Recommendations	Strength Rating
1. Restrict living-donor nephrectomy to specialized centers.	Strong
2. Offer long-term follow-up to all living kidney donors.	Weak
3. The surgeon should have adequate training and experience for the surgical approach used for the donor nephrectomy.	Weak
4. Pure or hand-assisted laparoscopic nephrectomy is considered as the standard of care for living-donor nephrectomy.	Strong
5. Perform open living-donor nephrectomy in centers which lack the required facilities for endoscopic techniques or in patients with extensive adhesions.	Strong

6. Perform laparo-endoscopic single site surgery and robotic surgery-assisted living donor nephrectomy in specialized centers only with great experience in renal transplantation.	Weak

Several systematic reviews and meta-analyses comparing between open and laparoscopic approaches, supported laparoscopic living-donor nephrectomy (LLDN) as the standard of care. LLDN offers similar rates of graft function and rejection, urological complications, and patient and graft survival. On the contrary, LLDN is associated with significantly lower postoperative pain, less analgesic requirements, and shorter hospital stay and time to return to work. ⁽¹²⁻¹⁴⁾

“Mini-open” laparoscopy or hand-assisted laparoscopy by trained surgeons should be offered as optimal approach to donor nephrectomy. However, in some circumstances, such as donors with extensive previous surgery and/or adhesions, and at centers where laparoscopy is not routinely performed, open nephrectomy (flank or laparotomy) may be acceptable. ⁽¹⁵⁾ Generally, laparo-endoscopic single site surgery and robotic -assisted living donor nephrectomy should be performed in highly specialized centers only. Non-transfixing clips, (e.g., Weck Hem-o-lok) should not be used to ligate the renal artery in donor nephrectomy; instead, renal artery transfixation by suture ligature or anchor staple within the vessel wall should be used. ⁽¹⁶⁾

In the absence of reasons to procure the right kidney (vascular, urological, or other abnormalities), the left kidney should be procured in laparoscopic donor nephrectomy because of the relative technical ease associated with a longer venous pedicle. We suggest laparoscopic procurement of the right rather than the left living donor kidney may be performed if the surgeon has adequate training and experience. Procurement of a living donor kidney with 3 or more arteries should only be undertaken by surgeons with adequate experience. ⁽¹⁷⁾

116.2 Surgery on the Renal Transplant Recipient:

116.2.1 Immediate preoperative preparation

Table 147: Recommendations of Recipient's preparation

Recommendations	Strength Rating
Dialysis or conservative measures may be considered to manage fluid and electrolyte imbalance before the surgery taking into consideration the likelihood of immediate graft function	Weak
Operating on patients taking anti-platelet and anti-coagulation agents	
1. Anti-platelet therapy should not be stopped in patients on the transplant waiting list.	Weak
2. A multidisciplinary team consisting of urologist, cardiologist, hematologist, and nephrologist should be considered in the counseling	Weak

of kidney transplant candidates who take anti-platelet and/or anticoagulant.	
Prevention of venous thrombosis including deep vein thrombosis during and after renal transplant	
1. Routine post-operative prophylactic anti-coagulants in the form of unfractionated or low molecular-weight heparin is not recommended for low-risk living donor transplant recipients.	Weak
Peri-operative antibiotics in renal transplant	
1. Single-dose perioperative prophylactic antibiotics represents a good alternative to multi-dose antibiotics in routine renal transplant recipients.	Strong
Specific fluid regimes during renal transplantation	
1. Renal graft function is improved by optimizing patient's hydration throughout the entire process of transplantation (pre, peri, and postoperative).	Strong
2. Use balanced crystalloid solutions for intraoperative intravenous fluid therapy	Weak
3. Use target directed intra-operative hydration to decrease delayed graft function rates and optimize early graft function.	Strong
Dopaminergic drugs in renal transplantation	
1. Do not routinely use low-dose dopaminergic agents in the early postoperative period.	Weak

The timing of renal transplantation surgery is a point of special interest. Kidney transplantation is an elective or semi-elective surgery performed on patients who have undergone careful preoperative assessment and preparation. There are numerous advantages to preemptive kidney transplantation (transplantation before dialysis) including a survival advantage. Yet, rates of preemptive kidney transplantation are still low. ⁽¹⁸⁻²⁰⁾

The decision to dialyze a patient before transplantation depends on the timing of the previous dialysis, clinical assessment of volume status, and serum electrolyte levels, particularly potassium. ⁽¹⁷⁾ Noteworthy, pre-transplant dialysis is associated with an increased incidence of delayed graft function because of the danger of intraoperative or postoperative hyperkalemia in oliguric patients. In this setting, dialysis should be considered for patients with serum potassium level of more than 5.5 mEq/L. In well-dialyzed patients, preoperative dialysis for fluid removal is usually unnecessary and if it is needed it should be done with care to maintain the patient at or somewhat above dry weight to facilitate postoperative diuresis. ⁽²¹⁾

As regards the operative risk in patients using anti-coagulant and/or anti-platelet, there are some evidence that continuing anti-platelet therapy with aspirin, ticlopidine, or clopidogrel does not confer a significantly greater risk of peri- or postoperative complications. ^(22,23) Furthermore, a small randomized controlled trial (RCT) performed in Egypt demonstrated no significant

difference in early postoperative graft loss or thromboembolic complications with or without prophylactic anticoagulation. ⁽²⁴⁾

Interestingly, a multicentric, prospective RCT showed no difference at one month in surgical site, bacterial, fungal, or viral infection between those receiving a single-dose broad-spectrum antibiotic at induction of anesthesia compared with those receiving antibiotic twice daily for 3–5 days. ⁽²⁵⁾

116.2.2 Native kidney

Table 148: Recommendations for Native nephrectomy

Recommendations	Strength Rating
1. Pre-transplant routine native nephrectomy is not recommended unless there is recurrent upper urinary tract infection or high risk of malignancy.	Strong
2. Native nephrectomy (uni- or bi-lateral) is recommended in patients with autosomal dominant polycystic kidney disease (ADPKD) in case of severe and/or recurrent symptomatic complications such as bleeding, stones, or infection.	Strong
3. Ipsilateral native nephrectomy can be performed concomitant with transplantation in patients with asymptomatic ADPKD when there is not enough space for the transplant kidney.	Strong

Pre-transplant recipient native nephrectomy is not the standard practice in kidney transplantation and usually both native kidneys are left in place. Several indications exist for native nephrectomy either unilateral or bilateral including symptomatic or complicated autosomal dominant polycystic kidney disease, suspicious renal or urothelial cancer, recurrent infection associated with nephrolithiasis, and/or heavy proteinuria and hypoalbuminemia. ⁽²⁶⁻²⁸⁾

116.2.3 Surgical approach:

Table 149: Recommendations for surgical technique

Recommendation	Strength Rating
1. Open approach to renal transplantation is the approach of choice	Strong
2. Renal transplantation should be limited to highly specialized centers	Strong
3. Right or left iliac fossae are the common sites for placement of the graft during first or second single kidney transplant	Weak

4. It is recommended to carefully ligate perivascular lymphatics during vascular dissection of the iliac vessels to reduce the risk of postoperative lymphocele	Weak
5. A drain can be placed to reduce the incidence of postoperative lymphoceles	Weak

Generally, the patient is placed in the supine position and a “hockey-stick”-shaped incision is performed in the lower quadrant starting the midline (approximately one to two finger breadths above the pubic bone) and curving upwards as it extends laterally until it reaches the edge of the rectus muscle. Finally, the incision is extended superiorly along the lateral margin of the rectus muscle. The graft is commonly placed in a retroperitoneal location (either the right or left iliac fossa; however, right iliac fossa is preferred as the right iliac vein is more superficial.^(29,30) On the other hand, some surgeons routinely place drains, while others do not. We strongly suggest putting drain, as placement of a drain may reduce the incidence of lymphoceles.⁽³¹⁾

116.2.4 Vascular anastomosis:

Table 150: Recommendations for Vascular anastomosis

Recommendations	Strength Rating
1. The length of donor renal vein is an important determinant of the technique of vascular anastomosis. In case of short vein consider one of the available techniques to optimize the venous anastomosis such as transposition of the recipient’s iliac vein.	Weak
2. The external iliac vein is most commonly used for outflow. The renal vein is anastomosed to the iliac vein in an end-to-side fashion.	Weak
3. The external or common iliac arteries are most commonly used for arterial anastomosis with the donor’s renal artery in an end-to-side arterial fashion.	Weak
4. End-to-end anastomosis between the internal iliac artery and graft artery can be used as an alternative to the external or common iliac arteries.	Weak
5. An intimal rupture/flap of the donor and the recipient arteries must be repaired before the arterial anastomosis. Thus, thorough inspection of the intima of both the donor and recipient artery is a must.	Strong
6. Careful preoperative surgical planning is recommended in case of $\geq$ third transplant to guarantee appropriate arterial inflow and venous outflow with sufficient space for graft implantation	Strong

For adult recipients, the vascular anastomoses are usually performed to the iliac vessels. The venous anastomosis is performed first. Commonly, the external iliac vein is used for the outflow,

where the optimal site of anastomosis depends on the position and lie of the allograft kidney. In certain conditions where the graft renal vein is short or the recipient iliac vein is deep, the branches of the recipient's internal iliac vein can be ligated and divided to bring the vein in a more superficial position. Generally, an end-to-side tension free venous anastomosis is performed. Clamps can be placed proximally and distally on the vein, or a single auricular clamp may be used. A venotomy of appropriate size is made. There are several ways to perform the actual anastomosis, none of which have proven advantage over the others. ^(32,33)

For arterial inflow, the common, external, or internal iliac artery may be used with similar postoperative results. ⁽³⁴⁾ Generally, the external iliac artery is preferred; however, if it is diseased or narrow in caliber there should be no hesitation in using the common iliac artery. Noteworthy the best option to choose the site of anastomosis is to place the kidney in the fossa then choose the site where the artery will lie more naturally without tension, redundancy, or angulation. ⁽³⁵⁾ Overall, the arterial anastomosis is performed in a way similar to that of the vein.

Finally, the clamp on the iliac vein is flashed open, and if no bleeding, removed carefully. Massive bleeding should prompt immediate re-clamping and suture repair. Then the distal arterial clamp is removed. The renal artery is occluded with a pickup. The proximal arterial clamp is released. After approximately three heartbeats, the occlusion of the renal artery by the pickup is released. The distal arterial clamp is removed first, followed by the proximal arterial clamp. ^(32,34)

116.2.5 Ureteral anastomosis:

Table 151: Recommendations for Ureteral anastomosis

Recommendations	Strength Rating
1. In patients with normal urological anatomy, it is recommended to use Lich-Gregoir-like extravesical ureteric implantation technique to reduce the risk of urinary tract complications	Strong
2. In very short or poorly vascularized allograft ureter, consider pyelo/uretero-ureteral anastomosis	Strong
3. Routine use of ureteric stenting in the transplanted ureter with early removal (within 30 days) is suggested to reduce major urinary complications	Weak
4. Duplex allograft ureters are not an indication to abandon the procedure, and they can be implanted either separately or combined in the same principle as a single ureter	Strong

The continuity of the urinary tract is established by anastomosing the allograft ureter to the bladder. Several techniques are available for the ureterovesical anastomosis; however, the most important factors to ensure the vascularity and perfusion of the ureter are the tension-free

anastomosis and the lack of redundancy. The distal ureter is prepared by ligating the accompanying ureteral vessels, trimming excess length of ureter and spatulating its distal end. It is advisable to create a tunnel at the distal graft ureter to decrease urinary reflux. ^(35,36)

117 Post-Transplant complications

117.1 Medical Complications

117.1.1 Infection

117.1.1.1 7.1.1.1-Bacterial Infections

Table 152: Recommendations for Baterial infection

Recommendations	Strength Grading
1. Six-months antibiotic prophylaxis is recommended to guard against different microbial infections in transplant patients. Prophylaxis should be adjusted according to patients' age, comorbidities, history of infection, and immunosuppressives used.	Strong
2. Close monitoring is recommended for patients with asymptomatic bacteriuria following renal transplantation; however, no treatment is required.	Strong
3. In patients with symptomatic urinary tract infections: 1- Removal or replacement of urinary tract device such as (urethral catheter or stent). 2- Urine culture and sensitivity. 3- Start empirical treatment with fluoroquinolones, amoxicillin-clavulanate or third generation cephalosporin. 4- If persistent, shift to antimicrobial shown by the urine culture and sensitivity.	Strong

Bacterial infections are among the most common complications following renal transplantation surgery and they represent one of the leading causes of graft rejection in the first few months. This may be explained by the higher prevalence of urinary tract infection (UTI) in renal transplant recipients compared to general population.^(37,38) Interestingly, a recent systematic review and meta-analysis reported that the prevalence of UTI following renal transplantation surgery in the Middle East countries is 37.9% of which, the most common causative organisms were Escherichia Coli, Klebsiella, Coagulase Negative Staphylococcus, and Enterococci (accounting for 57.5%, 15%, 15%, and 11.2%, respectively). ⁽³⁸⁾

The management of asymptomatic bacteriuria (ASB) in transplant patients is highly controversial, as the overuse of antibiotics may be associated with the development of resistant bacterial strains and increased cost of management, while, theoretically ASB may increase the

risk of symptomatic UTI and worsen the graft function, however most recent evidence in the literature showed that the management of ASB does not have an impact on the development of symptomatic UTI or graft function. ^(37,39)

117.1.1.2 Viral Infections

Poloyoma (BK) virus

Table 153: Recommendations for Polyoma (BK) virus

Recommendation	Strength Rating
1. Screening for BK Polyoma virus using plasma quantitative polymerase chain reaction should be performed monthly in all renal transplant patients for nine-months, then every three months till the end of the 2 nd year, then annually till the end of the fifth-year post-transplant.	Strong
2. BK Virus nephropathy is diagnosed by needle biopsy of the allograft.	Strong
3. When BK virus levels in the plasma reaches 10,000 /ml, reduce the level of immunosuppressive medications to guard against BK virus nephropathy.	Strong

Latent BK polyoma virus may become reactivated in the transplanted kidneys due to the use of strong immunosuppressive medications to maintain the graft function that may lead to BK nephropathy. ⁽⁴⁰⁾ The prevalence of BK virus nephropathy following renal transplantation is 10%; however, the virus can be isolated in the urine of 30-60% and the blood of 10-30% of transplant patients. ⁽⁴¹⁾ Currently, there are no specific treatment available for BK virus nephropathy, thus it is recommended to start treatment as plasma PCR levels reach 10,000 copies/ mL as it reflects a high risk for the development of nephropathy. The main management strategy for BK virus infection is the reduction of immunosuppressive agents in the form of reduction of Calcineurin inhibitors by 25-50% with the discontinuation of antimetabolites. ^(41,42)

Cytomegalovirus (CMV)

Table 154: Recommendations for Cytomegalovirus

Recommendation	Strength Rating
1. Risk for Cytomegalovirus (CMV) infection after renal transplantation is high in the following conditions: 1- CMV positive donor and negative recipient 2- CMV positive donor and recipient 3- CMV negative donor and positive recipient	Strong

2. CMV prophylaxis with ganciclovir, or valganciclovir is recommended for at least three months after transplantation.	Strong
3. Prophylactic doses of valganciclovir should be adjusted according to the creatinine clearance.	Strong
4. CMV prophylaxis is recommended for at least 6 weeks, whenever a lymphocyte depleting agents are considered for the management of rejection episodes.	Strong
5. Oral valganciclovir or intravenous ganciclovir are recommended for the management of transplant patients with mild or moderate CMV infection, while in case of severe CMV infections, intravenous ganciclovir is used.	Strong
6. In case of persistent CMV infection despite of the antiviral treatment, consider reducing the immunosuppressive therapy.	Strong

CMV is the most important virus in solid organ transplantation as it is associated with significant morbidity of the recipient. The risk of CMV infection is based on both the donor and recipient, thus CMV serology is recommended for all donors and recipients. ⁽⁴⁰⁾

Epstein-barr virus (EBV)

Table 155: Recommendations for Epstein Barr virus (EBV)

Recommendation	Strength Rating
1. Screening for Epstein-Barr virus (EBV) by nucleic acid testing should be performed monthly in high-risk renal transplant patients (positive donors) for 3-6 months, then every three months till the end of the 2 nd year.	Weak
2. EBV high risk transplant patients should be monitored for EBV infection following treatment of acute rejection.	Weak
3. It is recommended to reduce immunosuppressive therapy for EBV positive transplant patients.	Strong

Importantly, EBV disease may be associated with increased risk of some cancers including EBV-associated lymphomas. ⁽⁴²⁾

117.1.1.3 Fungal Infections

Table 156: Recommendations for Fungal infection

Recommendations	Strength Rating
1. Pneumocystis Jirovecii prophylaxis using trimethoprim-sulfamethoxazole is recommended for 3-6 months after renal transplantation.	Strong

2. Prophylactic doses of trimethoprim-sulfamethoxazole are recommended for at least 6 weeks during and following episodes of acute rejection to guard against <i>Pneumocystis Jirovecii</i> .	Strong
3. Treatment of <i>Pneumocystis Jirovecii</i> Pneumonia should include intravenous trimethoprim-sulfamethoxazole, corticosteroids, and reduction of immunosuppressive drugs.	Strong
4. Prophylactic doses of oral clotrimazole, or fluconazole are recommended for 1-3 months after renal transplantation to protect against esophageal candida.	Strong

Generally, the incidence of invasive fungal infections in kidney transplant patients ranges from 5% to 9.2%. Most of the fungal infections occurs within six months of transplantation. ^(43,44)

117.1.2 Rejection

Table 157: Recommendations for Rejection

Recommendation	Strength Rating
1. Renal biopsy should be done before treating an acute rejection episode except if deferring treatment is considered of high risk to the patient	Strong
2. We recommend using a 16-gauge needle and to obtain at least 2 core renal tissue biopsies for more accurate diagnosis	Strong
3. We suggest testing for human leucocyte antigen (HLA)-specific antibodies if suspecting rejection	Weak
4. Acute cellular rejection (ACR) should be managed with high-dose intravenous steroids as a first line of treatment	Strong
5. ACR refractory to steroids should be treated with lymphocyte-depleting antibodies as a second line of treatment	Weak
6. Antibody-mediated rejection (AMR) can be treated with intravenous steroids, plasmapheresis, intravenous immunoglobulin, monoclonal anti-CD20 antibody, lymphocyte-depleting antibodies	Weak
7. We suggest modifying/intensifying the maintenance immunosuppressive therapy after treating acute rejection episode	Weak

Rejection after kidney transplantation should be suspected in all recipients with persistently delayed or deteriorating graft function, as well as proteinuria. ⁽⁴⁵⁾ Renal biopsy is recommended prior to initiating treatment, except in the few conditions where the patient would be at risk if treatment is delayed. Rejection is histologically diagnosed according to Banff criteria. ⁽⁴⁶⁾ With a negative pretransplant crossmatch, hyperacute rejection is rarely seen. Acute rejection can be cellular or antibody-mediated (vascular). Acute cellular rejection should be treated with bolus high-dose intravenous methylprednisolone followed by anti-thymocyte globulin in steroid-

refractory cases. ^(47,48) In addition, antibody-mediated rejection (AMR) can be treated with therapeutic Plasma Exchange, Intravenous Immunoglobulin, anti-CD20 antibody. ⁽⁴⁹⁾ There is some evidence in literature that suggests modifying and intensifying the maintenance immunosuppressive protocol after treatment of acute rejection reduces the risk of subsequent attacks. ^(50,51) Chronic rejection is suspected with slowly deteriorating graft function and should be confirmed by a renal biopsy. ⁽⁵²⁾

117.1.3 Malignancy

Table 158: Recommendations for Post-transplant malignancy

Recommendations	Strength Rating
1. A personalized malignancy screening strategy should be tailored according to each patients’ history, comorbidities, and tobacco use.	Strong
2. This personalized strategy should include screening for the following cancers based on the patients’ risks and the local guidelines: 1- Renal cell carcinoma. 2- Hepatocellular and colon cancers. 3- Bladder cancer. 4- Prostate cancer. 5- lung cancer. 6-Breast and cervical cancers.	Weak
3. For de novo cancers after renal transplantation, it is recommended to reduce the immunosuppressive medications.	Weak

Generally, transplant recipients may be at higher risk for development of different malignancies. A recent observational study of 1,417 transplant patients showed that the incidence of de novo malignancy after transplantation is 10.9%. Renal cell carcinoma was the most commonly reported malignancy (27.4%), followed by gastrointestinal (16.8%), urological (13.4%), lung (10.1%), gynecological (8.4%), hematological (7.8%), cancers of unknown primary (3.9%). ⁽⁵³⁾ The risk of other cancers such as Kaposi’s sarcoma, non-Hodgkin’s lymphoma, non-melanoma skin cancers, and melanoma may also be increased in transplant patients. ⁽⁵⁴⁾

Currently, there is no consensus for the management of localized allograft renal cell carcinoma; however, different treatment options may be recommended including graftectomy, nephron sparing surgery or focal ablation of the tumor. ⁽⁵⁵⁾

117.1.4 Post-transplantation Diabetes Mellitus

Table 159: Recommendations for Post-transplant diabetes Mellitus

Recommendation	Strength Rating

1. All non-diabetic transplant patients should be monitored by fasting plasma glucose, oral glucose tolerance test, and or hemoglobin A1c at: 1- weekly for first month after transplantation. 2- every three months for the first year. 3- then annually.	Strong
2. All transplant patients with new onset diabetes mellitus should be monitored with fasting plasma glucose, oral glucose tolerance test, and or hemoglobin A1c with the initiation or increasing the dose of calcineurin inhibitors, mTORi, or corticosteroids.	Weak
3. For new onset diabetes after renal transplantation consider reducing the dose of diabetogenic immunosuppressives. Furthermore, consider using daily aspirin for protection against cardiovascular complications.	Weak

The pathogenesis of new-onset diabetes mellitus following renal transplantation is complex and multifactorial, however, it may be generally related to changes in insulin resistance and insulin secretion. ⁽⁵⁶⁾

117.1.5 De novo or recurrent glomerulonephritis

Table 160: Recommendations for Post-transplant Glomerulonephritis

Recommendation	Strength Rating
1. Kidney transplant patients who originally suffered different types of glomerulonephritis (as a primary disease) should be screened for proteinuria, microhematuria, or other urinary abnormalities to detect de novo or recurrent glomerulonephritis.	Strong
2. If screening is suggestive for recurrent or de novo glomerulonephritis, percutaneous allograft biopsy is recommended to confirm the diagnosis.	Strong
3. In case of confirmed diagnosis on biopsy consider the following: 1-Plasma exchange for patients showing focal segmental glomerulonephritis. 2-High doses corticosteroids and cyclophosphamide for patients presenting with recurrent antineutrophil cytoplasmic autoantibody-associated vasculitis or anti-glomerular basement membrane disease. 3-Angiotensin converting enzyme-inhibitors or angiotensin II receptor blockers are recommended for patients with proteinuria and recurrent glomerulonephritis	Strong

Recurrence of glomerulonephritis (GN) is reported to be the third common cause of late graft loss after kidney transplantation (5-8% at 10 years); however, most renal diseases should not be considered as contraindications of renal transplantation. Recurrence of GN in transplanted

kidney is usually late, except with primary focal segmental glomerulosclerosis (FSGS) which may lead to early graft loss. ^(57,58)

117.2 Surgical Complications

117.2.1 Urological complications

117.2.1.1 Ureteral Stenosis and Obstruction

Table 161: Recommendations for Ureteral Obstruction

Recommendation	Strength Rating
1. Persistent hydronephrosis of the allograft on ultrasound in patients with renal function deterioration is suggestive for ureteric stricture or obstruction.	Strong
2. Initial treatment strategy of post-transplantation ureteric stricture consists of: 1- Relief of obstruction by the placement of percutaneous nephrostomy. 2- Antegrade pyelography for the localization and characterization of the stricture.	Strong
3. Contrast enhanced CT is recommended for evaluation of post-transplant ureteric obstruction as it can provide information about intrinsic and extrinsic causes of obstruction.	Strong
4. Management of ureteral stricture differs according to the length of the stricture: 1- Stricture <3 cm can be treated endoscopically using balloon dilatation or laser incision. 2- Strictures ≥3cm in length or failed endoscopic treatment in patients with <3 cm strictures should be treated by surgical reconstruction.	Strong

Ureteral stricture may occur in 2-10% of renal transplant patients with the distal ureter being the most commonly involved location. ⁽⁵⁹⁾ Ureteral ischemia is responsible for 90% of post-transplant ureteric strictures. Generally, ureteric obstruction can be classified into early (<3 months), which results from ureteric stricture, technical errors during ureteric implantation, external compression, or kinking of the ureter. On the other hand, late obstruction may be due to ureteral ischemia, fibrosis, lymphocele, or vasculitis secondary to acute rejection. ⁽⁶⁰⁾

117.2.1.2 Urinary Leak

Table 162: Recommendations for Urinary Leak

Recommendation	Strength Rating

1. Urine leak is suspected by the reduction of urine output and high creatinine level in drain fluid.	Strong
2. Management of urinary leakage consists of: 1- Double J stenting and indwelling urethral catheter or percutaneous nephrostomy. 2- If endoscopic management failed consider surgical treatment.	Strong

Urinary leakage may occur as a result of ureteral necrosis or poor surgical technique. It can be classified according to the source of leakage into ureteral or vesical. Generally, the prevalence of post-transplantation urinary leakage ranges from 0 to 9%.⁽⁶¹⁾ Ureteric stenting has been proposed to reduce the risk of urine leak, however, a recent systematic review and meta-analysis demonstrated that routine ureteric stenting do not significantly reduce the risk of urine leak but may increase the risk of UTIs.⁽⁶²⁾ Furthermore, another systematic review and meta-analysis showed that early removal of the ureteral stent (around three weeks) reduce the risk of UTIs without compromising the risk of urine leak compared to late removal (> 3 weeks).⁽⁶³⁾

117.2.1.3 Hematuria

Table 163: Recommendations for Hematuria

Recommendation	Strength Rating
1. Consider conservative treatment option in the form of bladder irrigation for post-transplantation hematuria.	Strong
2. In case of persistent hematuria consider endoscopy and fulguration of bleeding sites.	Strong

117.2.1.4 Vesicoureteric Reflux

Table 164: Recommendations for Vesicoureteric reflux

Recommendation	Grade
1. Voiding cystourethrogram (VCUG) is recommended to diagnose vesicoureteric reflux (VUR) in transplant recipients showing persistent hydronephrosis in the absence of clinically significant stricture.	Strong
2. Minimally invasive techniques such as injection of bulking agents are recommended as the primary treatment options for VUR.	Weak
3. In case of failed endoscopic treatment or high grade VUR ureteric re-implantation or pyelo-ureterostomy with the native ureter may be indicated	Weak

Vesicoureteric reflux (VUR) can be observed in up to 86% of transplant recipients and it commonly related to the surgical technique. The impact of VUR on graft function and pyelonephritis is still debatable; however, antibiotic prophylaxis, endoscopic treatment have been considered for management of low to moderate grade VUR.⁽⁶⁰⁾

117.2.1.5 Lymphocele

Table 165: Recommendations for Lymphocele

Recommendation	Strength Rating
1. Large or symptomatic lymphocele should be treated by percutaneous drain placement.	Strong
2. Sclerosing agents such as povidone iodine, ethanol or fibrin glue reduce the recurrence rate of lymphocele.	Strong
3. Open or laparoscopic marsupialization is recommended if conservative treatment with drain placement failed.	Strong

Lymphocele is a common complication following renal transplantation that affects approximately 1-26% of all recipients.⁽⁵⁹⁾ Lymphoceles may result from the damage of the perivascular lymphatics around the iliac vessels due to the extensive dissection. Furthermore, other risk factors may play a role in the development of lymphocele such as obesity, diabetes, immunosuppressive drugs, and delay in graft function. Lymphocele is a serious complication as it may affect the graft function and it may be associated with increased risk of deep venous thrombosis.⁽⁶⁴⁾

117.2.1.6 Urolithiasis

Table 166: Recommendations for Urolithiasis

Recommendation	Strength Rating
1. Complete history taking and metabolic evaluation of the patients are required to identify the underlying cause of urolithiasis.	Strong
2. Non contrast enhanced CT is the main imaging study for evaluation of post-transplant urolithiasis.	Strong
3. If the stone causes obstruction of the urinary tract, consider double J stenting or percutaneous nephrostomy to relieve obstruction.	Strong
4. For stones <15 mm, consider shockwave lithotripsy, antegrade or retrograde ureteroscopy or nephroscopy as the main treatment options.	Strong
5. For stones >20 mm, consider percutaneous nephrolithotomy as the main treatment options.	Weak

Urolithiasis after renal transplantation is a relatively rare complication that may occur in up to 1.8% of patients. The average time to allograft stone disease diagnosis is 30.5 months.⁽⁶⁵⁾ Generally, urolithiasis may result from post-transplantation hyper-filtration, renal tubular acidosis, and disturbance of serum and urinary electrolytes level.⁽⁶¹⁾

117.2.2 Wound complications

Table 167: Recommendations for Wound complications

Recommendation	Strength Rating
1. In case of wound infection and superficial collection, ultrasound guided drainage of the collection and systemic antibiotics (according to culture and sensitivity of the fluid) is recommended.	Strong
2. Risk factors for wound dehiscence include old age, diabetes mellitus, obesity, anemia, hypoalbuminemia, and longer surgical time.	Weak
3. Wound dehiscence can be treated according to the type: 1- Superficial wound dehiscence is managed by washout and debridement 2- Complete fascial wound dehiscence is managed by primary repair with (in the absence of infection) or without synesthetic mesh reinforcement	Strong
4. Incisional hernia can be managed by open or laparoscopic repair	Weak

Wound complications are relatively common following kidney transplantation surgery (10.5-15.5%). These complications include wound infection, superficial dehiscence, complete fascial dehiscence, wound collection, and incisional hernia. Several risk factors may contribute to the occurrence of wound complications such as smoking, malnutrition, diabetes mellitus, obesity, and poor surgical techniques. ⁽⁶⁶⁾ These complications are challenging and may be associated with increased duration of hospitalization and cost.

117.2.3 Vascular complications

117.2.3.1 Hemorrhage and hematomas

Table 168: Recommendations for Hemorrhage and hematomas

Recommendation	Grade
1. Small asymptomatic hematomas require follow up without any intervention.	Weak
2. Large hematomas causing graft dysfunction or hemodynamic instability can be managed by CT or US guided drainage or exploration	Weak

117.2.3.2 Graft thrombosis (arterial or venous)

Table 169: Recommendations for Graft thrombosis

Recommendation	Strength Rating

1. Perform color doppler US in case of graft thrombosis (arterial or venous) suspicion	Strong
2. Poor or impaired graft perfusion is a strong indication for surgical exploration	Strong
3. If an arterial or venous thrombosis is confirmed during the surgical exploration perform surgical thrombectomy if the allograft is salvageable	Weak
4. In case of non-viable allograft, nephrectomy of the allograft is indicated	Strong
5. Prophylactic anticoagulant is not recommended as a preventative measure against transplant vein thrombosis	Strong

Graft thrombosis (either arterial or venous) is a rare complication that may occur in up to 3.5-4% of kidney transplant patients. This complication usually occurs as a result of technical errors during kidney harvesting or the anastomosis.⁽⁶¹⁾ Renal vein thrombosis is an early complication that might present with lower limb edema, swollen allograft, anuria, and ultimately allograft loss.⁽⁶⁷⁾ Similarly, renal artery thrombosis (RAT) usually presents with significant reduction in the urine output with elevated serum creatinine.⁽⁶⁸⁾ Overall, color doppler US is the imaging study of choice for evaluation of those patients as it shows poor renal perfusion in case of arterial thrombosis and absence of venous flow with abnormal arterial signal (plateau-like reversed diastolic flow) in case of venous thrombosis.⁽⁶⁸⁾ Once a graft thrombosis is diagnosed on color doppler US, surgical exploration is indicated and either allograft nephrectomy (in case of non-viable graft) or thrombectomy (in case of salvageable allograft) is recommended.⁽⁵⁶⁾ Prophylactic anticoagulant therapy after renal transplantation is not associated with reduced risk of graft thrombosis.⁽⁶⁷⁾

117.2.3.3 Transplant renal artery stenosis

Table 170: Recommendations for Transplant Renal artery stenosis

Recommendation	Strength Rating
1. Perform color doppler US in case of suspicious transplant renal artery stenosis (refractory hypertension not responding to medical treatment and/or elevated serum creatinine in the absence of hydronephrosis or infection).	Strong
2. In case color doppler US is not diagnostic, perform CT or MRI angiography.	Strong
3. In mild transplant, renal artery stenosis (<50% of the arterial caliber) with the absence of symptoms and no deterioration of the allograft function, no intervention is required just consider color doppler US follow up	Strong

4. Consider minimally invasive endovascular options (percutaneous transluminal angioplasty/stent) as the first line of treatment for transplant renal artery stenosis.	Strong
5. Consider surgical intervention in the following conditions: 1- Failed minimally invasive endovascular options 2- Recent transplant 3- Complex stenosis (long, narrow, and/or multiple)	Strong

Transplant renal artery stenosis is one of the well-recognized vascular complications following renal transplantation. Its incidence is highly variable ranging from 1-25%. It is associated with deterioration of the allograft function and development of cardiovascular complications including post-transplant hypertension. Generally, transplant artery stenosis are diagnosed between 3 and 24 months after the transplantation surgery.⁽⁶⁹⁾ Several risk factors play may play a role in the development of transplant renal artery stenosis including renal artery factors (caliber, atherosclerosis, or trauma), surgical technique (continuous versus interrupted sutures, absence of arterial patch, or injury of the iliac artery during the anastomosis), and immunological factors (CMV infection).^(61,69) On color doppler US, a peak systolic velocity of >200 cm/s is alarming for significant transplant renal artery stenosis.⁽⁷⁰⁾

117.2.3.4 Arteriovenous fistula and pseudoaneurysm

Table 171: Recommendations for Arteriovenous fistula and pseudoaneurysm

Recommendation	Strength Rating
1. Perform color doppler US in case of suspicious pseudoaneurysm or arteriovenous fistula (hypertension, hematuria, and/or deterioration of the allograft function).	Strong
2. Consider angiographic selective embolization as the first line of treatment for pseudoaneurysm and arteriovenous fistula	Strong
3. Consider partial or complete allograft excision in case of failed other treatment options	Strong

Arteriovenous (AV) fistulas and pseudoaneurysm are common vascular complications that occurs after percutaneous biopsy of the allograft in patients with suspected graft rejection. Fortunately, most of the AV fistulas and pseudoaneurysms are asymptomatic and resolve spontaneously; however, 30% of cases may become symptomatic and require intervention.^(61,71)

117.3 Other Complications

117.3.1 Cardiovascular complications

Table 172: Recommendations for Cardiovascular complications

Recommendation	Grade
1. Measure blood pressure at each follow up visit after renal transplantation.	Strong
2. Perform a complete lipid profile for all transplant patients: 1- Within 2-3 months of the transplantation surgery 2- Within 3 months after the change of treatment or development of any condition that might cause dyslipidemia 3- Annually	Weak
3. Counsel all kidney transplant patients to stop smoking	Strong
4. Screen all transplant patients for obesity by assessing the patients' weight, height, and body mass index at each follow up visit	Weak

Renal transplant recipients are at higher risk for developing cardiovascular complications compared to general population. Furthermore, mild impairment of the renal function in this population is associated with higher risk of cardiovascular mortality. ⁽⁷²⁾ Post-transplantation hypertension is the most common cardiovascular complications after renal transplantation. ⁽⁶⁹⁾

117.3.2 Bone disease

Table 173: Recommendations for Bone disease

Recommendation	Strength Rating
1. Measure the serum calcium and phosphorous levels once weekly until stable, then the interval of measurement should be adjusted according to the chronic kidney disease progression and the baseline levels.	Strong
2. Measure the serum level of vitamin D and parathormone within 3 months of the transplantation surgery, then the intervals of follow up should be adjusted based on the baseline levels and the chronic kidney disease progression.	Weak
3. In patients with estimated GFR >30 ml/min/1.73 m ² , the bone mineral density should be evaluated at 3 months' post-transplantation, then the follow up should be determined based on the patient's condition and baseline levels.	Strong

Loss of organ function is associated with deterioration of the bone mass and increased risk of fracture. However, the transplantation surgery improves the patients' quality of life, the bone

health and the risk of fracture are not improved particularly during the first year following the transplantation. Furthermore, immunosuppressive agents may worsen the pre-transplant bone disease. ⁽⁷³⁾

117.3.3 Fertility and sexual function

Table 174: Recommendations for Fertility and sexual function

Recommendation	Strength Rating
1. Assess patient’s sexual function after the transplantation surgery	Weak
2. Female patients should wait at least one year before becoming pregnant	Weak
3. Inform male patients about the potential fertility risks associated with the use of mTOR inhibitors	Strong

Generally, patients with chronic kidney disease usually suffer from subfertility or infertility due to several causes including hypogonadism and/or erectile dysfunction. Fortunately, transplantation surgery is usually associated with improvement of sexual and reproductive health. ^(74,75)

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Committee XIII

Sexual Dysfunction



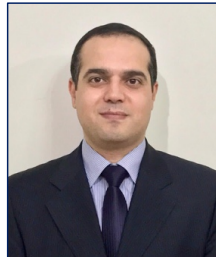
Ahmed El Sakka



A Rahman Zahran



Ahmed El Taher



Emad Salem



Magdy Elbahnasawy



M Abd Elrasoul

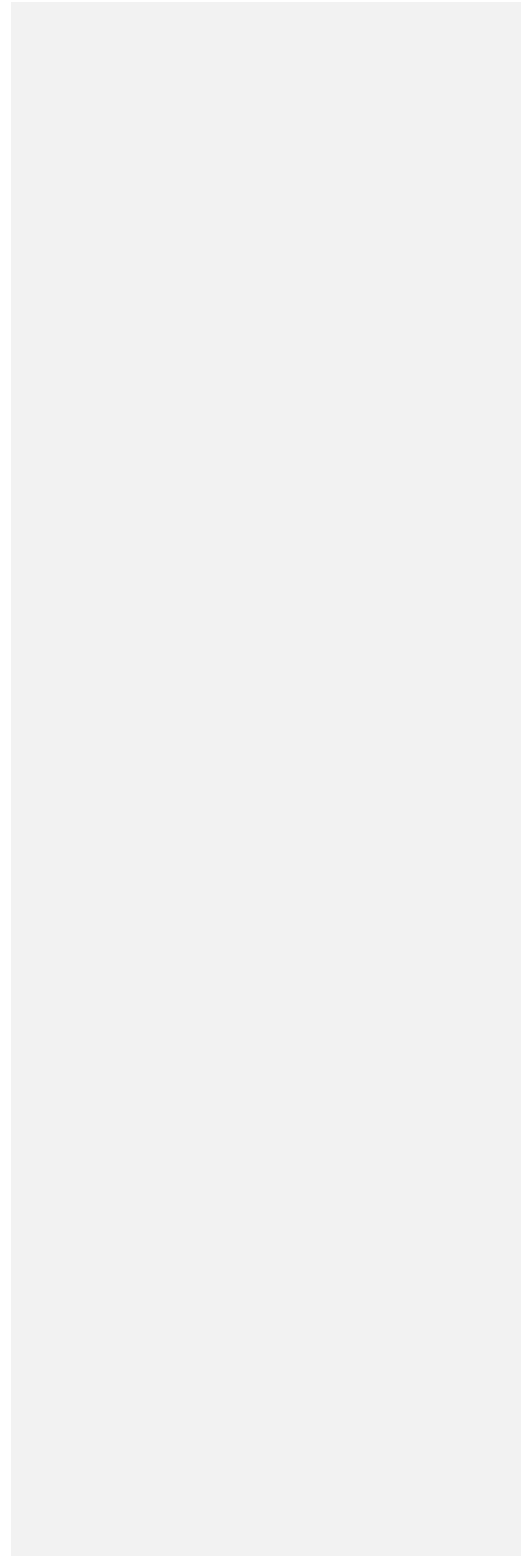


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Egyptian Urological Guidelines On Male Sexual Dysfunction



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119 Abbreviations:

AUA	American Urological Association
AIPE	Arabic Index of Premature Ejaculation
BSSM	British Society for Sexual Medicine
CCH	Clostridium Collagenase
CDU	Color Duplex Ultrasonography
ED	Erectile Dysfunction
EMA	European Medicines Agency
EUA	European Urological Association
ISSM	International Society of Sexual Medicine
IHD	Ischaemic Heart Disease
NPT	Nocturnal penile tumescence
PP	Penile Prosthesis
PE	Premature Ejaculation
PEDT	Premature Ejaculation Diagnostic Tool
PSA	Prostate-Specific Antigen
QoL	Quality of Life
RP	Radical Prostatectomy
RT	Radiotherapy
SCs	Stem Cells
TA	Tunica Albuginea
VED	Vacuum Erection Device

120 Abstract

120.1 Objectives:

To present the contemporary evidence for medical practice in Egypt for the diagnosis and treatment of male patients suffering from sexual dysfunction.

120.2 Methods:

Our recommendations are based on 4 resource categories;

4. Four international guidelines namely European Urological Association [EUA], American Urological Association [AUA], British Society for Sexual Medicine [BSSM], International Society of Sexual Medicine [ISSM];
5. A panel of 8 high-caliber urologists and andrologists representing different universities, institutions and private practice in Egypt.
6. A systematic literatures search was conducted using PubMed, Embase, and the Cochrane Library for English-language journal articles between January 2000 and January 2020, using the terms, “erectile dysfunction” (ED), “ejaculatory dysfunction”, “low sexual desire”, “Peyronie’s disease” “hypogonadism” and “priapism”.
7. Criteria included all pertinent review articles, randomized controlled trials with tight methodological design, cohort studies, and retrospective analyses. We also manually reviewed references from selected articles.

120.3 Results:

The Egyptian urological guideline for sexual dysfunction reflects the consensus of the authors that was guided by international guideline recommendations, it was modified to suit the Egyptian environment dominated by a rich bioecological environment, specific demographics, social constraints and limited financial resources.

120.4 Conclusion:

To help guide Egypt practitioners on effectively diagnosing and properly managing men with sexual dysfunction. This approach should not only provide sexual and psychosocial benefits for our patients but also insuring improvement in their quality of life.

121 Introduction:

Erectile dysfunction (ED) and premature ejaculation (PE) are the two main complaints in male sexual medicine in the Middle East ⁽¹⁻²⁾. Pharmacological therapies have completely changed the diagnostic and therapeutic approach to ED ^(3,4). The prevalence of ED is 20–90% among patients with different risk factors and medical comorbidities in Arab region countries. The high prevalence of severe ED in patients in this region could be attributed to:

1. The high prevalence of risk factors;
2. The poor control of those risk factors;
3. The delay in seeking medical advice; and
4. The non-compliance with treatment ⁽¹⁻²⁾.

Unfortunately, in Arab countries there are no firm data on the true prevalence of sexual dysfunction. This prompted several investigators in the region to conduct research to identify the magnitude of the current problem ⁽¹⁻²⁾.

This article integrates recent international guidelines with local experience and also highlights the apparent lack of congruency between available treatment and communication, cultural, and gender norms of Middle East populations that may inhibit treatment seeking. We clarified in our recent publication that strategies for diagnosis and treatment should consider the sociocultural-factors that influence diagnosis and treatment seeking and engagement behaviors necessary for successful outcomes. Specifically, the detrimental effects of sexual problems on quality of life and the potential benefits of proper diagnosis and treatment should be more widely communicated in order to diminish the social disgrace associated with sexual problems and their management ⁽⁵⁾.

122 Methodology

122.1 Resources of Recommendations:

Our recommendations are based on 4 resource categories:

- Four international guidelines and recommendations, namely European Urological Association [EUA], American Urological Association Guidelines [AUA], British Society for Sexual Medicine [BSSM], International Society of Sexual Medicine [ISSM], ⁽⁶⁻¹²⁾.
- Review of several guides, reviews, statements, recommendations, standards ⁽¹⁰⁻¹⁴⁾.
- Relevant Egyptian publications.

- A panel of 8 high-caliber urologists and andrologists representing different universities, institutions and private practice in Egypt.

122.2 Strength of clinical practice recommendation:

All statements were graded according to strength of clinical practice recommendation, reflecting the consensus of the authors and was guided by other international guideline recommendations. They were modified to suit the Egyptian environment dominated by a rich bioecological environment, specific demographics, social constraints and limited financial resources. Statements were graded into strong or weak.

122.3 Synthesis of Recommendations:

All recommendations related to, erectile dysfunction (ED), ejaculatory dysfunction, low desire, Peyronie's disease, hypogonadism and priapism were discussed by a panel of 8 expert urologists and andrologists. The committee members are high caliber academics and clinicians who are dealing with sexual dysfunction from different aspects and they represent different regions of Egypt with different sociodemographic characteristics. A systematic literatures search was conducted using PubMed, Embase, and the Cochrane Library for English-language journal articles between January 2000 and January 2020, using the terms, "erectile dysfunction" (ED), "ejaculatory dysfunction", "low sexual desire", "Peyronie's disease" "hypogonadism" and "priapism". Criteria included all pertinent review articles, randomized controlled trials with tight methodological design, cohort studies, and retrospective analyses. We also manually reviewed references from selected articles. The participant physicians have disclosed no conflict of interest.

123 Erectile dysfunction:

123.1 Definition:

Erectile Dysfunction (ED) is defined as the persistent or recurrent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance ⁽¹⁵⁾.

123.2 Epidemiology:

123.2.1 General population:

Prevalence of ED in the United States, the United Kingdom, Australia, Japan, and Korea were reported to be 52%, 32%, 43%, 26%, and 37%, respectively ⁽¹⁶⁾.

123.2.2 Egypt and Arabic countries:

In cross-sectional office-based studies, El-Sakka showed that ED was very prevalent and ED risk factors were very common. In all, 92.6% of the patients had ED, 50.8% had premature ejaculation, and 7.6% had low sexual desire. Furthermore, 20% of the patients had psychogenic while 80% had organic causes of ED. Of the patients, $\approx$ 10% had mild, 40% had moderate and 50% had severe ED ^(1,2,17).

Shaer and Shaer explored epidemiological aspects of male sexuality using an online survey. They found that among Arab-speaking Internet users, the overall prevalence of ED was 45.1%, strongly correlating with various risk factors ⁽¹⁸⁾. In another study from Upper Egypt, Zedan et al., showed that of 658 men with ED, 17.3% had hypertension, 21.4% had DM and 40.1% were smokers ⁽¹⁹⁾.

In a cross-sectional community-based random sample of Egyptian men, Seyam et al., found that men with complete ED comprised 13.2% of the sample, 26% of men in their 50s, 49% of men in their 60s and 52% of those aged $\geq$ 70 years ⁽²⁰⁾.

123.3 Pathophysiology:

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic. ED may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partner's ⁽²¹⁻²³⁾. There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease ⁽²¹⁻²³⁾.

123.4 Diagnostic evaluation:

The diagnostic pathway and treatment of ED have been reported in many studies, but they are not yet well addressed in the Arab region. This provoked several investigators in Arab countries

to assess different methods for the diagnosis and treatment of sexual dysfunction among patients in this region (24).

The tailored diagnosis of ED not only allows the physician to avoid further costly evaluation, but also saves the patient from unnecessary and sometime invasive diagnostic techniques (24, 25). In general, the following should be obtained in every patient:

8. 1. A detailed medical and psycho-sexual history
9. 2. A thorough physical examination; and
10. 3. Appropriate laboratory tests (complete blood count, fasting glucose, lipid profile, kidney function, testosterone, and others if indicated) (24-27).

For a satisfactory and cost-effective treatment, the evaluation methods should answer these inquiries:

11. 1. Whether the cause of ED is organic or psychogenic;
12. 2. The severity and possible reversibility of ED;
13. 3. The patient's and probably the partner's goals and expectations (24).

123.5 Basic work-up.

123.5.1 Sexual history:

The first step in evaluating ED is always a detailed medical and sexual history of patients and, when available, their partner's. In this context, taking a comprehensive medical history may reveal one of the many common disorders associated with ED. It is important to establish a relaxed atmosphere during history taking (28). Validated questionnaires may provide an opportunity to initiate a conversation about ED; examples include the Erection Hardness Score (29) and the Sexual Health Inventory for Men (30), IIEF Arabic version (31). Elnashar and his colleague assess the use of IIEF-5 as a diagnostic tool to determine the severity of vasculogenic ED, and they concluded that IIEF-5 cannot be used to diagnose the severity of vascular affection in ED patients (32).

The sexual history must include information about onset and duration of the erectile problem, prior surgeries, medications, family history of vascular disease, and substance use, and previous consultations and treatments. The presence of nocturnal and/ or morning erections suggests a psychogenic component to ED symptoms (33).

123.5.2 Physical examination:

A thorough physical examination with particular attention to the genital area can sometimes reveal an obvious cause (e.g. micropenis, penile chordee, Peyronie's plaque, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity.). The finding of small soft atrophic testes or gynecomastia needs endocrine evaluation. Patients with some genetic

syndromes, e.g. Kallmann's or Klinefelter's, can present with obvious physical signs of hypogonadism or a distinctive body habitus.

A careful neurological examination should also be conducted. Testing for genital and perineal sensation and the bulbocavernosus reflex is also useful in assessing possible neurogenic ED ^(6-8,33). Kamel et al., compared penile measurements in normal subjects and patients with ED. The average fully stretched penile length in normal men was 12.9 cm, but was 11.2 cm in patients with ED (significantly different, $P < 0.001$), although the mean fully stretched penile girths were not statistically different between the groups ⁽³⁴⁾.

A history and physical examination had 95% sensitivity but only 50% specificity in diagnosing organic ED. In many cases, a careful history and physical examination will direct the physician to the most expedient and cost-effective approach, and eliminate the need for unnecessary diagnostic tests ⁽³⁵⁾.

123.5.3 Laboratory testing:

The routine laboratory investigation should be directed at identifying treatable conditions or previously undetected medical illnesses that might be contributory, e.g. renal insufficiency, DM and endocrine abnormalities (hypogonadism, hyperprolactinaemia) ^(36,37).

Laboratory evaluation includes fasting blood glucose, HbA1c, lipid profile if they have not recently been assessed, renal function, a complete blood count, urine analysis, should be done in the initial evaluation. Hormonal tests and additional laboratory tests may be considered in selected patients e.g., prostate-specific antigen (PSA), FSH and LH ^(36,37).

El-Sakka et al. reported a possible association between sexual dysfunction, e.g. ED, premature ejaculation (PE) and low desire, and hypogonadism. They also found that 23.8% of patients had endocrinopathy. There were significant associations between low desire and low testosterone level, hyperprolactinaemia and hypothyroidism ($P < 0.05$ for each). Furthermore, they investigated the effect of testosterone replacement therapy on the PSA level in hypogonadal men with ED ^(38,39). Zohdy et al. concluded in their study that obesity is associated with lower total testosterone levels and disturbances of penile haemodynamics ⁽⁴⁰⁾.

123.5.4 Specialized diagnostic tests:

Most patients with ED can be managed based on medical and sexual history, physical examination and laboratory investigations; conversely, some patients may need specific diagnostic tests ⁽⁶⁻⁸⁾.

123.5.4.1 Nocturnal penile tumescence (NPT) and rigidity test:

Many investigators have advocated the use of NPT studies to differentiate organic from psychogenic ED. The shortcomings associated with various NPT tests, such as false-negative results were documented ⁽⁴¹⁾.

123.5.4.2 Intracavernous injection test:

The intracavernous injection test gives limited information about the vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within ten minutes after the intracavernous injection and lasts for 30 minutes. Overall, the test is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted ⁽⁴²⁾.

123.5.4.3 Duplex ultrasound of the penis:

A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are generally considered normal. Further vascular investigation is unnecessary if a duplex ultrasound examination is normal. The hemodynamic parameters were measured several times (starting after 5 min from self-stimulation) in the same sitting to obtain the most optimal results ⁽⁴³⁾. El-Sakka and his colleague reported a significant association between increasing severity of ED and increased values of EDV, and decreased values of PSV and RI on penile Doppler ultrasonography and rigidometer tests. In addition, they showed that a low PSV can be used as a screening tool for ischaemic heart disease (IHD) in patients with ED ⁽⁴⁴⁾.

123.5.4.4 Rigidometer tests:

Rigidometry evaluate the minimal axial pressure that can bend the erect penis [39]. El-Sakka investigated the association between the IIEF and axial penile rigidity values in ED patients with or without DM ⁽⁴⁵⁾. There was a significant association between the overall presence of ED and low axial penile rigidity ^(46,47).

123.5.4.5 Arteriography and dynamic infusion cavernosometry & cavernosography:

Arteriography and dynamic infusion cavernosometry & cavernosography should be performed only in patients who are being considered for vascular reconstructive surgery. Recent data suggested the use of computed tomography angiography in cases of penile artery angioplasty for patients with ED and isolated penile artery stenoses ⁽⁴⁸⁾.

123.5.5 Psychiatric assessment:

Whenever clinically indicated, patients with psychiatric disorders should be referred to a psychiatrist who is particularly interested in sexual health. In younger patients (< 40 years) with long-term primary ED, psychiatric assessment may be helpful before any clinical assessment is carried out ⁽⁴⁹⁾.

Indications for specific diagnostic tests ⁽⁶⁻⁸⁾

- Primary ED (not caused by organic disease or psychogenic disorder).
- Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative revascularization surgery or angioplasty
- Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital penile curvature)

- Patients with complex psychiatric or psychosexual disorders.
- Patients with complex endocrine disorders.
- Specific tests may be indicated at the request of the patient or his partner.
- Medico-legal reasons (e.g., implantation of penile prosthesis to document end stage ED, sexual abuse).

123.5.6 Recommendations for the diagnosis of ED:

Table 175: Recommendations for Diagnosis of ED

Recommendations	Strength Rating
1. Take a comprehensive medical and sexual history in every patient. Strength rating	Strong
2. Use a validated questionnaire especially Arabic version (if available) related to ED to assess all sexual function domains and the effect of a specific treatment modality	Strong
3. Perform physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED	Strong
4. Assess routine laboratory tests, including glucose-lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
5. Include specific diagnostic tests in the initial evaluation only in the presence of “Indications for specific diagnostic tests” mentioned above	Strong

123.6 Treatment of ED

123.6.1 Non-surgical treatment of ED:

Determining an appropriate treatment requires that the man, his clinician, and ideally his partner navigate all of these issues in order to arrive at a treatment choice that is aligned with the man and his partner's priorities and values. In each scenario, the clinician's role is to ensure that the man and his partner have full understanding of the benefits and risks/burdens of the various management strategies. All men, regardless of the decision to treat ED, should be strongly advised to address any underlying medical issues that may contribute to the ED and that constitute independent risk factors for poor health, reduced QoL, and decreased survival. Each man brings to the clinical encounter not only his symptoms, but his degree of distress; his associated health conditions; his partner's concerns and issues of relationship quality; and his sociocultural, educational, and religious context (5).

123.6.2 Conservative treatment

It remains the initial step for the treatment of ED. This kind of therapy consists of different modalities including: oral treatments, intracavernosal pharmacotherapy, and evolving modalities such as soluble guanylate cyclase activators, stem cells (SCs), and alternative treatments such as herbal treatment and transdermal/topical pharmacotherapy. However, it should be noted that the currently available pharmacotherapy is still far from ideal. One hopes to witness new drugs and technologies that may revolutionize ED treatment in the future, especially in such complex cases as DM and cardiovascular diseases ⁽⁵⁰⁾.

The interest in PDE5Is as targets for pharmacologic treatment has evolved with the development of selective PDEIs ⁽⁵¹⁾. The effectiveness and tolerability of 12 weeks of open-label treatment with sildenafil citrate for erectile dysfunction (ED) associated with a diagnosis of diabetes mellitus and/or hypertension were assessed in clinical practice in three Middle Eastern countries ⁽⁵²⁾. Furthermore, interesting data add to the body of knowledge regarding testosterone level and sexual function and suggested that testosterone level play a role in sexual desire, frequency of nocturnal erection and frequency of intercourse, further approximately 20 % of men with complains of sexual dysfunction have hypogonadism ⁽⁵³⁾. Makhlof et al shows that both conditions are fairly prevalent in an ED clinic population, and that there is increased likelihood of finding depression among men with hypogonadism ⁽⁵⁴⁾.

Early treated rats with vardenafil had preserved erection and normal cavernosal structure, ultrastructure and gene expression of iNOS ,nNOS, eNOS, and TGF-β1. Clinical application of this result may encourage early administration of PDE5I ⁽⁵⁵⁾. Recent study had shown that single intracavernosal dose of Botox either 50 or 100 U in my be of benefit in PDE5I non responders in patients with vasculogenic ED ⁽⁵⁶⁾.

Several studies have established the role of ICI of vasoactive materials as a very common alternative tool in treatment of severe ED particularly in diabetic patients, post-RP, PDE5I non-responders. Further, new studies have denoted the potential future role of intracavernosal treatment for ED in the era of stem cells and gene therapy. ICI of vasoactive material continues to be a highly effective and safe treatment tool for men with wide varieties of ED etiologies. Several experimental and clinical studies are currently investigating new ICI materials. Hopefully in the near future, we might witness evolved molecules and innovative strategies that could help to treat ED patients with different etiologies ⁽⁵⁷⁾.

123.6.2.1 Recommendations for non-surgical treatment of ED:

123.6.2.1.1Recommendations for lifestyle modifications

Table 176: Recommendations for Life Style

Recommendation	Strength Rating

Advise for lifestyle modifications, including changes in diet, increased physical activity, stopping smoking, improving overall health at or before treatment of erectile dysfunction.	Strong

123.6.2.1.2 Recommendations for men who are prescribed PDE5Is

Table 177: Recommendations for men who are prescribed PDE5Is

Recommendations	Strength Rating
1. Patients should be informed regarding approved PDE5Is, including discussion of benefits and risks/burdens	Strong
2. Prescribe PDE5Is as first-line therapy. The dose should be titrated to provide optimal efficacy	Strong

123.6.2.1.3 Recommendations after treatment for prostate cancer by radical prostatectomy (RP) or radiotherapy (RT)

Table 178: Recommendations after treatment for prostate cancer by radical prostatectomy (RP) or radiotherapy (RT)

Recommendation	Strength Rating
Early rehabilitation programs (use of PDE5I and VED) post-RP may improve erectile function	Strong

123.6.2.1.4 Recommendations for men with Erectile Dysfunction and hypogonadism

Table 179: Recommendations for men with Erectile Dysfunction and hypogonadism

Recommendation	Strength Rating
Patients should be informed that PDE5Is may be more effective if combined with testosterone therapy when indicated	Strong

123.6.2.1.5 Recommendations for PDE5Is failure in patients with ED

Table 180: Recommendations for PDE5Is failure in patients with ED

Recommendation	Strength Rating
Assess patients for, inadequate/incorrect prescriptions, poor sexual stimulation, and fat meals when not advised	Weak

123.6.2.1.6 Recommendations for ED treatment with a vacuum erection device (VED)

Table 181: Recommendations for ED treatment with a v|Vacuum Erection Device (VED)

Recommendation	Strength Rating

Discuss benefits and risks/burdens on the use of VED, especially in in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED	Weak

123.6.2.1.7 Recommendations for the use of ICI therapy

Table 182: Recommendations for men who are prescribed PDE5Is

Recommendation	Strength Rating
1. An in-office injection test should be performed. Home therapy after positive office ICI test. Strength rating	Weak
2. Alprostadil (PGE1) is the best agent however its cost is a limitation	Weak

123.6.2.1.8 Recommendations for intracavernosal stem cell therapy.

Table 183: Recommendations for ED treatment with a v|Vacuum Erection Device (VED)

Recommendation	Strength Rating
Intracavernosal stem cell therapy should be considered investigational for treatment of ED. Strength rating	Weak

123.6.3 Surgical treatment for ED

123.6.3.1 Vascular surgery

123.6.3.1.1 Surgery for post-traumatic arteriogenic ED

The highest success rates are reported in young men (less than 30 years of age) with isolated arterial stenosis after perineal or pelvic trauma ⁽⁵⁸⁾. Success of these surgeries has been variable and depends on careful patient selection. Penile arteriography is required to establish a penile arterial anatomic defect, and other organic causes of ED (e.g., venous incompetence) that would limit surgical success should be excluded.

According to the current literature, the following inclusion criteria should be met when selecting patients for arterial surgery ⁽⁵⁹⁾:

- Age less than 55 years,
- Cessation of tobacco smoking,
- Nondiabetic
- Absence of venous leakage
- Radiographic confirmation of focal stenosis of the internal pudendal artery.
- No atherosclerosis
- Usually result from perineal or pelvic trauma

Several Arterial revascularization procedures have been described to create arterial inflow to the corpora, similarly creating an anastomosis of the inferior epigastric artery either to the corpus cavernosum directly or to vascular conduits of the penis such as the dorsal artery (i.e., revascularization), the deep dorsal vein (i.e., arterialization), or the deep dorsal vein with venous ligation (i.e., arterialization with venous reconstruction) (59). Complications of arterial revascularization surgery include glans hyperemia (13%), shunt thrombosis (8%), and inguinal hernias (6.5%) (60).

Previous studies reported outcomes for arterial reconstruction procedures, the most commonly used outcome measure was the percentage of men in different response categories post-surgery. Typically, high response rates (complete or partial) were reported at short intervals post-surgery, with declining rates over time. Overall, there was considerable variability regarding response rates, particularly complete (range 12 to 81.6%) and partial response rates (range 7.7 to 53.3%) (6-8).

123.6.3.1.2 Venous ligation surgery

Venous ligation surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results (61).

123.6.3.1.3 Penile Prosthesis

The surgical implantation of a penile prosthesis may be considered in patients who:

1. Are not suitable for different pharmacotherapies or prefer a definitive therapy; and,
2. Do not respond to pharmacological therapies (62).

Men and their partners should be thoroughly counseled regarding the benefits and potential risks of this modality of treatment to ensure appropriate choice of device, realistic post-operative expectations, and high levels of satisfaction (63).

The two currently available classes of penile implants include inflatable (2- and 3-piece) and semi-rigid devices (malleable, mechanical, soft flexible) (64,65).

There are two main surgical approaches for inflatable penile prosthesis implantation: penoscrotal and infrapubic (64,65). Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED based on appropriate consultation (66). There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rates (67). There are also currently no head to head studies comparing the different manufacturers' implants, demonstrating superiority of one implant type over another.

Complications of penile prostheses

The two main complications of penile prosthesis implantation are mechanical failure and infection. Careful surgical techniques with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduces infection rates to 2-3% with primary implantation in low-

risk patients and in high volume centers ⁽⁶⁸⁾. Higher-risk populations include patients undergoing revision surgery, those with impaired host defenses (immunosuppression, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis ⁽⁶⁹⁾.

123.6.3.2 Recommendations for Surgical management of erectile dysfunction.

Table 184: Recommendations for Surgical management of Erectile Dysfunction

Recommendation	Strength Rating
1. Surgery should be reserved for men in whom less invasive reversible treatment has not succeeded or is contraindicated or undesirable	Strong
2. Arterial revascularization surgery is offered only to select patients with ED who meet strict clinical and radiographic criteria for surgical success. Strength rating	Strong
3. Vascular surgery for veno-occlusive dysfunction is no longer recommended. Strength rating	Strong
4. Use implantation of a penile prosthesis as third-line therapy if other treatments fail or based upon patient preference. Strength rating	Strong

124 Premature Ejaculation

124.1 Definition:

The first evidence-based definition of PE considered that ejaculation that always or nearly always occurs prior to or within about one minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired PE). In association with the inability to delay ejaculation on all or nearly all vaginal penetrations; and with negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy ⁽⁷⁰⁾.

Two more PE syndromes have been proposed: ‘Variable PE’ is characterized by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance. ‘Subjective PE’ is characterized by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology. The addition of these new types may help in overcoming the limitations of each individual definition and it may support a more flexible view of PE for patient stratification, diagnosis and treatment

124.2 EPIDEMIOLOGY

The overall prevalence of PE ranges between 19.8-25.8%. According to the four PE subtypes, the prevalence rates is 2.3-3.18% (lifelong PE), 3.9-4.8% (acquired PE), 8.5-11.38% (variable PE) and, 5.1-6.4% (subjective PE) ^(71, 72).

124.3 Recommendation for Assessment of PE

Recommendations for assessment of PE are in the below table. ⁽⁷¹⁻⁷⁶⁾

Table 185: Recommendation for Assessment of PE

Recommendation	Strength Rating
1. Performing the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction	Strong
2. Perform physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction (ED).	Strong

3. Use the patient-reported outcomes tools: Premature Ejaculation Diagnostic Tool (PEDT) and Arabic Index of Premature Ejaculation (AIPE) in daily clinical practice.	Weak
4. Don't perform routine laboratory or neuro-physiological tests. They should only be directed by specific findings from history or physical examination	Strong

124.4 Recommendations for Treatment of PE

Recommendations for treatment of PE are in below table ⁽⁷³⁻⁷⁶⁾.

Table 186: Recommendations for Treatment of PE

Recommendation	Strength Rating
1. Define the subtype of PE and discuss patient's expectations thoroughly before starting any treatment	Strong
2. Treat the underlying cause (e.g., ED, prostatitis, LUTS, anxiety, hyperthyroidism) as the initial goal for patients with acquired PE	Strong
3. Pharmacotherapy must be considered as the first-line treatment for patients with lifelong PE i.e. dapoxetine.	Strong
4. The use of off-label topical anesthetic agents i. e. the lidocaine/prilocaine spray is considered as a viable alternative to oral treatment with SSRIs	Weak
5. Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE	Weak
6. Suggest various behavioral techniques in treating variable and subjective PE	Weak
7. Offer Tramadol on-demand as a weak alternative to SSRIs.	Weak
8. Offer PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Weak

125 Delayed Ejaculation

125.1 Definition:

Marked delay in ejaculation or marked infrequency or absence of ejaculation on almost all or all occasions (75-100% of the times) of partnered sexual activity without the individual desiring delay persisting for at least 6 months and causing significant distress to the individual ⁽⁷⁷⁾.

125.2 Background:

Multiple terms including delayed ejaculation, anorgasmia, anejaculation, aspermia, retarded ejaculation, inhibited ejaculation or intra-vaginal ejaculatory dysfunction are used in this domain.

Of all the male sexual dysfunctions, DE is the least understood, least common and least studied ⁽⁷⁸⁾. Lack of consistent definition and overlap with other dysfunctions such as anejaculation or anorgasmia adds to the difficulty of understanding, diagnosis and management. There is currently no single gold standard for diagnosing DE; the history is the keypoint for the diagnosis. Post-coital urine analysis for sperms to exclude retrograde ejaculation is a strong adjunct for the diagnosis. If applicable treatment should be cause-specific. There are different approaches for its management, including psychosexual interventions, drug therapy, and specific measures for patients with SCI and infertile men. Several drugs were used for treatment of DE however no single drug was approved. Currently, no drug has been approved by FDA for DE. Successful drug treatment of DE is still in its infancy ⁽⁷⁹⁾. For namely spinal cord injuries (SCI) and refractory cases seeking fertility penile vibratory stimulation (PVS) or electro-ejaculation (EE) were applied with good success rates of semen retrieval. Otherwise different epididymal or testicular sperm extraction methods were applied for IVF/ICSI.

125.3 Recommendations for assessment of DE

Table 187: Recommendations for Assessment of DE

Recommendation	Strength Rating
1. Analyze thoroughly the complaints to exclude misdiagnosed other sexual dysfunctions, stressing on anorgasmia	Strong
2. Perform detailed medical and sexual history to exclude risk factors (medications especially SSRIs, antipsychotics, drug abuse, DM, depression, LUTS, etc)	Strong
3. Determine if DE is lifelong or acquired, global or situational.	Strong
4. Ask for assessment of intravaginal ejaculatory latency time (IELT) (self-estimated)	Weak

5. Include physical examination in the initial assessment of DE to identify hypogonadism or anatomical abnormalities that may be associated with DE or other sexual dysfunctions, particularly erectile dysfunction	Strong
6. Request post-coital first voided urine sample to exclude retrograde ejaculation	Strong
7. Use specific questionnaires, specialized lab tests and radiologic investigation when indicated only	Weak

125.4 Recommendations for the treatment of DE

Table 188: Recommendations for treatment of DE

Recommendation	Strength Rating
1. If acquired DE consider stopping or modifying underlying incriminated drug regimen	Strong
2. Improving erectile function and maximizing stimulation may trigger ejaculation	Weak
3. Psychosexual therapy can be particularly helpful in primary DE	Weak
4. Testosterone replacement in hypogonadal patients may improve DE	Weak
5. Cabergoline and bupropion could be beneficial for some cases of delayed ejaculation	Weak
6. PDE5I treatment significantly improved ejaculation and orgasm	Strong
7. Sympathetic $\alpha 1$ receptor agonists may help ejaculation with variable success rates in non-SCI patients	Weak
8. For fertility issues and patients with SCI, penile vibratory stimulation or electro-ejaculation help sperm retrieval in high percentage of patients	Strong

126 Peyronie's Disease

Peyronie's disease (PD) is a symptomatic disorder characterized by a constellation of penile symptoms and signs, such as penile pain, curvature, shortening, narrowing, hinge deformity, and palpable plaque with subsequent ED. It is believed to occur as a result of aberrant penile wound healing in genetically susceptible individuals, with formation of fibrous inelastic plaque(s) within the bilayered tunica albuginea (TA). The exact etiology is unknown. Microvascular trauma to the penile shaft associated with penile buckling in the semi-erect state secondary to sexual activity is thought to be the most common inciting event; however, many patients do not recall an incident that preceded symptom onset ^(6-8, 80-85).

126.1 EPIDEMIOLOGY

Multiple demographics studies have been performed worldwide and these have indicated a prevalence rate as high as 9% in adult sexually active men ^(6-8, 80-85). The natural history of PD has been evaluated in only a few level 2 and 3 studies, indicating that spontaneous resolution is uncommon. The published literature has shown a strong association between PD and cardiovascular risk factors and medical comorbidities ^(6-8, 80-85).

126.2 PATHOPHYSIOLOGY

The most widely accepted hypothesis on the aetiology consider PD as an accentuated wound-healing disorder occurring in a presumed genetically susceptible man in whom TA responds inappropriately to repeated minor trauma is. A prolonged inflammatory response with overexpression of cytokines and growth factors such as TGF- β result in remodeling of connective tissue into a fibrotic plaque ⁽⁸⁶⁻⁸⁸⁾.

126.3 PATIENT EVALUATION

Currently there is no international standard for evaluation of or reporting on treatment outcomes for PD. A detailed history should be obtained with specific emphasis on various characteristics of PD, such as disease onset, duration, pain, deformity, and erectile status as well as associated comorbidities such as diabetes mellitus. ^(6-8, 80-85)

Physical examination should include genital examination, such as plaque size and site, multiplicity as well as assessment of the degree of penile deformity based on clinical assessment and self-photography. An in-office intracavernosal injection of a vasoactive agent test is recommended before invasive intervention. Penile CDU provides an objective assessment of various PD characteristics especially calcified plaques and vascular flow parameters. Routine use of plain radiography, computed tomography, and magnetic resonance imaging are not recommended.

126.4 MANAGEMENT OF PD

Management of PD is as follows: (6-8, 80-85)

126.4.1 Non-operative treatment

Clostridium collagenase (CCH) has been approved by the European Medicines Agency (EMA) and the FDA for the treatment of PD. Although no other drug has been approved for this purpose, however, there is a long list of drugs which were frequently used in the active phase of PD. Those drugs are eventually stabilizing agents rather than true medical lines of treatment. In the Egyptian market CCH is not yet available probably due to its high cost for general use in treatment of PD in this community.

126.4.2 Operative treatment

Plication surgery should be preferred for men with adequate erectile function (with or without pharmacotherapy), adequate penile length, and minimal to moderate curvature but without the presence of hourglass deformity. Grafting procedures should be offered for men with good erectile function, severe deformity (significant or severe curvature and/or indentation or hourglass deformity), and concern regarding penile length loss. (89-91)

Penile prosthesis should be considered in men with complex penile deformities and refractory erectile dysfunction.

126.5 Recommendations for evaluation of PD:

Table 189: Recommendations for Evaluation of PD

Recommendation	Strength Rating
1. There is currently no international standard evaluation and treatment for PD and a detailed history should be obtained with specific emphasis on various characteristics of PD, such as onset, duration, course, pain, deformity or ED	Strong
2. Perform physical examination, including assessment of palpable plaques, penile length, extent of curvature (self-photograph, or pharmacological-induced erection)	Strong
3. Do not use specific PD questionnaire, ultrasound measurement of plaque size in everyday clinical practice.	Weak
4. Proper pre-operative counselling includes the available treatment options and the known benefits and risks of each treatment. Patients' expectation will reduce post treatment patient dissatisfaction	Weak

126.6 Recommendations for the non-operative treatment of PD

Table 190: Recommendations for The Non-Operative Treatment of PD

Recommendation	Strength Rating
1. Use conservative treatment in patients not fit for surgery or when surgery is not acceptable to the patient	Weak
2. Intralesional collagenase injection has shown some outcome benefits in PD management.	Weak
3. Extracorporeal shockwave treatment may only be offered in the active stage of the disease to alleviate penile pain. Do not use extracorporeal shockwave treatment to improve penile curvature and reduce plaque size.	Weak
4. Use penile traction devices and vacuum devices to reduce penile deformity and increase penile length	Weak
5. Do not use oral treatment with vitamin E and tamoxifen for significant reduction in penile curvature or plaque size	Strong
6. Do not offer other oral treatments in chronic phase of PD (acetyl esters of carnitine, pentoxifylline, colchicine).	Weak

126.7 Recommendations for Surgical treatment

Table 191: Recommendations for Surgical Treatment of PD

Recommendation	Strength Rating
1. Perform surgery only when PD has been stable for at least three months (without pain or deformity deterioration), which is usually the case after twelve months from the onset of symptoms. Strength rating	Strong
2. Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of ED) and patient expectations.	Strong
3. Use tunical shortening procedures, especially plication techniques, as the first treatment option for PD with adequate penile length, curvature < 60°, absence of special deformities (hour-glass, hinge) and adequate erection	Strong

4. Use grafting techniques for patients with PD with less than adequate penile length, curvature > 60°, presence of special deformities (hour-glass, hinge) and adequate erection.	Weak
5. Use penile prosthesis implantation, with or without any additional procedure (modelling, plication, relaxing parallel incisions, grafting), in PD patients with ED not responding to pharmacotherapy	Strong

127 Priapism

127.1 Definition:

Persistent penile erection for more than four hours and not related to sexual stimulation or relieved by ejaculation.

127.2 Pathophysiology:

Priapism is one of the challenging conditions facing the urologists during diagnostic or therapeutic phase. This is because priapism carries high risk of structural damage to the cavernosal tissue which may lead to permanent ED ^(92,93).

127.3 Types of Priapism:

- **Ischemic priapism "veno-occlusive"**

It is a persistent erection within corpora cavernosa and no or little cavernous arterial flow. The patient typically complains of penile pain and clinical examination reveals a rigid erection.

- **Non-ischemic priapism**

It is a persistent erection caused by increased cavernous arterial inflow. The patient typically reports an erection that is not fully rigid and is not associated with pain.

- **Stuttering (recurrent or intermittent) priapism**

It is a distinct condition that characterized by recurrent attacks of painful and prolonged erections. They are often self-limited with intervening periods of detumescence.

- **Primary/Secondary**

127.4 Diagnosis

127.4.1 Ischemic Priapism

127.4.1.1 Clinical History:

Should include duration of erection, presence or absence of pain, sickle cell disease and sickle cell crisis, past attacks of priapism, previously used drugs, the status of erectile function before the priapism episode ^(92,93).

127.4.1.2 Physical examination:

Inspection and palpation of the penis to assess degree tumescence or rigidity, corporal body involvement and tenderness ^(92,93).

In ischemic priapism, both corpora cavernosae are usually rigid and tender while non-tender, partially tumescent corpora cavernosa suggest a non-ischemic priapism. Abdominal, perineal, and rectal examinations may help in diagnosing pelvic trauma, infection or malignancy, also full neurologic exam maybe needed in patients with spinal cord injury or lesions ^(92,93).

127.4.1.3 Laboratory investigations:

Laboratory testing should include a complete blood count, white blood cell differential, and platelet count which may reveal the presence of acute infections or hematologic abnormalities.

Reticulocyte counts and hemoglobin electrophoresis may signify the presence of Sickle cell disease/trait or other hemoglobinopathies. Cavernous blood gas aspiration and analysis allows immediate differentiation between the variants of priapism ⁽⁹²⁻⁹⁴⁾.

Clinical History, Physical Examination, Laboratory Investigations and Radiologic Assessment in Different Types of Priapism are shown in below table ⁽⁹⁵⁾.

Table 192: Clinical History, Physical Examination, Laboratory Investigations and Radiologic Assessment in Different Types of Priapism.

Color Duplex ultrasonography findings	Penile blood gas findings	Penile blood appearance	History and clinical examination	Variant
Minimal or absent blood flow	pO ₂ > 30 mmHg pCO ₂ >60 mmHg pH<7.25	Corpus cavernosum testing: blood is hypoxic and dark in color	Tender and rigid corpora cavernosa	Ischemic priapism
Blood flow is normal to high in velocity	pO ₂ <90 mmHg pCO ₂ <40 mmHg pH=7.4 similar to normal arterial blood)	Corpus cavernosum testing: blood is oxygenated and red	Perineal or penile trauma; non tender, partially tumescent corpora cavernosa	Nonischemic priapism

Minimal or absent blood flow during acute priapism; normal blood flow otherwise	Blood gases: pO ₂ <30 mmHg; pCO ₂ >60 mmHg pH <7.25	Corpus cavernosum testing: blood is hypoxic and dark in color	Similar attacks	Stuttering (recurrent) priapism

pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen.

127.4.1.4 Radiologic assessment:

Color duplex ultrasonography [CDU] of the perineum and penis can assess intracorporeal arterial blood flow. CDU should not be used as an alternative to arterial blood gas testing.

Penile MRI allows good judgment on smooth muscle viability within the corpora after episodes of priapism. It also helps in detecting malignant infiltration and segmental cavernosal thrombosis. Drawbacks of this technique include costs, MRI accessibility of and the time consumption ^(92,95).

127.4.1.5 Recommendations for diagnosis of ischemic priapism

Table 193: Recommendations for diagnosis of ischemic priapism

Recommendation	Strength Rating
1. Thorough history taking is important in making the diagnosis, etiology and type of priapism	Strong
2. Physical examination of the genitalia, the perineum and the abdomen are mandatory in the diagnosis of priapism	Strong
3. Laboratory investigations should include blood count, white blood count with cell differential, platelet count and coagulation profile	Strong
4. Perform color duplex ultrasound of the penis and perineum for the differentiation between ischemic and non-ischemic priapism	Strong
5. In cases of prolonged ischemic priapism, use magnetic resonance imaging of the penis to predict smooth muscle viability	Weak
6. Perform selected pudendal arteriogram when embolization is planned for the management of non-ischemic priapism	Strong

127.5 Management of Priapism

127.5.1 Ischemic Priapism:

127.5.1.1 Non-surgical management

The first step is cavernosal aspiration of blood with irrigation of the corpora cavernosa, in combination with normal saline or in combination with ICI of an α -adrenergic sympathomimetic

agent ⁽⁹²⁻⁹⁵⁾. All patients should be monitored by blood pressure assessment and electrocardiogram especially if they are known to have hypertension, coronary artery disease, or other cardiac comorbidities. The patient should be monitored for known systemic adverse effects, including hypertension, headache, reflex bradycardia, tachycardia, palpitations, and cardiac arrhythmia ⁽⁹²⁻⁹⁵⁾.

Drugs used ICI treatment include: Epinephrine (adrenaline) 2 ml of 1/100,000 adrenaline solution up to five times over a twenty-minute period, Nor-epinephrine (nor adrenaline) 10–20 mcg [as occasion requires], Ephedrine: 50–100 mg [as occasion requires] and Phenylephrine (preferable agent) 200 µg every three to five minutes with a maximum dosage is 1 mg within one hour ⁽⁹²⁻⁹⁵⁾. Lower doses are recommended in children and patients with severe cardiovascular disease.

Administration of α-adrenergic agonists is contraindicated in patients who have malignant or poorly controlled hypertension or are concurrently using monoamine oxidase inhibitors. In these patients, early surgical intervention may be necessary.

For priapism specifically related to SCD, medical therapies such as intravenous hydration, oxygenation, alkalization, and exchange transfusion maybe performed.

However, these interventions should never precede the first-line treatment for all episodes of ischemic priapism mentioned above. Ischemic priapism of extended durations (typically greater than 48 h) is unlikely to resolve with ICI/irrigation therapy alone, therefore these patients may be counseled to consider more immediate surgical intervention ⁽⁹²⁻⁹⁵⁾.

127.5.1.2 Surgical shunts

There are four subdivisions of shunts: percutaneous distal shunts, open distal shunts, open proximal shunts, and vein anastomoses/shunts ⁽⁶⁻¹²⁾. Table 21.

Table 194: Percutaneous distal shunts, open distal shunts, open proximal shunts, and vein anastomoses/ shunts

shunt Large biopsy needle is inserted through glans	Winter (corporoglanular)	Percutaneous distal shunts	Distal shunts
shunt #11 blade scalpel is percutaneously passed	Ebbehoj (corporoglanular)		
Modified Ebbehoj using #10 blade scalpel and introducing the scalpel rotating it inside 90°	T shunt (corporoglanular shunt)		
A 1 cm incision is made distal to coronal sulcus with excision of 5 × 5 mm cone segment of distal tunica albuginea from each corporal body	Al-Ghorab	Open distal shunt	
Modification of Al-Ghorab shunt. A Hegar dilator is	Burnett ‘snake’ maneuver		

used to evacuate ischemic blood through a distal tunical window In lithotomy position, bulbocavernosus muscle is dissected from corpus spongiosum and 1 cm staggered ellipses of tissue are incised/excised from spongiosal/corporal bodies, and the defects anastomosed together	Quackels or Sacher (corporospongiosal) shunt	Open proximal shunt	Proximal shunts
The saphenous vein is ligated and anastomosed with corpora cavernosa The superficial or deep dorsal vein is ligated and anastomosed to the corpora cavernosa	Grayhack shunt Barry shunt	Corporo saphenous vein or superficial/deep dorsal vein shunts	

127.5.2 Penile prosthesis (PP)

There are no defined indications for implanting a penile prosthesis in patients with priapism. Priapism episodes may be definitively treated with penile prosthesis implantation, especially in the context of priapism duration exceeding 72 h, where complete ED is likely to ensue ^(96,97). Early penile prosthesis insertion for acute ischemic priapism is simple and successful. Distal cylinder protrusion through the defective corpora due to previous shunt surgery remains to confound surgical success ^(96,97). Therefore, recent studies and systematic review have not demonstrated superiority of immediate PP implantation which necessitate high expertise settings with available resources and motivated patients over delayed PP implantation ^(98,99).

127.5.3 Recommendations for the Treatment of Ischemic Priapism:

Table 195: Recommendations for The Treatment of Ischemic Priapism

Recommendation	Strength Rating
1. Start management of ischaemic priapism as early as possible (within four to six hours) and follow a stepwise fashion.	Strong
2. First, decompress the corpora cavernosa by penile aspiration until fresh red blood is obtained (with or without irrigation).	Strong
3. In priapism that persists despite aspiration, proceed to the next step, which is ICI of a sympathomimetic drug	Strong

4. Repeated injections and aspiration should occur for at least up to 1 h prior to proceeding with surgical intervention in patients presenting with a priapism of less than 24 h	Strong
5. Ischemic priapism of extended durations (typically greater than 72h) is unlikely to resolve with ICI therapy alone, therefore, consider more immediate surgical intervention	Strong
6. Perform distal shunt surgical procedures first followed by proximal procedures in case of failure	Strong
7. Consider insertion of a penile prosthesis only if priapism episode is > 36 hours, or in cases for which all other interventions have failed	Strong

127.5.4 Recommendations for the treatment of non-ischemic priapism

Table 196: Recommendations for The Treatment of Non- Ischemic Priapism

Recommendation	Strength Rating
1. Perform definitive management at the discretion of the treating physician, because non-ischaemic priapism is not an emergency	Weak
2. Manage conservatively with the use of site-specific perineal compression as the first step, especially in children. Consider androgen deprivation therapy only in adults	Weak
3. Perform superselective arterial embolization, using temporary material	Strong
4. Repeat the procedure with temporary or permanent material for recurrent nonischaemic priapism following selective arterial embolization	Weak
5. Reserve selective surgical ligation of a fistula as a final treatment option when embolization has failed	Weak

127.5.5 Recommendations for the treatment of Stuttering Priapism

Table 197: Recommendations for The Treatment of Stuttering Priapism

Recommendation	Strength Rating
1. Manage each acute episode similar to that for ischaemic priapism	Weak
2. Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or anti-androgens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached	Weak

3. Initiate treatment with phosphodiesterase type 5 inhibitors only when the penis is in its flaccid state	Strong
4. Use digoxin, α -adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with very frequent and uncontrolled relapses	Weak
5. Use intracavernous self-injections of sympathomimetic drugs until ischaemic priapism has been alleviated	Weak

128 Conclusions:

It should be emphasized that clinical guidelines present the best evidence available to the experts. However, following guidelines recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandating and should not be used as a legal standard of care.

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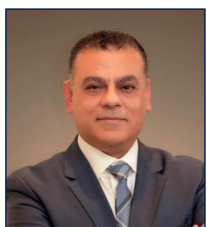
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Committee XIV

Male Infertility



Ayman Rashed



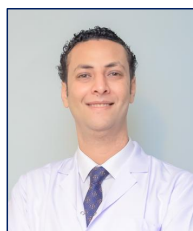
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130 Abbreviations:

ARTs	Assisted Reproductive Techniques
AZF	Azoospermia Factor Gene
CBAVD	Congenital Bilateral Absence Of Vasa
CFTR gene	Cystic Fibrosis Transmembrane Conductance Regulator gene mutation
DFI	Defragmentation Index
EDO	Ejaculatory Duct Obstruction
E2	Estradiol
FISH	Fluorescent In-Situ Hybridization
GnRH	Gonadotropin Releasing Hormone
hCG	Human Chorionic Gonadotropin
HPG	Hypothalamo Pituitary-testis
IVF	In vitro Fertilization
ICSI	IntraCytoplasmic Sperm Injection
ITT	Intra-Testicular Testosterone
IUI	Intrauterine Insemination
LH	Luteinizing Hormone
MENA	Middle East and North Africa
NOA	Non-Obstructive Azoospermia
OATs	OAT Syndrome
OA	Obstructive Azoospermia
OAT	Oligo-Asthen-Teratozoospermia
PGD	Pre-Implantation Diagnosis
PGT	Preimplantation Genetic Testing
ROS	Reactive Oxygen Species
US	Ultrasound
SERM	Selective Estrogen Receptors Modulators
SCD	Sperm Chromatin Dispersion
SCSA	Sperm Chromatin Structure Assay
SDF	Sperm DNA fragmentation
SRR	Sperm Recovery Rate

ASRM	The American Society for Reproductive Medicine
TT	Total Testosterone
TRUS	Trans-Rectal Ultrasound
YCMD	Y- Chromosome Microdeletion

131 Abstract

131.1 Objectives

The Urologic Egyptian Guidelines on Female Urology aim to help and guide clinical practitioners to have knowledge of the incidence, standard definitions, diagnosis, therapy, and follow-up of male infertility. This chapter integrates recent international guidelines with local experts' opinions based on Egyptian healthcare and socioeconomic circumstances.

131.2 Methods

Databases searched included Medline, Cochrane Libraries, EAU and AUA guidelines. Review of several meta-analyses, leading institutional protocols and relevant Egyptian publications were taken into consideration. All statements were graded according to 2 parameters: Level of evidence and strength of recommendation. Each information was given a strength rating (strong or weak).

131.3 Results

These guidelines represent the best clinical evidence-based medicine available. These guidelines are not solely based upon the level of evidence of the international publications but also include expertise of the treating doctor and expectations of every patient.

131.4 Conclusions

These guidelines provide practical evidence-based guidance on the clinical aspect of many male infertility. The main target is entirely focused on assessment and treatment, reflecting the recommended clinical practice. This can provide the basis for thinking through patient's management and also for planning and designing clinical services.

132 ASSESSMENT OF MALE INFERTILITY

132.1 Definition and classification

Infertility is the inability of a couple to achieve pregnancy within 12 months of active, non-contraceptive sexual life. It is subdivided into; primary infertility in which the couple never had child nor achieve pregnancy, and secondary infertility in which the couple had previous child or at least achieved one pregnancy before ⁽¹⁾.

132.2 Epidemiology

The overall percentage of infertile couples is 15%, of which, male factor accounts for at least 50% ⁽²⁾. Those figures are higher in the Middle East and North Africa (MENA) region according to a recent systematic review and meta-analysis of prevalence surveys on infertility in this region, which, concluded that the overall infertility rate is 22.6%. Unfortunately, there is no recent accurate data or registry that can reflect the actual percentage of male infertility in Egypt, however, there is a consensual opinion from expertise that male infertility rate in Egypt is significantly increasing which favors the aforementioned studies ^(3,4).

132.3 Etiology

Male infertility could be due to:

- Increased scrotal temperature
- Hormonal disruption
- Environmental factors
- Congenital genital anomalies
- Genetic abnormalities
- Erectile dysfunction
- Genital infection
- Immunological factors
- Malignancy
- Idiopathic

Male infertility can be classified according to the topographic localization of the cause (e.g. central, peripheral). Subsequently, it can be subclassified according to the nature of cause (e.g. genetic, congenital, endocrine, inflammatory, environmental, ...etc.).

Interestingly, despite abnormal semen analysis is the main finding in infertile male, normal semen analysis does not exclude other male factors that may play a role in male infertility. This is a clear finding in couples with idiopathic infertility ⁽⁶⁾.

Table 198: Recommendations for epidemiology and etiology of male fertility

Recommendations	Strength Rating
1. Every couple seeking conception should be investigated to define which partner is the cause of the problem.	Strong
2. Even in secondary infertility, either partners should not be excluded from investigation work up (Masculinity cultural concept).	Strong
3. Normally appeared semen analysis does not exclude male factor and more investigations may be needed particularly in couples with unexplained infertility.	Strong

133 Evaluation of male infertility

133.1 Why to evaluate?

The aim of evaluation of infertile male is to recognize the following ⁽⁶⁾:

- Correctable diagnosed conditions.
- Irreversible conditions that are amenable to assisted reproductive techniques (ARTs).
- Irreversible conditions that is not amenable to treatment or ARTs, to save time and cost of unnecessary procedures. In such cases it is better to direct the treatment to other condition e.g. erectile dysfunction due to hypogonadism.
- Underlying life-threatening conditions that may presented by infertility (e.g. testicular tumor).
- Genetic abnormalities that may have impact on the offspring.

133.2 Timing of evaluation?

The Egyptian culture may have an impact on infertile couples as males usually seek infertility evaluation after thorough examination of their female partners at more than one gynecologist. This cultural concept may cause some potential delay in the evaluation of the male partner.

In the era of assisted reproductive techniques (ARTs), female age above 35 years is another risk factor that may influence the treatment protocol of male factor. This is a potential factor as the fertilization, implantation and pregnancy rates are significantly lower in female above 35 years old compared to females below this age when using ARTs ⁽⁶⁻⁸⁾.

133.3 Medical history

Medical history should include:

- Duration of infertility and if primary or secondary infertility.
- Partner age and relevant history.
- Sexual history including (erectile function, intercourse rate, ejaculatory disorders, STDs)
- Childhood relevant diseases (e.g. mumps orchitis) and developmental and pubertal history (e.g. undescended testes, hypospadias, ...etc.)
- Gonadotoxins exposure e.g. chemotherapy, radiotherapy, medications, heat, ...etc.
- Systemic medical diseases (e.g., DM, dyslipidemia and upper respiratory diseases)
- History of previous relevant surgeries e.g. herniorrhaphy, varicocelectomy, hydrocelectomy, urethral surgery, abdomino-perineal surgery, ...etc.

133.4 Physical examination

133.4.1 General Examination

As usual for any other medical condition with concentration directed to the following:

- Scars of relevant previous operations
- General facies status of the patient
- Hair distribution
- Body proportion and fat distribution
- Gynecomastia
- Any apparent congenital anomalies

133.4.2 Local Examination

Should be concentrated on genitalia including:

- Penile examination for size and position of external meatus
- Scrotal examination for development of scrotal sac, and size and consistency of both testes, examination of epididymis and vasa differentia, and examination for varicocele, hydrocele or masses

133.5 Laboratory investigations

133.5.1 Semen Analysis

Semen analysis is the basic and initial investigative tool. According to the WHO 2010 manual of examination and processing of human semen, 5th edition, the sample should be collected after a minimum of 2 days and a maximum of 7 days of sexual abstinence. If additional follow up samples are required, the days of sexual abstinence should be the same as the previous sample. The minimal requirements of normal semen analysis (5 centiles and their 95% confidence interval) below which male sub-fertility is considered are shown in (**Table 2**), as per WHO 5th edition ⁽⁹⁾.

Table 199: Minimal normal semen parameters

Lower reference limit	Parameter
1.5 (1.4-1.7)	1. Semen volume (ml)
39 (33-46)	2. Total sperm number (10^6 per ejaculate)
15 (12-16)	3. Sperm concentration (10^6 per ml)
40 (38-42)	4. Total motility (PR+NP, %)
32 (31-34)	5. Progressive motility (PR, %)
58 (55-63)	6. Vitality (live spermatozoa, %)
4 (3.0-4.0)	7. Sperm morphology (normal forms, %)
Other consensus threshold values	
≥ 7.2	8. pH
< 1.0	9. Peroxidase-positive leukocytes (10^6 per ml)
< 50	10. MAR test (motile spermatozoa with bound particles, %)
< 50	11. Immunobead test (motile spermatozoa with bound beads, %)
≥ 2.4	12. Seminal zinc (μmol /ejaculate)
≥ 13	13. Seminal fructose (μmol /ejaculate)
≥ 20	14. Seminal neutral glucosidase (mU/ejaculate)

133.5.2 Semen cryopreservation

Semen cryopreservation is an essential procedure for a category of patients with high risk of fertility problems. Semen analysis in these patients should be done at well-equipped andrology laboratory with facility of semen banking.

133.5.2.1 Indications for semen cryopreservation are:

- Cases of severe oligozoospermia (<5 mil/cc): should utilize semen cryopreservation before starting treatment. This makes it easy to concentrate considerable count for artificial insemination (IUI) or In-vitro-fertilization (IVF)⁽¹⁰⁾
- Cases of essential relevant diseases in which loss of fertility is impending due to either surgical procedure (e.g. oncological, testicular torsion, etc.) or due to medications (e.g. chemotherapy, radiotherapy, immunosuppressive treatment, etc.)⁽¹⁰⁾.
- Cases of non-obstructive azoospermia (NOA) who are receiving specific medical treatment for specific treatable conditions (e.g. hypogonadotropic hypogonadism, Testosterone/E2 imbalance, etc.). This category of patients may have positive ejaculatory sperms, which are commonly temporary and/or severe oligozoospermia ^(11–14).

133.5.3 Sperm DNA fragmentation (SDF) test

SDF test is done through a variety of assays, all of which indicate a DNA defragmentation index (DFI) expressed as a percentage above which the male fertility is questionable.

Four assay tests are the most commonly used namely ⁽¹⁵⁾:

- Sperm chromatin structure assay (SCSA), ($n = < 30\%$)
- Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling (TUNNEL), ($n = < 12\%$)
- Single cell gel electrophoresis (SCGE or COMET) ($n = < 25\%$)
- Sperm Chromatin Dispersion (SCD) ($n =$ Large chromatin halo dispersion around the sperms)

Indications for DNA Fragmentation Testing ⁽¹⁶⁾:

- Unexplained Infertility
- Recurrent pregnancy loss either spontaneous or after IVF/ICSI
- Recurrent IUI failure
- Borderline abnormal or normal semen analysis with risk factors (e.g. clinical varicocele, smoking, poor lifestyle, exposure to gonadotoxins, etc).

Several studies demonstrated that high SDF is associated with impaired semen parameters, including either more than one parameter or just one parameter as isolated asthenozoospermia.

High SDF was also, found to negatively affect the fertilization process, embryo quality, and pregnancy outcome during ARTs. ⁽¹⁷⁻¹⁹⁾ Moreover, male infertility factors such as unexplained infertility, varicocele, old age and obesity, have significant impact on SDF. ^(18,20)

SDF test practicing is still controversial. This controversy is due to different assays used to measure SDF, with different normal cutoffs and reliability as regard sensitivity and specificity of these assays. ^(17,19)

The American Society for Reproductive Medicine (ASRM) published an assessment of SDF testing in literature, including 62 meta-analysis and studies. They concluded that: There is fair evidence of correlation between increased SDF and male infertility. Moreover, testicular sperm proved to have lower levels of SDF when compared to ejaculated sperm ⁽²¹⁾. Couples with male high SDF may benefit from TESE /ICSI combination. However, further evidence is needed to support this practice in the routine clinical setting ⁽²²⁾.

133.6 Hormonal evaluation

Fertility hormones evaluation is well documented as a part of male infertility assessment. Some investigators believe that it is a must in all infertile men.

Indications of hormonal evaluation: ^(6,7)

- Subfertile semen analysis particularly if count < 10 mil/cc
- Associated sexual dysfunction
- Clinical conditions that suggest endocrinopathy

Serum FSH, LH, and Total Testosterone (TT) are the main fertility hormones to be evaluated in cases of male infertility. Serum Prolactin is usually evaluated during the work up of male infertility if it is suspected to be high (e.g. gynecomastia evident low s. TT or past history of pituitary adenoma) ^(6,7).

Estradiol (E2) is also another hormone, which play a role in spermatogenesis, however if elevated, it would interfere with the process, particularly, when the TT/E2 ratio is less than 10:1 ^(13,14).

In cases of primary testicular failure, serum FSH is usually elevated in patients with markedly reduced spermatogenesis, while in patients with maturation arrest, it may be normal or elevated. Nevertheless, serum FSH is an inaccurate predictor of spermatogenesis, particularly, if TESE or micro-TESE is planned for NOA patients before ICSI. ^(8,23)

133.7 Genetic tests

It is estimated that at least 15% of infertile males are related to genetic causes with chromosomal or single gene alteration ⁽²⁴⁾. The most common genetic abnormalities include: numerical

chromosome abnormality (e.g. XXY, Trisomy), structural chromosome abnormality (e.g. inversion, translocation, microdeletion)⁽⁸⁾.

15. The importance of genetic testing in male infertility arises from:

- Finalizing the diagnosis of infertility problem.
- The risk of passing genetic problems to offspring.
- Saving money and time if the male infertility due to untreatable genetic problems e.g. XX male

133.7.1 Indications for Genetic testing:

Indications for genetic testing are:^(5,8,14,22,24–27)

- Suspected obstructive azoospermia (OA)
- Patients with sperm count < 10 mil/cc
- Severe oligozoospermia (< 5 mil/cc), particularly, in patients, who did not show any documented sperm count above 5 mil/cc.
- In cases of sexual differentiation disorders
- Patients with high FSH, low TT, and low testicular volume
- Apparent facial or body disconfiguration, or known congenital disorder relevant to male infertility (e.g. patients with, polycystic kidney disease, Prader-Willi Syndrome, Noonan Syndrome, etc.)
- Recurrent miscarriage and/or recurrent failure of ARTs.
- Recurrent failure of TESE/mTESE.

133.7.2 Basic Genetic Testing in Male Infertility:

133.7.2.1 Cystic Fibrosis Transmembrane Conductance Regulator gene mutation (CFTR gene)

Congenital bilateral absence of vasa (CBAVD) is strongly linked with CFTR gene mutation. Which may be found in approximately 70% of patients who have CBAVD without clinical cystic fibrosis. Clinical scrotal examination can easily detect bilateral vas absence, while in azoospermic patients with unilateral absence of vas, transrectal ultrasonography (TRUS) must be done to confirm if the contralateral vas has proximal segmental loss ^(6,28,29).

In such couples, it is essential to test the female partner for CF mutation before planning for ICSI, as the offspring will have 50% risk of having cystic fibrosis or/and CBAVD. The prevalence of CAVDs in men is reported to be approximately 0.1%. This figure is probably underestimated because the cases with unilateral absent vas may pass without diagnosis ^(28,30).

133.7.2.2 Karyotype

Karyotype is the analysis of individual chromosomes including sex chromosomes (X, Y). The test analyzes numerical (gain or loss) as well as structural (translocations, inversions, deletions and duplications) anomalies. The prevalence of chromosomal abnormality inversely proportionate to the sperm count; it comprises <1 % in men with normospermia, 5% in men with count < 5 mil/cc and 10 – 15% in azoospermic men ^(6,31).

133.7.2.3 Numerical Autosomal Abnormalities

Trisomy 13 (Patau Syndrome), Trisomy 18 (Edwards Syndrome), and Trisomy 21 (Down Syndrome) are the only embryos with numerical autosomal abnormalities that can survive to birth with low percentage.

Trisomy 21 patients usually present with azoospermia or severe oligozoospermia ⁽³²⁾. In the literature, only three male patients with Trisomy 21 had spontaneous pregnancy, which may be explained by cognitive, physical and psychological problems rendering it difficult for those patients to achieve conception. ICSI could be tried for these patients with aid of pre-implantation diagnosis (PGD) to select chromosomal abnormality-free embryos ⁽³³⁾.

133.7.2.4 Numerical Sex Chromosome Abnormalities

The most common type is Klinefelter's Syndrome (47XXY), the estimated prevalence is 1:700 of male newborns. Two common types are identifiable, the non-mosaic Klinefelter (47XXY) and the mosaic Klinefelter (46XY/47XXY), other types will include more X chromosomes (e.g. 48XXXXY). The majority of cases is non-mosaic. The secondary male characters and normal body features reflect the Leydig cell function with normal serum testosterone level. It is estimated that 66% of these patients will have normal serum testosterone (34). Furthermore, Klinefelter syndrome is the most common chromosomal abnormality in azoospermic patients (particularly, NOA) accounting for approximately 73% of all abnormalities ^(35,36).

Karyotyping using multi-color fluorescent in-situ hybridization (FISH) will differentiate between non-mosaic and mosaic types. Almost all non-mosaic patients are azoospermic, while, the mosaic patients may have severe oligozoospermia as well as azoospermia with higher chance of sperm retrieval using TESE or m-TESE. Moreover, according to a recent study 7% of adolescents have seminal sperms ^(32,37).

A recent meta-analysis on sperm recovery and outcome of ICSI in couples where the male partner is Klinefelter, reported that sperm recovery rate (SRR) is about 40% and final birth rate is 16% ⁽³⁴⁾.

Other numerical sex chromosome abnormalities include 47XYY. In these patients, sperm counts range from normal to azoospermia. Virtually, all offspring of XYY males, through spontaneous pregnancy or ICSI, are chromosomally normal ⁽³²⁾.

133.7.2.5 Y-chromosome Microdeletion (YCMD)

Y- chromosome microdeletion (YCMD) is the second most common cytogenetic abnormality in male infertility after Klinefelter Syndrome. It is estimated to be present in 1:4000 men of general population, this prevalence is increased in azoospermic and oligospermic patients ⁽³⁸⁾.

There are three regions on the Azoospermia Factor gene (AZF) on the Y-chromosome, where microdeletion takes place, namely: AZFa, AZFb, and AZFc. Microdeletion on these regions may occur solely or on a mixed pattern. The microdeletions, which are clinically observed in severe oligozoospermia and azoospermia patients are AZFa in 0.5-4%, AZFb in 1-5%, AZFc in 80%, and AZFbc in 1-3% of patients. AZFabc microdeletion may be detected in 46 XX male variants (38). The prevalence of YCMD in Egypt is approximately 12% ⁽³⁸⁾.

Clinical implication of YCMD include: TESE should not be recommended in cases of complete deletion of the AZFa region, or complete deletion of AZFb or deletions of the AZFbc / AZFabc regions. Moreover, in patients with microdeletions of the AZFc region sperms can be recovered for ARTs in 50 – 75 % of patients; however, it may be transmitted to male offspring. ^(5,7,8,38)

133.7.2.6 Reactive Oxygen Species (ROS)

Seminal leukocytes and sperms produce ROS that have a role in capacitation and acrosome reaction. On the other hand, excess ROS may interfere with male fertility through peroxidation of sperm lipid membrane and creation of toxic fatty acids, in addition to damaging of sperm DNA integrity. This negative impact could be represented in recurrent miscarriage and failed ARTs. Excess ROS is associated with poor lifestyle and environmental exposure. Unfortunately, there is no standardized method for ROS measurement. Antioxidants and improving lifestyle may help in reducing ROS and hence sperm function. However, the studies in this area are deficient and contradictory as there is no RCTs that can support usage of antioxidants. Therefore, ROS measurement is not recommended as routine and may be used in selected group of patients with recurrent miscarriage and recurrent failed ARTs ⁽⁶⁻⁸⁾.

133.8 Imaging

133.8.1 Scrotal ultrasound (US)

Although clinical examination of the scrotum is quite enough in most cases; scrotal US is a reliable, and cost-effective tool for the evaluation of difficult cases, particularly, in the assessment of testicular size and texture and in the exclusion of other pathologies (e.g. masses, calcifications, etc.) or in cases of ambiguous scrotum. Noteworthy, non-palpable varicocele detected by US is considered clinically insignificant ⁽³⁹⁾.

133.8.1.1 Trans-rectal ultrasound (TRUS)

TRUS is a valuable tool in cases where CAVD or ejaculatory duct obstruction (EDO) are suspected from semen analysis. Patients with low volume, negative fructose test and acidic pH may show absent vasa and atrophic seminal vesicles in cases of CBAVD or they may show dilated seminal vesicles (>2cm in long axis or honeycomb appearance) if EDO is present.

Furthermore, patients with severe oligozoospermia and low semen volume, TRUS may detect partial obstruction due to (midline prostatic cyst or ejaculatory duct cyst) ^(40,41).

Table 200: Recommendations on Male Infertility Diagnostic Workup

Recommendation	Strength Rating
1. Evaluation of male partner should be done if no pregnancy after one year of regular unprotected sexual life	Strong
2. Evaluation of male partner should be done in less than 6 months if female partner's age above 35 years or known male or female potential fertility issue.	Strong
3. Immediate evaluation of male partner should be done if known infertility factor is ensue or upon request.	Strong
4. Semen analysis is the cornerstone investigation and must be done according to WHO 2010 (5th Ed.), in two separate occasions with at least one week apart	Strong
5. Semen Cryopreservation is strongly recommended in patients with, or expected to be severe oligozoospermia (< 5 mil/cc) e.g. due to chemo-radiotherapy, patients receiving medical treatment for NOA	Strong
6. SDF as routine examination is recommended in selected cases e.g unexplained infertility, recurrent pregnancy loss	Weak
7. Hormonal lab examination is strongly recommended in patients with oligo- or azoospermia including FSH, LH, TT	Strong
8. Hormonal Lab. Investigations extending is recommended if abnormal FSH, LH, TT; to evaluate, E2, Prolactin	Weak
9. Genetic testing is strongly recommended in azoospermic and severe oligozoospermic (< 1 mil/cc) males and	Strong
10. Consider genetic counselling of infertile couples, if any genetic or chromosomal abnormalities are found	Weak
11. Genetic counseling should be offered to sperm retrieval candidates even if abnormal genetic testing resulted negative	Strong
12. Scrotal US is reliable tool for examination of scrotal contents if suspected pathology in clinical examination	Weak
13. TRUS is strongly recommended if partial or complete EDO is suspected	Strong

134 VARICOCELE

134.1 Definition

Varicoceles are defined as abnormally dilated veins within the scrotum ⁽⁴²⁾

134.2 Incidence

Varicoceles are present in almost 15% of men from the general healthy population. Moreover, the prevalence of varicocele is estimated to be 45% among men with primary infertility and 80% among men seeking care for secondary infertility ⁽⁴³⁾. The prevalence of varicocele increases with age, it shows an about 10% increase in the incidence per each decade of life. It is rarely reported in children < 10 years of age; and affects approximately 7-14% of boys during puberty ^(39,44,45).

The incidence of left-sided varicoceles are 10 times more popular than on the right and occur bilaterally in fewer than 10% of patients and isolated to the right in <1% ⁽⁴⁶⁾.

134.3 Diagnosis and classification

Physical examination is the mainstay of varicocele diagnosis. Varicocele is diagnosed clinically as a “cord like structures” felt in the scrotum above the testis in the upright position that disappears on lying down. Varicocele of any grade that does not disappear in the supine position should raise suspicion of retroperitoneal pathology ⁽⁴⁷⁾.

According to Dubin and Amelar, varicocele can be classified into ⁽⁴⁸⁾:

- Grade I varicocele (palpable with Valsalva maneuver)
- Grade II (palpable at rest, but not visible)
- Grade III (varicocele visible without palpation).

Subclinical varicocele cannot be detected by clinical examination but is only evident during radiological examination. However, only clinically diagnosed, significant varicoceles associated with infertility have the clearest indications for repair ⁽⁴⁹⁾. Thus, there is no need to hunt for subclinical varicocele and hence, scrotal ultrasonography, thermography, Doppler examination, radionuclide scanning, and spermatic venography, should not routinely ordered without a palpable abnormality. However, in case of inconclusive or difficulties in the physical examination due anatomic abnormalities such as in situations where a patient is obese, has had prior scrotal surgery, has a small scrotum, or has thick scrotal skin, scrotal ultrasonography is recommended (multiple spermatic veins >3.0 mm in diameter (at rest and with Valsalva) is most probably associated with the presence of clinically significant varicoceles ⁽⁵⁰⁾.

134.4 Management

There are no effective medical treatments. Surgery remains the mainstay of management of varicocele. Although radiologic embolization is promoted as a minimally invasive procedure with less pain in infertile men with varicocele, it has interventional failure up to 27% and higher postpone complications ⁽⁵¹⁾. Varicocelectomy can be performed surgically with macroscopically, or microsurgical techniques with different approaches including retroperitoneal, subinguinal, and scrotal. Increasing evidence supports the superiority of open microsurgical inguinal or subinguinal varicocelectomy, owing to reduced complication rates and increased pregnancy rates compared with other techniques ⁽⁵¹⁾.

Much controversy exists in the literature as regards the effect of varicocelectomy on semen parameters ⁽⁵²⁾. The current available evidence supports varicocele repair for infertile couples with men suffering from clinical varicocele and abnormal sperm parameters, a female partner that has no or potentially treatable cause of infertility, and the time to conception is not a concern ⁽⁵³⁾.

In case of patients with subclinical varicoceles, data from RCTs and meta-analysis failed to prove such benefits ^(54–57). Although varicocelectomy for subclinical varicocele alone is not indicated, data demonstrated the potential role of subclinical varicocele repair in augmenting the surgical outcome of repair of clinical varicocele over the contralateral side ^(58,59). Also, no benefit has been proven regarding treatment of varicocele in infertile men with normal semen parameters ⁽⁴⁹⁾. In addition, most contemporary data do not support varicocele repair based on abnormal strict morphology only without other semen parameter abnormalities ^(50,60,61).

Evidence from a meta-analysis of nonrandomized, retrospective studies supports that varicocele repair in infertile couples undergoing ART, wherein the male partner has a diagnosis of oligospermia or non-obstructive azoospermia, is associated with improved pregnancy and Live birth rates ⁽⁶²⁾. In this setting, several studies from the Middle East have assessed the potential benefit of varicocelectomy in the management of patients with NOA ^(63–66).

Firstly, most of these studies showed that a small number of motile sperms was identified in the ejaculate following varicocelectomy in 26.6% - 34% of patients, thus, enhancing the rate of spontaneous pregnancy (7.7%) ^(63–66). Similarly, a study from Iran supported these findings, where 14% (7 patients) of the NOA patients showed viable sperms in the ejaculate after surgery, of which, only one couple was able to achieve spontaneous pregnancy ⁽⁶⁷⁾. On the contrary, Schlegel P et al ⁽⁶⁸⁾, demonstrated that the role of varicocelectomy in NOA may be over-estimated.

Secondly, varicocelectomy may improve the quality of sperms and the sperm retrieval rates ^(69,70). Generally, several systematic reviews and meta-analysis supported the beneficial value of varicocelectomy prior to surgical sperm retrieval in patients with NOA ^(62,71,72).

Furthermore, strong evidence from RCTs supports varicocele repair in adolescents with clinically palpable varicocele when progressive testicular growth retardation is reported ^(73–75).

For patients with chronic scrotal pain associated with a varicocele that has not responded to conservative measures, a recent meta-analysis has reported that varicocelectomy has shown to be safe and effective, however, proper diagnosis of the cause of pain is necessary, many urological causes e.g. prostatitis, may cause scrotal pain, so justification of varicocele as the cause of pain must be meticulous ⁽⁷⁶⁾. Varicocele repair may also be beneficial for men with clinically palpable varicoceles with documented low serum testosterone levels; to significantly increase and restore their testosterone levels ^(77,78).

Data from RCT and prospective studies indicated varicocelectomy for addressing elevated sperm DNA fragmentation, when the male partner has been found to have high DNA fragmentation of the spermatozoa with or without abnormal semen parameters ^(79–81).

Table 201: Recommendations on the management of varicocele in infertile men

Recommendations	Strength Rating
1. Perform varicocelectomy for men with clinically palpable varicocele and abnormal sperm parameters	Strong
2. No benefit has been proven regarding the treatment of varicocele in infertile men with normal semen parameters	Weak
3. No benefit of varicocele repair based on abnormal strict morphology (isolated teratozoospermia) only when not accompanied by other semen parameter abnormalities	Weak
4. Do not perform varicocele repair in men with subclinical varicocele	Strong
5. Perform bilateral varicocelectomy in infertile men with one side clinical and subclinical in the other side	Weak
6. Varicocelectomy is recommended for male with non-obstructive azoospermia or severe oligospermia undergoing ICSI treatment, unless genetic pathology is present e.g. Klinefelter's syndrome	Weak
7. Varicocelectomy is indicated for chronic scrotal pain associated with a varicocele	Weak
8. Perform varicocelectomy in adolescents with clinically palpable varicocele when progressive testicular growth retardation is reported	Strong
9. varicocelectomy is recommended for men with clinically palpable varicoceles with documented low serum testosterone levels.	Weak
10. varicocelectomy is indicated for addressing elevated sperm DNA fragmentation, when the male partner has been found to have high DNA fragmentation of the spermatozoa with or without abnormal semen parameters.	Weak

135 AZOOSPERMIA

135.1 Assessment of Azoospermia patients

Azoospermia defines a condition in which, no sperm is identified using high-powered microscope in a centrifuged semen specimen (for at least 15 minutes at room temperature). It can be found in approximately 1% of all men and 10-15% of the infertile men ⁽⁸²⁾. Interestingly, prevalence of azoospermia may show some variation according to the geographical and racial differences. In this setting, several epidemiological studies from Africa showed that the prevalence of azoospermia ranges between 3.4% - 32.2% of infertile men, reflecting a potential higher prevalence in African countries ⁽⁸³⁻⁸⁵⁾. On the same hand, a study including 13,892 infertile men from different geographical regions demonstrated that the prevalence of azoospermia among MENA men is approximately 6% ⁽³⁾. Generally, azoospermia can be classified into OA and NOA (also known as testicular or primary spermatogenic failure) ⁽⁸⁶⁾.

Table 202: Recommendations on initial diagnosis of Azoospermia

Recommendations	Strength Rating
1. The diagnosis of azoospermia requires the absence of sperms under high-powered microscope in two separates occasions with one-month apart, and centrifuged semen specimens (for at least 15 minutes at a centrifugation speed of more than or equal 3000x at room temperature)	Strong
2. The evaluation of azoospermia patients should start with a detailed medical, surgical, sexual, and reproductive history (as described before in the assessment of infertile males)	Strong
3. Further initial evaluation of azoospermic patients should include physical examination by a urologist or andrologist (as described before in the assessment of infertile males)	Strong
4. Some patients (with low s. testosterone levels) may extended require hormonal investigations including LH, TT, E2 and Prolactin	Strong
5. TRUS is recommended in obstructive azoospermic patients with low volume semen, normal testicular volume and normal hormonal profile	Strong
6. Diagnostic testicular biopsy is not recommended as a separate setting and should only be performed as a part of TESE and cryopreservation and/or IVF/ICSI	Strong
7. Genetic investigations should be performed in all patients with NOA and in patients with OA due to CBAVD as described in the assessment of infertile males	Strong

Semen analysis as mentioned above; is the core diagnostic test for azoospermia ⁽⁸⁷⁾. For instance, semen volume and PH may reflect the cause of azoospermia, where a low volume ejaculate with

acidic PH may indicate obstructive causes CBAVD, or bilateral ejaculatory duct obstruction, while, a normal ejaculate volume with alkaline PH demonstrate functional seminal vesicle with patent ejaculatory duct ⁽⁸⁸⁾. Similarly, complete hormonal investigation is considered an integral part of the initial diagnosis of azoospermic patients as it is essential to plan the diagnostic and therapeutic strategies, where hypogonadism may coexist in approximately 30% of patients with NOA ⁽⁸⁹⁾.

Routine use of scrotal and/or TRUS in the diagnosis of azoospermic patients is a matter of debate ⁽⁹⁰⁾, However, it may be used to differentiate between OA and NOA ^(40,41). An interesting study from Egypt, reported that scrotal US is characterized by a sensitivity and specificity of 75% and 72%, respectively, for detection of NOA, while, for OA its sensitivity and specificity are 29.8% and 87%, respectively. Similarly, TRUS demonstrated 39% sensitivity and 88% specificity for NOA, and 45% sensitivity and 83% specificity for OA. Generally, the authors recommended that US can be used in the diagnosis of NOA ⁽⁴¹⁾.

135.2 Further assessment of Azoospermic patients

After the initial workup, further investigations should be directed to differentiate OA from NOA and should be tailored according to the clinical scenario. Identifying the etiology of azoospermia allows the physician to detect a potentially correctable underlying cause and decide on the best treatment options.

Etiologies of azoospermia fall into three categories: pre-testicular (2%), testicular (49%) and post-testicular (7-51%). Pre-testicular causes are the endocrinal disorders that can adversely affect spermatogenesis. Testicular causes are the factors that are intrinsic to the testes. Post-testicular factors involve either ejaculatory dysfunction or obstruction of sperm pathway from the testis to the urethral meatus ⁽⁹¹⁾. Generally, OA represents 30-40%, while NOA represents 60-70% of azoospermic cases ⁽⁹⁰⁾.

Table 203: Recommendations on NOA investigations

Recommendations	Strength Rating
1. Testicular biopsy in patients with NOA should ONLY be performed simultaneously with mTESE or cTESE to provide the patient with the possibility of sperm cryopreservation without the need for further invasive procedures.	Strong
2. Karyotyping is strongly recommended for all patients with NOA	Strong
3. Testing for Y chromosome microdeletion is recommended for all patients with NOA	Strong
4. Patients with low testosterone level require extended hormonal investigations including luteinizing hormone (LH), estradiol, and prolactin	Strong

The OA can be classified according to the level of obstruction into intra-testicular obstruction (15%), epididymal obstruction (30-67%), vas deferens obstruction (2-6%) that includes the CBAVD, ejaculatory duct obstruction (1-3%), and functional obstruction of distal seminal ducts ⁽⁹⁰⁾. As regards the genetic evaluation for patients with OA, it is well documented in the literature that CBAVD is associated with high frequency of CFTR mutations ⁽⁹²⁾. In this setting, almost all patients with cystic fibrosis suffer from CBAVD, of which, 70% have identifiable CFTR mutations. Similarly, 4% of the female partners may be carriers of the CFTR gene mutations that render testing of both partners an important part of the investigations of OA due to CBAVD. Furthermore, renal agenesis may occur in 11% of patients suffering from vasal agenesis. ⁽⁹³⁾

Table 204: Recommendations on OA investigations

Recommendations	Strength Rating
1. In patients with unilateral or bilateral congenital absence of vas deferens, both the male and female partners should be offered genetic counseling and testing for CFTR.	Strong
2. It is recommended to perform renal imaging to detect any associated abnormalities in patients with CBAVD and no evidence of CFTR	Weak
3. Y chromosome microdeletion testing is not recommended in patients with OA	Strong
4. Vasography should only be performed if a reconstructive surgery will be performed in the same setting	Weak
5. TRUS is recommended as a minimally invasive technique for diagnosis of ejaculatory duct obstruction in patients with low ejaculate and bilateral palpable vas deferens	Strong

135.3 Management of Azoospermia

A meta-analysis showed that mTESE is associated with 1.5 folds higher likelihood of successful sperm retrieval compared to cTESE (52% versus 35%, respectively) ⁽⁹⁴⁾. However, a more recent systematic review and meta-analysis showed no difference between the pooled sperm retrieval rate of mTESE and cTESE. This finding was consistent when considering only randomized controlled trials or high-quality studies. On the contrary, when considering only the studies directly comparing between both techniques the sperm retrieval rate was significantly higher with the mTESE (57% versus 39%). Furthermore, this review showed that the sperm retrieval rate was not affected by age or hormonal status at diagnosis; however, it was correlated with the testicular volume. Retrieved sperms resulted in a live birth rate of 28% per ICSI cycle ⁽⁹⁵⁾. However, mTESE may be associated with lower complication rates compared to cTESE ⁽⁹⁸⁾. Interestingly, a recent systematic review and meta-analysis demonstrated that the outcomes of ICSI (including fertilization, implantation, and clinical pregnancy) was not affected by whether the sperm was fresh or frozen-thawed ⁽⁹⁹⁾.

On the other hand, donor sperm has been used as a treatment for male infertility for more than a century and it has been offered for NOA patients who failed sperm retrieval. However, in Arabic and Islamic countries like Egypt, this treatment modality is obsolete due to the religious and cultural constraints.

135.4 Idiopathic male infertility and Oligo-astheno-teratozoospermia (OAT)

Oligo-astheno-teratozoospermia (OAT) is a clinical condition, with a reduced number of spermatozoa in the ejaculate, which is also characterised by a reduced motility and morphology; often referred to as OAT syndrome (OATs) of unknown etiology.

- Empirical treatments
- Life-style modification (weak recommendation)
- Weight loss (weak recommendation)
- Physical activity (weak recommendation)
- Smoking cessation (weak recommendation)
- Alcohol consumption (weak recommendation)
- Antioxidant treatment: oxidative stress may induce idiopathic infertility, so antioxidant may show a response in treatment of Idiopathic Male Factor Infertility (weak recommendation)
- Idiopathic Male Factor Infertility

There is some evidence that FSH treatment increases sperm parameters in idiopathic oligozoospermic men with FSH levels within the normal range (generally 1.5 - 8 mIU/mL). It has also been reported that FSH may improve sperm DNA fragmentation rates as well as ameliorating AMH and inhibin levels. FSH treatment resulted in higher live birth and pregnancy rates compared to either placebo or no treatment. (Strong recommendation).⁽¹⁰⁰⁾

Table 205: Recommendations on the management of NOA

Recommendations	Strength Rating
1. It is strongly recommended to perform multiple testicular biopsies during the cTESE or mTESE in men with NOA to identify areas of spermatogenesis, provide sperms for cryopreservation/IVF, and diagnose germ cell neoplasia	Strong
2. mTESE may be associated with higher sperm retrieval rates (SRR) compared to other techniques (cTESE and TESA)	Strong
3. In patients with NOA, the results of ICSI is not affected by the status of sperm (fresh versus frozen-thawed)	Strong
4. TESA is not recommended in patients with NOA due to the modest retrieval rates	Strong

5. In patients with NOA due to hypogonadotropic hypogonadism, it is recommended to use hormonal treatment such as gonadotropin releasing hormone (GnRH). On the contrary, the use of testosterone is contraindicated.	Strong
6. Considering the religious and cultural environment in Arabic countries, it is obsolete to offer donor sperm or adoption for NOA patients who failed sperm retrieval.	Strong

Microsurgical reconstruction of the vas deferens is associated with 70-95% recovery of sperms in the normal ejaculate and may result in 30-75% normal pregnancy without the need for ARTs ⁽¹⁰¹⁾. Similarly, transurethral resection of ejaculatory duct is associated with successful normal pregnancy in 25% of patients ⁽¹⁰²⁾.

Table 206: Recommendations on the management of OA

Recommendations	Strength Rating
1. In patients with vasal or epididymal obstruction, it is recommended to perform microsurgical vasovasostomy, vasoepididymostomy or tubule-vasostomy	Strong
2. Sperm retrieval may also be performed at the time of microsurgical reconstruction to provide the patient with an extra chance of success without the need of second procedure if failed reconstruction and IVF/ICSI is planned	Weak
3. Transurethral resection of ejaculatory duct is considered in patients with ejaculatory duct obstruction	Strong
4. Sperm retrieval techniques are only recommended if cryopreservation of the retrieved sperm is possible in the facility	Strong
5. The timing of sperm retrieval in relation to the oocyte retrieval should be based on the patient preference, the surgeon expertise and available facilities	Strong

136 POST-PUBERTAL CRYPTORCHIDISM

Given the small number of patients with this condition, it has been difficult to establish a standard treatment of post-pubertal cryptorchidism ⁽¹⁰³⁾. Post-pubertal cryptorchid testes cannot produce spermatozoa, associated with impaired endocrine function but have a significant risk of malignant changes and hence orchiectomy was the standard of care ^(104,105). On the contrary, successful testicular sperm extraction and paternity in an azoospermic man after bilateral post-pubertal orchiopexy was reported ⁽¹⁰⁶⁻¹⁰⁸⁾. Orchiectomy, orchiopexy, and observation with no operation are the treatment options for post-pubertal cryptorchidism ⁽¹⁰⁹⁾.

Table 207: Recommendations on the management post-pubertal cryptorchidism

Recommendations	Strength Rating
1. In unilateral post-pubertal cryptorchidism with normal contralateral testis below 50 years of age, the preferred treatment is orchiectomy due to the high risk of malignancy.	Strong
2. In palpable unilateral post-pubertal cryptorchidism with normal contralateral testis above 50 years of age, due to very low incidence of malignancy and the associated risk of mortality during surgery, the preferred treatment is observation.	Weak
3. In bilateral cases or single testis when fertility and patient's endocrine function is concerned, orchiopexy might be the preferred treatment with close follow up by regular self-examination.	Weak
4. Laparoscopy is the preferred approach in post-pubertal cryptorchidism with non-palpable testes.	Strong

137 MALE HYPOGONADISM

137.1 Introduction

Testosterone is essential for the development and maintenance of male sexual organ and function. In addition, it has a role in maintaining body composition, erythropoiesis, bone and teeth and cognitive function. Also, Intra-testicular testosterone (ITT) is an absolute prerequisite for normal spermatogenesis normally; ITT concentrations are roughly 50–100 times serum levels. Reduction of ITT to less than 20 ng/mL results in significant reduction of spermatogenesis ⁽¹¹⁰⁾.

The current guideline aims to provide practical recommendations for diagnosis and proper management of hypogonadism in infertile men.

137.2 Definition and epidemiology

Male hypogonadism is a clinical syndrome of androgen deficiency which has a negative impact on male fertility and sexual function ⁽¹¹¹⁻¹¹⁶⁾. The incidence in men aged 40-79 varies from 2.1-5.7%. It is more prevalent in older men, obese, those with co-morbidities, and in men with poor health status ^(113,115-119). Moreover, 20%–30% of infertile men will be found to have low T or increased LH levels ⁽¹¹⁰⁾. Hypogonadism results from a defect at various level of hypothalamo--pituitary axis. Primary (testicular) form is the most common form associated with low T level, impaired spermatogenesis and elevated gonadotrophins. Secondary (hypogonadotropic) hypogonadism is caused by central defect in the hypothalamus or pituitary gland with reduction of gonadotrophin and or GnRH ⁽¹¹¹⁾.

Table 208: Recommendations on definition and epidemiology of hypogonadism

Recommendations	Strength Rating
1.Male hypogonadism is a clinical and biochemical syndrome of androgen deficiency which adversely affect male sexual function and infertility	Strong
2.Male hypogonadism results from defects at various levels of the hypothalamo pituitary-testis (HPG) axis.	Strong
3.It can result from an impairment of Testosterone action because of decreased bioavailability or because of androgen receptor alterations.	Strong

137.3 Evaluation of hypogonadal men

Hypogonadism is diagnosed by manifestations of T deficiency on at least two occasions. Manifestation of T deficiency vary according to the age of onset, duration and the severity of the deficiency ⁽¹¹¹⁻¹¹⁶⁾. The cut-off value of lowest normal level of testosterone varies according to the different medical societies. Free T level is estimated if there is a discrepancy between

symptoms and total testosterone level (close to lower normal value) and abnormal SHBG ⁽¹¹³⁾. Patients' evaluation includes; in addition, patient examination to assess symptoms, physical examination for body habitus, signs of virilization and testicular examination as well as DRE in men >50 years old. In addition, FSH and LH is recommended to be assessed in case of seeking fertility ^(111–116).

Table 209: Recommendations on diagnosis of hypogonadism

Recommendations	Strength Rating
1. The clinical diagnosis of hypogonadism is only made when patients have low total testosterone levels below 350 ng/dl (12.1 nmol/L) combined with symptoms and/or signs of androgen deficiency.	Strong
2. The diagnosis of low testosterone should be made only after s. TT measurements are taken early morning (7-11 Am) in the fasting state on two separate occasions.	Strong
3. In men with low testosterone, it is recommended to measure LH to differentiate between primary and secondary hypogonadism.	Strong

137.3.1 Management of infertile men with hypogonadism

Underlying causes of hypogonadism especially modifiable causes should be evaluated and properly corrected. Exogenous testosterone results in negative feedback on the hypothalamic-pituitary axis, inhibiting GnRH, and, thus, inhibition of the secretion of FSH and LH. Suppression of gonadotropins results in a decrease in ITT levels and overall T production and consequently impairs spermatogenesis. So, TRT should be avoided in infertile men who are seeking conception ⁽¹²⁰⁾. The more appropriate approach is to increase endogenous T. This can be accomplished by human chronic gonadotrophin, anti-estrogens and aromatase inhibitors.

137.3.2 Human chorionic gonadotropin (hCG)

It stimulates testosterone production of Leydig cells. Normal physiological serum levels can be achieved with a standard dosage of 1,500-5,000 IU administered IM or SC twice weekly. Treatment for 4 months can initiate spermatogenesis. A combined treatment with FSH treatment (usually 150 IU three times weekly intramuscular or subcutaneous) is required for maintenance of quantitatively normal spermatogenesis ^(118,121). There is insufficient information about the therapeutic and adverse effects of long-term hCG treatment. This type of treatment can therefore not be recommended for long-term treatment of male hypogonadism, except in patients in whom fertility treatment is indicated ⁽¹¹¹⁾.

137.3.3 Selective estrogen receptors modulators (SERM):

Clomiphene competitively binds to ERs on the hypothalamus and pituitary gland. It increases secretion of GnRH from the hypothalamus which stimulates pituitary gonadotropin production

that could stimulate both testicular production of testosterone and spermatogenesis. Common dosing starts at 25 mg orally every other day with upward titration to 50 mg daily, as needed. It has been commonly used for the empiric treatment of infertile men with secondary hypogonadism ⁽¹¹⁰⁾. Enclomiphene citrate is a recently used drug with reported increased morning serum T, E₂, and LH and FSH levels in men with secondary hypogonadism and preserve sperm production ⁽¹²²⁾. Patients on long-term treatment should be warranted of the increased risk of venous thromboembolic complications and reduced bone density. Tamoxifen citrate is another oral SERM. Although the studies on tamoxifen use in men have largely focused on those with infertility, its mechanism of action suggests it can also be used to raise testosterone levels in hypogonadal men with elevated estradiol level. In men with oligospermia, it was associated with statistically significant increase in serum gonadotropins, testosterone, and semen parameters ⁽¹²³⁾.

137.3.4 Non-steroidal aromatase inhibitors (Anastrozole and Letrozole):

Indirectly increase serum levels of LH, FSH, and testosterone by blocking the conversion of T to estradiol which inhibit gonadotrophin secretion. Aromatase inhibitors have been used to treat men with idiopathic male infertility, primarily men with lower serum T-to-E₂ ratios (<10), and men with hypogonadism, often related to obesity. They also have been used for normalization of serum T levels before microscopic testicular sperm extraction (TESE) in men with Klinefelter syndrome ⁽¹¹⁰⁾. Also, addition of anastrozole increased sperm concentration and motility in oligoasthenospermia men not responding to anti-estrogen (tamoxifen) ⁽¹²⁴⁾. Follow-up of liver function and blood pressure are important during treatment with aromatase inhibitor. Other side effects include rash, paresthesia, malaise, aches, peripheral edema, glossitis, anorexia, nausea/vomiting, and, rarely, alopecia. Long-term suppression of E₂ may be associated with osteoporosis and osteopenia ⁽¹¹⁰⁾.

In infertile men with primary hypogonadism, fertility can be treated using artificial reproductive techniques (ART) ^(120,121).

Table 210: Recommendations on the management of infertility in hypogonadal men

Recommendations	Strength Rating
1. TRT is contraindicated in infertile men with hypogonadism and trying to conceive.	Strong
2. In infertile men with hypogonadotrophic hypogonadism, hCG, hMG and FSH are the recommended treatment	Strong
3. In primary hypogonadism wishing to conceive, ART is considered	Strong

138 ART AND MALE INFERTILITY

138.1 Introduction

Male factor infertility stands as a common infertility etiology, identified partly or completely in up to 50% of infertile couples ⁽⁷⁾. When faced with medically-explained cases of infertility, the current principle recommendation given is to pharmacologic and surgical treatment therapies as the first line of treatment ^(125,126). For a substantial portion of men are diagnosed with idiopathic male infertility, empiric medications, nutraceuticals vitamins, and lifestyle changes based on theoretical concepts is still recommended as a first line treatment ⁽¹²⁷⁾. Where empiric or specific treatments are not indicated or have failed to achieve natural conception after at least two spermatogenic cycles, ARTs are recommended for alleviating male factor infertility ^(125,128).

Male factor infertility management should first consider optimization of the female partner. The use of ART lead rapidly to pregnancy, thus it must be considered if the female partner with advanced maternal age and/or has diminished ovarian reserve ⁽¹²⁹⁾.

138.2 Intrauterine insemination (IUI)

IUI is a cost-effective and less invasive approach that involves placement of prepared sperm into the uterine cavity timed around ovulation ⁽¹³⁰⁾. It is proven that IUI successfully improve the likelihood of successful pregnancy for couples with idiopathic or with mild to moderate male factor infertility, therefore it must be the first-choice option ⁽¹³¹⁾. The available evidence strongly recommends that IUI must be performed with semen samples with at least one million progressive motile spermatozoa ⁽¹³²⁾.

Table 211: Recommendations on IUI

Recommendations	Strength Rating
1. IUI should be the first choice for couples with idiopathic infertility with at least one million progressive motile sperm count (Not responding to treatment options)	Strong

138.3 In vitro fertilization (IVF)

IVF bypasses the fallopian tubes and is usually recommended for women who have badly damaged or absent tubes or when no specific explanation for infertility. For patients with idiopathic or with mild male factor fertility, that have several failed rounds of IUI, the physician and patient should make the decision to move to IVF ^(133–135). IVF is not recommended for other indications of male factor infertility because it is associated with lower fertilization and pregnancy charges ⁽¹³⁶⁾.

Table 212: Recommendations on IVF

Recommendations	Strength Rating
1. Counsel patients with idiopathic or with mild to moderate male factor fertility, that have several failed rounds of IUI, to have IVF trail	Strong

138.4 Intracytoplasmic sperm injection (ICSI)

Since 1992, the introduction of ICSI, in which a single sperm is then directly injected into the cytoplasm of an oocyte, has revolutionized the treatment of male infertility⁽¹³⁷⁾. ICSI has proven to be vital for couples with severe male factor infertility in whom IVF is not an option⁽¹³⁸⁾, including men with severely impaired semen analysis (Sperm concentration $< 2 \times 10^2$ and/or sperm motility $< 5\%$ and/or strict criteria normal morphology $< 4\%$), OA and NOA patients⁽¹³⁸⁾. In contrast, many studies demonstrated that routine use of ICSI in unexplained infertility was not recommended to improve the clinical outcomes⁽¹³⁹⁾. However, couples with unexplained or with mild to moderate male factor infertility but suffering from poor or failed fertilization after IVF are recommended to undergo ICSI treatment⁽¹⁴⁰⁾. Moreover, infertile men with retrograde ejaculation or anejaculation should be counseled for testicular sperm retrieval followed by ICSI is the best option⁽¹⁴¹⁾. ICSI is also recommended for patients with globozoospermia to overcome the acrosome dysfunction⁽¹⁴²⁾. Furthermore, Necrospemic patients are recommended to undergo ICSI using testicular sperm retrieval^(143,144). ICSI is also indicated for infertile men with anti-sperm antibodies^(145,146).

Although ICSI is well established and provides patients with severely impaired sperm quality with an opportunity to father a child, the utilization of scarce and unselected spermatozoa in some cases with severe oligozoospermia or cryptozoospermia often have a lower ability to fertilize. Increasing evidence supports sperm retrieval from the seminiferous tubules that could provide more consistent fertilization and pregnancy outcomes than those retrieved from the ejaculate in such cases^(147–149).

Table 213: Recommendations on ICSI

Recommendations	Strength Rating
1. ICSI is recommended for severe oligoasthenoazoospermia, obstructive azoospermia and non-obstructive azoospermia	Strong
2. Couples with unexplained or with infertility but suffered from poor or failed fertilization after IVF are recommended to undergo ICSI treatment	Strong
3. Infertile men with retrograde ejaculation or anejaculation should be counseled for sperm retrieval and IVF/ICSI	Strong

4. ICSI is considered for patients with globozoospermia to overcome the acrosome dysfunction	Weak
5. Necrostermic patients are recommended to undergo ICSI using testicular sperm retrieval	Weak
6. Indicate ICSI for infertile men with anti-sperm antibodies	Weak
7. Use testicular sperm for patients with cryptozoospermia undergoing ICSI treatment	Weak

138.5 Preimplantation genetic testing (PGT)

PGT is a major diagnostic tool to prevent transmission of any known genetic disorder after ICSI. Chromosomal defects in infertile men accounts for 2-15%.The chromosomal abnormalities involve the sex chromosomes in 3.8 % cases and the autosomes in 1.3 % of cases ⁽¹⁵⁰⁾.Therefore, PGT is recommended for male infertility, in particular, severe cases ^(151–153).

Where a specific genetic disorder associated with male infertility is known or suspected, PGT should be offered. Moreover, infertile men who have genetic abnormalities after karyotype testing should be offered PGT. For example, Klinefelter’s syndrome, with either m-TESE or ejaculate, it is recommended to combine ICSI with PGT for selecting normal embryos to prevent the transmission of genetic anomalies to the offspring ^(154,155).

Table 214: Recommendations on PGT

Recommendations	Strength Rating
1. Where a specific genetic disorder associated with male infertility is known or suspected, PGT should be offered.	Weak

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