

EAU GUIDELINES ON SEXUAL AND REPRODUCTIVE HEALTH

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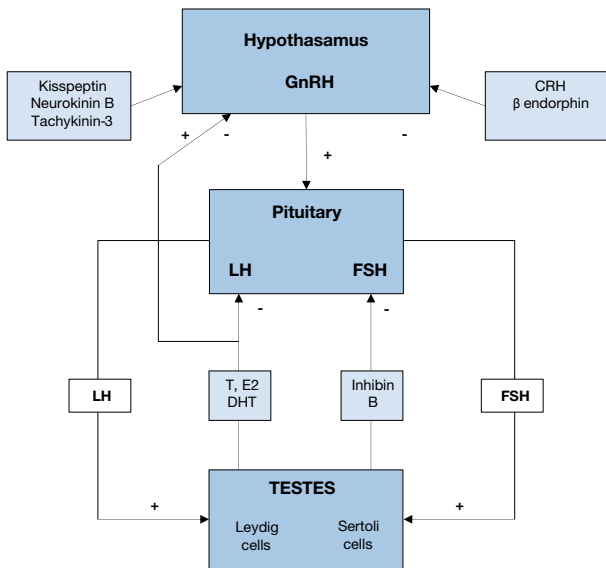
Introduction

This document presents a concise overview of the medical aspects relating to male sexual and reproductive health and combines the former guidelines on Male Sexual Dysfunction, Male Infertility and Male Hypogonadism.

Male Hypogonadism

Male Hypogonadism, also known as Testosterone Deficiency, is a disorder associated with decreased functional activity of the testes, with decreased production of androgens and/or impaired sperm production. It may adversely affect multiple organ functions and quality of life (QoL). The prevalence increases with age.

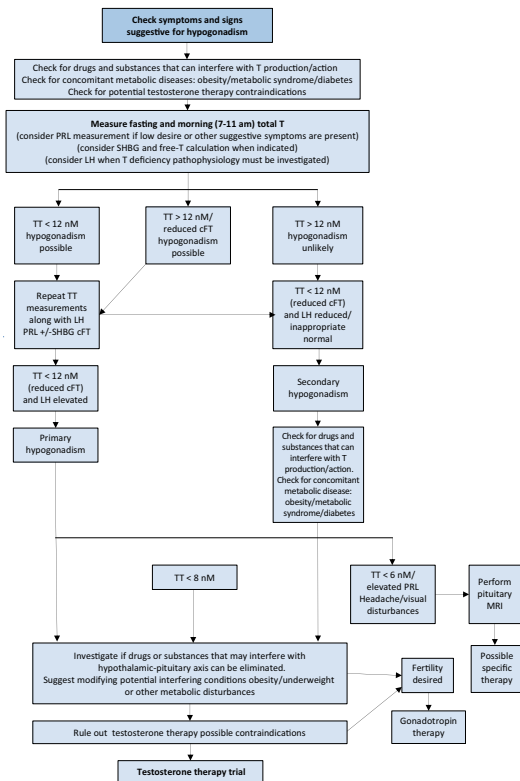
Figure 1: Physiology of testosterone production



GnRH = gonadotropin releasing hormone; LH = luteinising hormone; FSH = follicular stimulating hormone; T = testosterone; E2 = 7- β -estradiol; DHT = dehydroepiandrosterone; CRH = corticotrophin releasing hormone.

Diagnostic evaluation of Late-Onset Hypogonadism

Figure 2: Diagnostic evaluation of late-onset hypogonadism



TT = total testosterone; cFT = calculated free testosterone;
PRL = prolactin; SHBG = sex hormone-binding globulin;
LH = luteinising hormone; MRI = magnetic resonance imaging.

Recommendations for the diagnostic evaluation of late-onset hypogonadism

| Recommendations | Strength rating |
|---|-----------------|
| Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action. | Strong |
| Total testosterone must be measured in the morning (07.00 and 11.00 hours) and in the fasting state, with a reliable laboratory assay. | Strong |
| Repeat total testosterone on at least two separate occasions when < 12 nmol/L and before starting testosterone therapy. | Strong |
| 12 nmol/L total testosterone (3.5 ng/mL) represents a reliable threshold to diagnose late onset hypogonadism (LOH). | Strong |
| Consider sex hormone-binding globulin and free-testosterone calculation when indicated. | Strong |
| Calculated free-testosterone < 225 pmol/L has been suggested as a possible cut-off to diagnose LOH. | Weak |
| Analyse luteinising hormone and follicle-stimulating hormone serum levels to differentiate between primary and secondary hypogonadism. | Strong |
| Consider prolactin (PRL) measurement if low sexual desire (or other suggestive signs/symptoms) and low or low-normal testosterone is present. | Strong |

| | |
|--|--------|
| Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or specific symptoms of a pituitary mass and/or presence of other anterior pituitary hormone deficiencies. | Strong |
| Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L). | Weak |

Recommendations for screening men for late-onset hypogonadism

| Recommendations | Strength rating |
|--|-----------------|
| Screen for late-onset hypogonadism (LOH) (including in T2DM) only in symptomatic men. | Strong |
| Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have low specificity. | Strong |

Recommendations for disease management

| Recommendations for testosterone therapy outcome | Strength rating |
|--|-----------------|
| The use of testosterone therapy in eugonadal men is not indicated. | Strong |
| Use testosterone therapy as first-line treatment in patients with symptomatic hypogonadism and mild erectile dysfunction (ED). | Strong |
| Use combination of phosphodiesterase type 5 inhibitors (PDE5Is) and testosterone therapy in more severe forms of ED as it may result in better outcomes. | Weak |

| | |
|--|--------|
| Use conventional medical therapies for severe depressive symptoms and osteoporosis. | Strong |
| Do not use testosterone therapy to improve body composition, reduce weight and benefit cardio-metabolic profile. | Weak |
| Do not use testosterone therapy to improve cognition vitality and physical strength in ageing men. | Strong |

| Recommendations for LOH choice of treatment | Strength rating |
|---|------------------------|
| Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinemia, etc). | Strong |
| Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs that can impair testosterone production; treat co morbidity before starting testosterone therapy. | Weak |
| Fully inform patients about expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, only with fully informed patients. | Strong |
| The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men. | Weak |
| Use testosterone gels rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in the case of treatment-related adverse effects. | Weak |

| Recommendations on risks factors in testosterone treatment | Strength rating |
|---|------------------------|
| Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the benefits and lack of sufficient safety data on long-term follow-up. | Weak |
| Restrict treatment to patients with a low risk for recurrent PCa (i.e., pre-operative PSA < 10 ng/mL; Gleason score < 7 [International Society for Urological Pathology grade 1]; cT1-2a)* and treatment should start after at least 1 year follow-up with PSA level < 0.01 ng/mL. | Weak |
| Safety data on the use of testosterone therapy in men treated for breast cancer are unknown. | Strong |
| Assess cardiovascular risk factors before commencing testosterone therapy. | Strong |
| Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment. | Strong |
| Treat men with hypogonadism and pre-existing CVD, venous thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels. | Weak |

| | |
|---|--------|
| Exclude a family history of venous-thromboembolism before starting testosterone therapy. | Strong |
| Monitor testosterone, haematocrit at three, six and twelve months after testosterone therapy initiation, and thereafter annually. A haematocrit > 54% should require testosterone therapy withdrawal and phlebotomy. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations. | Strong |

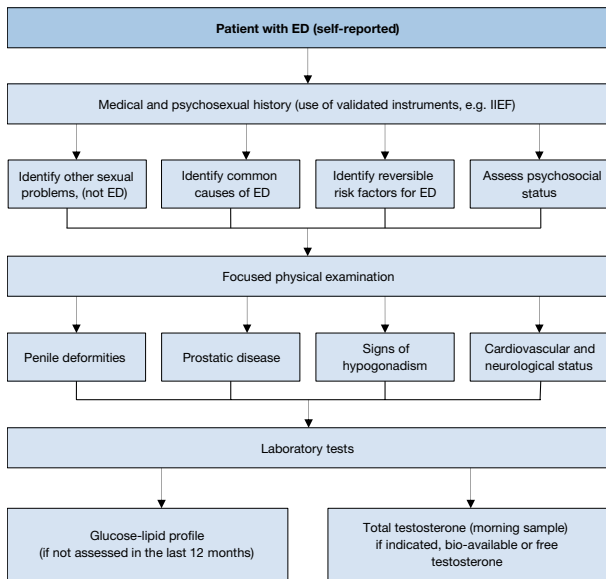
**As for EAU risk groups for biochemical recurrence of localised or locally advanced prostate cancer (see EAU Prostate Cancer Guidelines, 2022).*

Erectile dysfunction

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Erectile dysfunction may affect physical and psychosocial health and may have a significant impact on the QoL of sufferers and their partners. There is increasing evidence that ED can also be an early manifestation of coronary artery and peripheral vascular disease; therefore, ED should not be regarded only as a QoL issue, but also as a potential warning sign of CVD.

Diagnostic evaluation

Figure 3: Minimal diagnostic evaluation (basic work-up) in patients with erectile dysfunction



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

Table 1: Cardiac risk stratification (based on 2nd Princeton Consensus)

| Low-risk category | Intermediate-risk category | High-risk category |
|--|---|---|
| Asymptomatic, < 3 risk factors for CAD (excluding sex) | ≥ 3 risk factors for CAD (excluding sex) | High-risk arrhythmias |
| Mild, stable angina (evaluated and/or being treated) | Moderate, stable angina | Unstable or refractory angina |
| Uncomplicated previous MI | Recent MI (> 2, < 6 weeks) | Recent MI (< 2 weeks) |
| LVD/CHF (NYHA class I or II) | LVD/CHF (NYHA class III) | LVD/CHF (NYHA class IV) |
| Post-successful coronary revascularisation | Non-cardiac sequelae of Atherosclerotic disease (e.g., stroke, peripheral vascular disease) | Hypertrophic obstructive and other cardiomyopathies |
| Controlled hypertension | | Uncontrolled hypertension |
| Mild valvular disease | | Moderate-to-severe valvular disease |

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Table 2: Indications for specific diagnostic tests

| |
|---|
| Primary ED (not caused by acquired organic disease or psychogenic disorder). |
| Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative revascularisation 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 their partner. |
| Medico-legal reasons (e.g., implantation of penile prosthesis to document end stage ED, sexual abuse). |

Table 3: Specific diagnostic tests

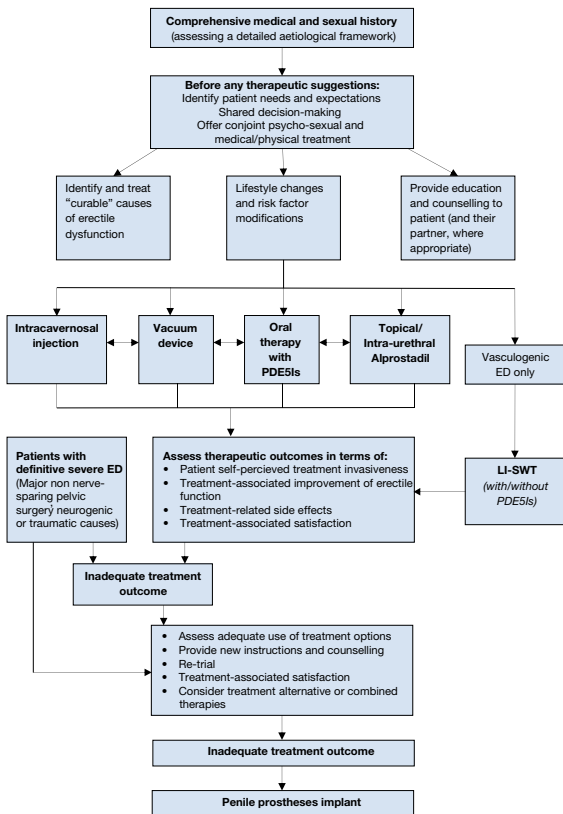
| |
|---|
| Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan® |
| Vascular studies: <ul style="list-style-type: none">- Intracavernous vasoactive drug injection- Penile dynamic duplex ultrasonography- Penile dynamic infusion cavernosometry and cavernosography- Internal pudendal arteriography |
| Specialised endocrinological studies |
| Specialised psycho-diagnostic evaluation |

Recommendations for the diagnosis of erectile dysfunction

| Recommendations | Strength rating |
|---|------------------------|
| Take a comprehensive medical and sexual history in every patient presenting with erectile dysfunction (ED). Consider psychosexual development, including life stressors, cultural aspects, and cognitive/ thinking style of the patient regarding their sexual performance. | Strong |
| Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) and the effect of a specific treatment modality. | Strong |
| Include a focused 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 |
| Assess routine laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified. | Strong |
| Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 2. | Strong |

Disease management

Figure 4: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors; LI-SWT = low-intensity shockwave treatment.

Table 4: Summary of the key pharmacokinetic data for the four PDE5Is currently EMA-approved to treat erectile dysfunction*

| Parameter | Sildenafil, 100 mg | Tadalafil, 20 mg | Vardenafil, 20 mg | Avanafil, 200 mg |
|-----------------------|-----------------------|---------------------|----------------------|---------------------|
| C_{max} | 560 µg/L | 378 µg/L | 18.7 µg/L | 5.2 µg/L |
| T_{max} (median) | 0.8-1 hours | 2 hours | 0.9 hours | 0.5-0.75 hours |
| $T_{1/2}$ | 2.6-3.7 hours | 17.5 hours | 3.9 hours | 6-17 hours |
| AUC | 1,685 µg.h/L | 8,066 µg.h/L | 56.8 µg.h/L | 11.6 µg.h/L |
| Protein binding | 96% | 94% | 94% | 99% |
| Bio-availability | 41% | NA | 15% | 8-10% |

* Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.

C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; $T_{1/2}$ = plasma elimination half-time; AUC = area under curve or serum concentration time curve.

Table 5: Common adverse events of the four PDE5Is currently EMA-approved to treat erectile dysfunction*

| Adverse event | Sildenafil | Tadalafil | Vardenafil | Avanafil, 200mg |
|---------------|------------|-----------|------------|--------------------|
| Headache | 12.8% | 14.5% | 16% | 9.3% |
| Flushing | 10.4% | 4.1% | 12% | 3.7% |
| Dyspepsia | 4.6% | 12.3% | 4% | uncommon |

| | | | | |
|------------------|------|------|------|------|
| Nasal congestion | 1.1% | 4.3% | 10% | 1.9% |
| Dizziness | 1.2% | 2.3% | 2% | 0.6% |
| Abnormal vision | 1.9% | | < 2% | None |
| Back pain | | 6.5% | | < 2% |
| Myalgia | | 5.7% | | < 2% |

* Adapted from EMA statements on product characteristics.

Table 6: Penile prostheses models available on the market

| Semi-rigid prostheses | Inflatable prostheses | |
|------------------------------------|-------------------------------------|---|
| | Two-piece | Three-piece |
| AMS Tactra™ [Boston Scientific] | AMS Ambicor™ [Boston Scientific] | Titan™ [Coloplast] |
| Genesis™ [Coloplast] | | Titan OTR NB™ (Narrow base) [Coloplast] Titan Zero Degree™ |
| Tube™ [Promedon] | | AMS 700 CX™ [Boston Scientific] |
| ZSI 100™ [Zephyr] | | AMS 700 LGX™ [Boston Scientific] |
| Virilis II™ [Subrini] | | AMS 700 CXR™ [Boston Scientific] ZSI 475™ [Zephyr] |

Recommendations for the treatment of erectile dysfunction

| Recommendations | Strength rating |
|--|-----------------|
| Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, as they are the main causes of a lack of response to phosphodiesterase type 5 inhibitors (PDE5Is). | Weak |
| Use Cognitive Behaviour Therapy as a psychological approach (include the partner) combined with medical treatment to maximise treatment outcomes. | Strong |
| Discuss with patients undergoing radical prostatectomy (any technique) about the risk of sexual changes other than erectile dysfunction (ED), including libido reduction, changes in orgasm, anejaculation, Peyronie's-like disease and penile size changes. | Strong |
| Initiate lifestyle changes and risk factor modification prior to, or at the same time, as initiating ED treatments. | Strong |
| Treat a curable cause of ED first, when found. | Weak |
| Use PDE5Is as first-line therapeutic option. | Strong |
| Use topical/intra-urethral alprostadil as an alternative first-line therapy in well informed patients who do not wish or are not suitable for oral vasoactive therapy. | Weak |

| | |
|--|--------|
| Use topical/intra-urethral alprostadil as an alternative first-line therapy, in well-informed patients, who do not wish to have intracavernous injections or in patients who prefer a less-invasive therapy. | Weak |
| Use low intensity shockwave treatment (LI-SWT) in patients with mild vasculogenic ED or as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy or desire a curable option. Use LI-SWT in vasculogenic ED patients who are poor responders to PDE5Is. | Weak |
| Use vacuum erection devices as first-line therapy in well-informed patients with infrequent sexual intercourse and comorbidity requiring non invasive, drug-free management of ED. | Weak |
| Use intracavernous injections as an alternative first-line therapy in well informed patients or as second-line therapy. | Strong |
| Do not use platelet-rich plasma to treat ED outside the confines of a clinical trial. | Weak |
| Use implantation of a penile prosthesis if other treatments fail or depending upon patient preference. | Strong |
| Data is inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy. | Strong |
| Pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/pelvic surgery and other curative treatments for prostate cancer. | Weak |

Disorders of ejaculation

Ejaculation is a complex physiological process, which is composed of emission and expulsion and is mediated by interwoven neurological and hormonal pathways. Any condition that interferes with these pathways may cause a wide range of ejaculatory disorders.

Table 7: Spectrum of ejaculatory disorders

| |
|---------------------------------|
| Premature ejaculation |
| Retarded or delayed ejaculation |
| Anejaculation |
| Painful ejaculation |
| Retrograde ejaculation |
| Anorgasmia |
| Haemospermia |

Diagnostic evaluation

Recommendations for the diagnostic evaluation of premature ejaculation

| Recommendations | Strength rating |
|--|-----------------|
| Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction. | Strong |
| Use of stopwatch-measured IELT is not compulsory in clinical practice. | Weak |

| | |
|---|--------|
| Use patient-reported outcomes in daily clinical practice. | Weak |
| Include 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. | Strong |
| Do not perform routine laboratory or neurophysiological tests. They should only be directed by specific findings from history or physical examination. | Strong |

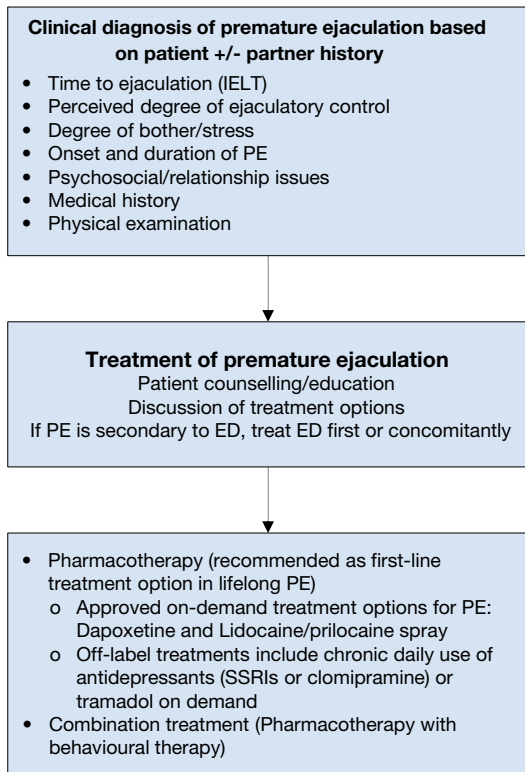
Disease management

Recommendations for the treatment of premature ejaculation

| Recommendations | Strength rating |
|--|-----------------|
| Treat erectile dysfunction (ED), and other sexual dysfunction or genitourinary infection (e.g., prostatitis) first. | Strong |
| Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE). | Strong |
| Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs). | Strong |
| Use off-label tramadol with caution as a viable on-demand alternative to on-demand SSRIs. | Strong |

| | |
|---|--------|
| Use PDE5Is alone or in combination with other therapies in patients with PE (without ED). | Strong |
| Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE. | Weak |

Figure 5: Management of premature ejaculation*



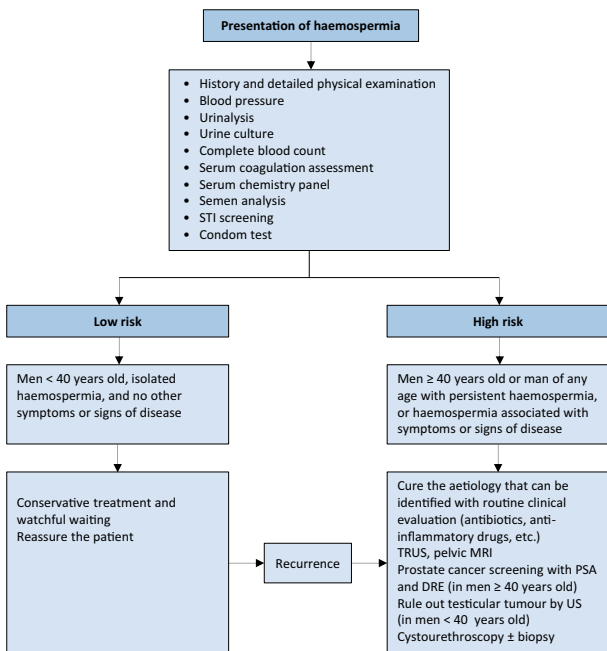
*Adapted from Lue *et al.*, 2004.

ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

Recommendations for the management of recurrent haemospermia

| Recommendations | Strength rating |
|---|-----------------|
| Perform a full medical and sexual history with detailed physical examination. | Strong |
| Men aged ≥ 40 years with persistent haemospermia should be screened for prostate cancer. | Weak |
| Consider non-invasive imaging modalities (TRUS and MRI) in men aged ≥ 40 years or men of any age with persistent or refractory haemospermia. | Weak |
| Consider invasive methods such as cystoscopy and vesiculoscopy when the non-invasive methods are inconclusive. | Weak |

Figure 6: Management algorithm for haemospermia



STI = sexually transmitted infections; PSA = prostate-specific antigen; DRE = digital rectal examination; US = ultrasonography; TRUS = transrectal ultrasonography; MRI = magnetic resonance imaging.

Low Sexual Desire

It has always been a challenge to define sexual desire because of its complex nature and the fact it can be conceptualised in many different ways. According to the ICD-10, lack or loss of sexual desire should be the principal problem with no other sexual problems accompanying it such as ED. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), male hypoactive sexual desire disorder was defined as *“the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity”*. The judgment of deficiency is made by the clinician, taking into account other factors that may affect sexual function, such as age and socio-cultural factors in an individual’s life. According to the fourth International Consultation on Sexual Medicine (ICSM-IV), the definition of male hypoactive sexual desire disorder was proposed as a *“persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)”*.

Table 8: The list of common causes of low sexual desire in men

| |
|------------------------------------|
| Androgen deficiency |
| Hyperprolactinaemia |
| Anger and anxiety |
| Depression |
| Relationship conflict |
| Stroke |
| Antidepressant therapy |
| Epilepsy |
| Post-traumatic stress syndrome |
| Renal failure |
| Coronary disease and heart failure |

| |
|--|
| Ageing |
| HIV infection |
| Body-building and eating disorders |
| Erectile dysfunction |
| Prostatitis/chronic pelvic pain syndrome |

Psychological intervention

Findings on treatment efficacy for psychological intervention are scarce. Accordingly, recommendations must be interpreted with caution. Psychological interventions with a focus on cognitive and behavioural strategies may be beneficial for low sexual desire (LSD) in men, as well as mindfulness treatments. Since both members of a couple may experience age-related changes concurrently and interdependently, it could be helpful to address the sexual health needs of the aging couple (including LSD) as a whole rather than treating the individual patient.

Disease management

Recommendations for the treatment of low sexual desire

| Recommendations | Strength rating |
|---|-----------------|
| Perform the diagnosis and classification of low sexual desire (LSD) based on medical and sexual history, which could include validated questionnaires. | Weak |
| Include physical examination in the initial assessment of LSD to identify anatomical abnormalities that may be associated with LSD or other sexual dysfunctions, particularly erectile dysfunction. | Weak |
| Perform laboratory tests to rule out endocrine disorders. | Strong |

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|---|--------|
| Modulate chronic therapies which can negatively impact toward sexual desire. | Weak |
| Provide testosterone therapy if LSD is associated with signs and symptoms of testosterone deficiency. | Strong |

Penile curvature

Congenital penile curvature (CPC) results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of the cases curvature is ventral but can be lateral and rarely dorsal.

Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish the diagnosis of CPC. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and a severe curvature can make intercourse difficult or impossible. Physical examination during erection (autophotograph or after intracavernosal injection of vasoactive drugs) is useful to document curvature and exclude other pathologies.

Disease management

The treatment of this disorder is surgical correction deferred until after puberty. Surgical treatments for CPC generally share the same principles as in Peyronie's disease (presented in detail in the next section). Nesbit's procedure with excision of an ellipse of the tunica albuginea is the optimum surgical treatment but many other techniques have been described and employed. Plication techniques are widely used including techniques producing a de-rotation of the corporal bodies. Most of the time, dissection and mobilisation of the penile dorsal neurovascular bundle are required in order to avoid loss of sensation and ischaemia to the glans penis.

| Recommendation for the treatment of congenital penile curvature | Strength rating |
|---|------------------------|
| Use plication techniques with or without neurovascular bundle dissection (medial/lateral) for satisfactory curvature correction, although there is currently no optimum surgical technique. | Strong |

Peyronie's disease

An insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology of the disease. Abnormal wound healing leads to the remodelling of connective tissue into a fibrotic plaque. Penile plaque formation can result in curvature which, if severe, may impair penetrative sexual intercourse. The most commonly associated comorbidity and risk factors are diabetes, hypertension, dyslipidaemia, ischaemic cardiopathy, autoimmune diseases, ED, smoking, excessive consumption of alcohol, low testosterone and pelvic surgery (e.g., radical prostatectomy).

Two phases of the disease can be distinguished. The first is the active inflammatory phase, which may be associated with painful erections and a palpable nodule or plaque in the tunica of the penis; typically, but not invariably, a penile curvature begins to develop. The second is the fibrotic phase with the formation of hard, palpable plaques that can calcify, with stabilisation of the disease and development of the penile deformity.

Diagnostic evaluation

The aim of the initial evaluation is to obtain information on the presenting symptoms and their duration (e.g., pain on erection, palpable nodules, deformity, length and girth and erectile function). It is important to obtain information on the distress

caused by the symptoms and the potential risk factors for ED and PD.

Recommendations for the diagnostic evaluation of Peyronie's disease

| Recommendations | Strength rating |
|--|-----------------|
| Take a medical and sexual history of patients with Peyronie's disease (PD), include duration of the disease, pain on erection, penile deformity, difficulty in vaginal/anal intromission due to disabling deformity and erectile dysfunction (ED). | Strong |
| Take a physical examination, including assessment of palpable plaques, stretched or erect penile length, degree of curvature (self-photography, vacuum-assisted erection test or pharmacological-induced erection) and any other related diseases (e.g., Dupuytren's contracture, Ledderhose disease) in patients with PD. | Strong |
| Use the intracavernous injection method in the diagnostic work-up of PD to provide an objective assessment of penile curvature with an erection. | Weak |
| Use the PD specific questionnaire especially in clinical trials, but mainstream usage in daily clinical practice is not mandatory. | Weak |
| Do not use ultrasound (US), computed tomography or magnetic resonance imaging to assess plaque size and deformity in everyday clinical practice. | Weak |

| | |
|---|------|
| Use penile Doppler US in the case of diagnostic evaluation of ED, to evaluate penile haemodynamic and vascular anatomy, and to assess location and calcification of plaques, especially prior to surgery. | Weak |
|---|------|

Disease management

Non-operative treatment

Table 9: Conservative treatments for Peyronie's disease

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|--|
| Oral treatments |
| Non-steroidal anti-inflammatory drugs (NSAIDs) |
| Phosphodiesterase type 5 inhibitors |
| Intralesional treatments |
| Verapamil |
| Nicardipine |
| Clostridium collagenase |
| Interferon $\alpha 2B$ |
| Hyaluronic acid |
| Botulinum toxin |
| Topical treatments |
| H-100 gel |
| Extracorporeal shockwave treatment |
| Other |
| Traction devices |
| Multimodal treatment |

Recommendations for the non-operative treatment of Peyronie's disease

| Recommendations | Strength rating |
|--|-----------------|
| Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient. | Strong |
| Discuss with patients all the available treatment options and expected results before starting any treatment. | Strong |
| Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifylline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD). | Strong |
| Non-steroidal anti-inflammatory drugs can be used to treat penile pain in the acute phase of PD. | Strong |
| Extracorporeal shockwave treatment (ESWT) can be used to treat penile pain in the acute phase of PD. | Weak |
| Phosphodiesterase type 5 inhibitors can be used to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration. | Weak |
| Intralesional therapy with interferon alpha-2b may be offered in patients with stable curvature dorsal or lateral > 30° seeking a minimal invasive procedure. | Strong |

| | |
|--|--------|
| Intralesional therapy with collagenase <i>Clostridium histolyticum</i> may be offered in patients with stable PD and dorsal or lateral curvature > 30°, who request non-surgical treatment, although the placebo effects are high. | Strong |
| Do not offer intralesional treatment with steroids to reduce penile curvature, plaque size or pain. | Strong |
| Do not use intralesional platelet-rich plasma or hyaluronic acid – either alone or in combination with oral treatment – to reduce penile curvature, plaque size or pain outside the confines of a clinical trial. | Weak |
| Do not offer ESWT to improve penile curvature and reduce plaque size. | Strong |
| Penile traction devices and vacuum devices may be offered to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited. | Weak |

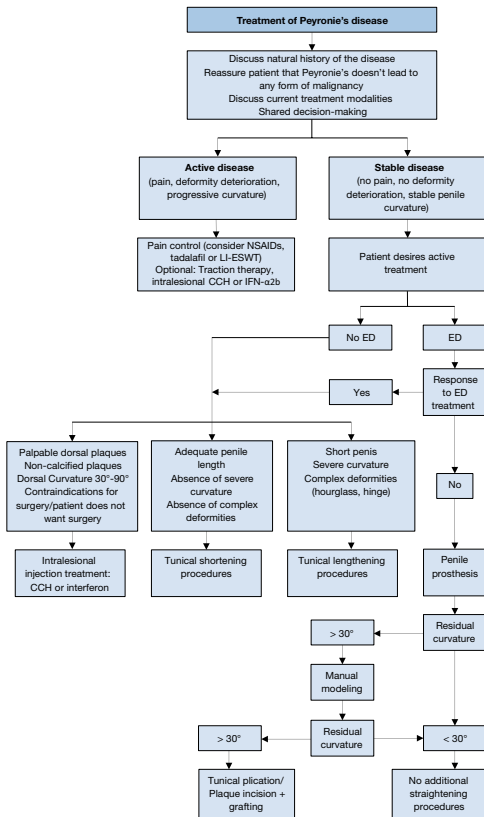
Surgical treatment

Recommendations for the surgical treatment of Peyronie's disease

| Recommendations | Strength rating |
|---|-----------------|
| Perform surgery only when Peyronie's disease (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, and intercourse is compromised due to the deformity. | Strong |

| | |
|---|---------------|
| <p>Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations.</p> | <p>Strong</p> |
| <p>Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, less severe curvatures and absence of complex deformities (hourglass or hinge). The type of procedure used is dependent on surgeon and patient preference, as no procedure has proven superior to its counterparts.</p> | <p>Weak</p> |
| <p>Use tunical lengthening procedures for patients with PD and normal erectile function, without adequate penile length, severe curvature or presence of complex deformities (hourglass or hinge). The type of graft used is dependent on the surgeon and patient factors, as no graft has proven superior to its counterparts.</p> | <p>Weak</p> |
| <p>Use the sliding techniques with extreme caution, as there is a significant risk of life changing complications (e.g., glans necrosis).</p> | <p>Strong</p> |
| <p>Do not use synthetic grafts in PD reconstructive surgery.</p> | <p>Strong</p> |
| <p>Use penile prosthesis implantation, with or without any additional procedure (modelling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.</p> | <p>Strong</p> |

Figure 7 : Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; LI-ESWT= low-intensity extracorporeal shockwave treatment; US = ultrasound; CCH = collagenase clostridium histolyticum; NSAIDs = non-steroidal anti-inflammatory drugs.

Priapism

Priapism is a persistent erection in the absence of sexual stimulation that fails to subside. It can be divided into ischaemic, non-ischaemic and stuttering priapism.

Ischaemic (low-flow or veno-occlusive) priapism

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow. Ischaemic priapism is the most common subtype of priapism, accounting for > 95% of all episodes.

Diagnostic evaluation

Table 10: Key points when taking the history of priapism

| |
|--|
| Duration of erection |
| Presence and severity of pain |
| Previous episodes of priapism and methods of treatment |
| Current erectile function, especially the use of any erectogenic therapies prescription or nutritional supplements |
| Medications and recreational drug use |
| Sickle cell disease, haemoglobinopathies, hypercoagulable states, vessel vasculitis |
| Trauma to the pelvis, perineum or penis |

Table 11: Key findings in priapism

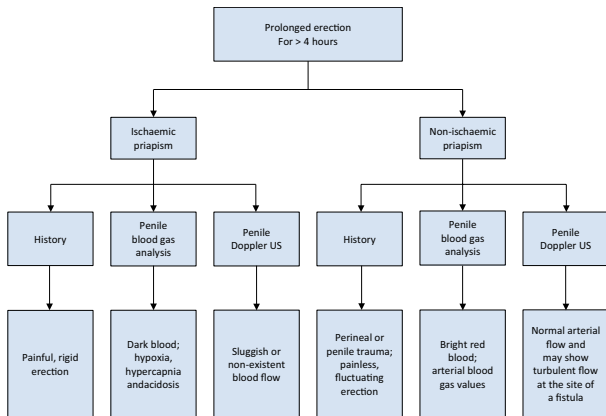
| | Ischaemic priapism | Non-ischaemic priapism |
|----------------------------------|---------------------------|-------------------------------|
| Corpora cavernosa fully rigid | Typically | Seldom |
| Penile pain | Typically | Seldom |
| Abnormal penile blood gas | Typically | Seldom |
| Haematological abnormalities | Sometimes | Seldom |
| Recent intracavernosal injection | Sometimes | Sometimes |
| Perineal trauma | Seldom | Typically |

Table 12: Typical blood gas values

| Source | pO₂ (mmHg) | pCO₂ (mmHg) | pH |
|--|------------------------------|-------------------------------|-----------|
| Normal arterial blood (room air) (similar values are found in arterial priapism) | > 90 | < 40 | 7.40 |
| Normal mixed venous blood (room air) | 40 | 50 | 7.35 |
| Ischaemic priapism (first corporal aspirate) | < 30 | > 60 | < 7.25 |

pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen.

Figure 8: Differential diagnosis of priapism



US = ultrasound.

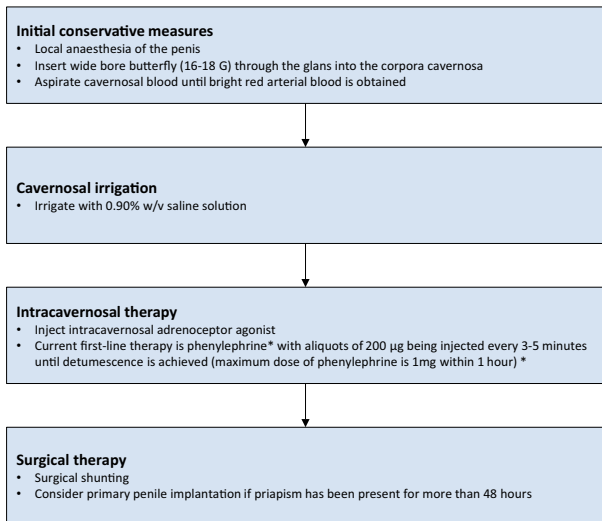
| Recommendations for the diagnosis of ischaemic priapism | Strength rating |
|---|------------------------|
| Take a comprehensive history to establish the diagnosis which can help to determine the priapism subtype. | Strong |
| Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation. | Strong |

| | |
|--|--------|
| For laboratory testing, include complete blood count, white blood cell count with blood cell differential, platelet count and coagulation profile. Directed further laboratory testing should be performed depending upon history and clinical and laboratory findings. In children with priapism, perform a complete evaluation of all possible causes. | Strong |
| Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism. | Strong |
| Perform colour duplex US of the penis and perineum before aspiration to differentiate between ischaemic and non-ischaemic priapism. | Strong |
| In cases of prolonged ischaemic priapism or refractory priapism, magnetic resonance imaging of the penis may be used as an adjunct to predict smooth muscle viability. | Weak |
| Perform selected pudendal arteriogram when embolisation is planned for the management of non-ischaemic priapism. | Strong |

Disease management of ischaemic priapism

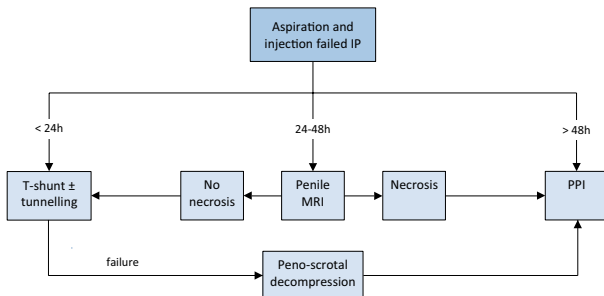
The treatment is sequential and physicians should move on to the next stage if treatment fails.

Figure 9: Medical and surgical management of ischaemic priapism



() Dose of phenylephrine should be reduced in children. It can result in significant hypertension and should be used with caution in men with cardiovascular disease. Monitoring of pulse and blood pressure is advisable in all patients during administration and for one hour afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.*

Figure 10: Algorithm on surgical management of priapism



MRI = Magnetic resonance imaging; PPI = penile prosthesis implantation; IP = ischaemic priapism.

| Recommendations for the treatment of ischaemic priapism | Strength rating |
|--|------------------------|
| Start management of ischaemic priapism as early as possible (within four to six hours) and follow a stepwise approach. | Strong |
| First, decompress the corpus cavernosum by penile aspiration and washout until fresh red blood is obtained. | Strong |
| In priapism secondary to intracavernous injections of vasoactive agents, replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step. | Strong |
| In priapism that persists despite aspiration, proceed to the next step, which is intracavernous injection of a sympathomimetic drug. | Strong |

| | |
|---|--------|
| In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, repeat these steps before considering surgical intervention. | Strong |
| Treat ischaemic priapism associated with sickle cell disease in the same fashion as idiopathic ischaemic priapism. Provide other supportive measures (intravenous hydration, oxygen administration with alkalinisation with bicarbonate, blood exchange transfusions), but do not delay initial treatment to the penis. | Strong |
| Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed. | Strong |
| Perform distal shunt surgical procedures first and combine them with tunnelling if necessary. | Weak |
| Proximal procedures may be used in cases of distal shunt failure (< 48 hours) or in patients who do not wish to proceed with immediate penile implant insertion. | Weak |
| Peri- and post-operative anticoagulation may decrease priapism recurrence. | Weak |
| A penile prosthesis may be preferred over proximal shunting particularly in delayed (> 48 hours) or refractory priapism | Weak |
| Implantation of a prosthesis may be considered in delayed presentation (> 48 hours) and in those cases refractory to injection therapy and distal shunting. | Weak |

| | |
|--|--------|
| If a shunt has been performed, then implantation of a penile prosthesis should be delayed to minimise the risk of infection and erosion of the implant. | Strong |
| The decision on which type of implant to insert is dependent on patient suitability, surgeons' experience and availability and cost of the equipment. If malleable penile prosthesis is implanted it can be later exchanged to an inflatable penile implant. | Strong |
| Patients must be fully counselled regarding the risks and benefits of implant insertion in every case of delayed presentation of refractory priapism. | Weak |

Priapism in special situations

Stuttering (recurrent or intermittent) priapism

Stuttering priapism is similar to ischaemic priapism in that it is low-flow and ischaemic and, if left untreated, can result in significant penile fibrosis, with Sickle Cell Disease being the most common cause.

| Recommendations for treatment of stuttering priapism | Strength rating |
|--|------------------------|
| Manage each acute episode similar to that for ischaemic priapism. | Strong |
| 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 |

| | |
|---|------|
| Initiate treatment with phosphodiesterase type 5 inhibitors only when the penis is in its flaccid state. | Weak |
| Use digoxin, α -adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with frequent and uncontrolled relapses. | Weak |
| Use intracavernous self-injections of sympathomimetic drugs at home for treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated. | Weak |

Non-ischaemic (high-flow or arterial) priapism

Non-ischaemic priapism is significantly less common than the ischaemic type, comprising only 5% of all priapism cases.

Diagnosis evaluation

A comprehensive history is also mandatory in the diagnosis of non-ischaemic priapism and follows the same principles as described in Table 10.

| Recommendations | Strength rating |
|--|-----------------|
| Take a comprehensive history to establish the diagnosis, which can help to determine the priapism subtype. | Strong |
| Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation. | Strong |
| Include a neurological examination if neurogenic non-ischaemic priapism is suspected. | Strong |

| | |
|---|--------|
| For laboratory testing, include complete blood count, with white blood cell differential, and coagulation profile. | Strong |
| Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism. | Strong |
| Perform colour duplex ultrasound of the penis and perineum to differentiate between ischaemic and non-ischaemic priapism. | Strong |
| Perform selected pudendal arteriography when embolisation is planned for non-ischaemic priapism. | Strong |

Disease management

| Recommendations for the treatment of non-ischaemic priapism | Strength rating |
|---|------------------------|
| As non-ischaemic priapism is not an emergency, perform definitive management at the discretion of the treating physician. | Weak |
| Manage conservatively with the use of site-specific perineal compression as the first step. Consider androgen deprivation therapy only in adults. | Weak |
| Perform selective arterial embolisation when conservative management has failed. | Strong |
| Perform first selective arterial embolisation using temporary material. | Weak |

| | |
|--|------|
| Repeat the procedure with temporary or permanent material for recurrent non-ischaeamic priapism following selective arterial embolisation. | Weak |
| Reserve selective surgical ligation of a fistula as a final treatment option when repeated arterial embolisations have failed. | Weak |

Male infertility

'Infertility is the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy in one year' (World Health Organization 2000).

Diagnostic evaluation

A focused evaluation of the male patient must always be undertaken and should include: a medical and reproductive history; physical examination; semen analysis – with strict adherence to World Health Organization (WHO) reference values for human semen characteristics, and hormonal evaluation. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and findings on semen analysis.

Semen analysis

A comprehensive andrological examination is always indicated if the semen analysis shows abnormalities when compared to reference values (Table 13).

Table 13: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

| Parameter | 2010 Lower reference limit (95% CI) | 2021 Lower reference limit (95% CI) |
|---|--|---|
| Semen volume (mL) | 1.5 (1.4-1.7) | 1.5 (1.3-1.5) |
| Total sperm number (10 ⁶ /ejaculate) | 39 (33-46) | 39 (35-40) |
| Sperm concentration (10 ⁶ /mL) | 15 (12-16) | 16 (15-18) |
| Total motility (PR + NP, %) | 40 (38-42) | 42 (40-43) |
| Progressive motility (PR, %) | 32 (31-34) | 30 (29-31) |
| Vitality (live spermatozoa, %) | 58 (55-63) | 54 (50-56) |
| Sperm morphology (normal forms, %) | 4 (3.0-4.0) | 4 (3.9-4.0) |
| Other consensus threshold values | | |
| pH | > 7.2 | > 7.2 |
| Peroxidase-positive leukocytes (10 ⁶ /mL) | < 1.0 | < 1.0 |
| Tests for antibodies on spermatozoa | | |
| MAR test (motile spermatozoa with bound particles, %) | < 50 | No evidence-based reference values. Each laboratory should define its normal reference ranges by testing a sufficiently large number of normal fertile men. |

| | | |
|--|------------|-------------------------------------|
| Immunobead test (motile spermatozoa with bound beads, %) | < 50 | No evidence-based reference limits. |
| Accessory gland function | | |
| Seminal zinc ($\mu\text{mol}/\text{ejaculate}$) | ≥ 2.4 | ≥ 2.4 |
| Seminal fructose ($\mu\text{mol}/\text{ejaculate}$) | ≥ 13 | ≥ 13 |
| Seminal neutral α -glucosidase (mU/ejaculate) | ≥ 20 | ≥ 20 |

CI = confidence intervals; MAR = mixed antiglobulin reaction; NP = non-progressive; PR = progressive (a+b motility).

* Distribution of data from the population is presented with one-sided intervals (extremes of the reference population data). The lower 5th percentile represents the level under which only results from 5% of the men in the reference population were found.

Recommendations for the diagnostic work-up of male infertility

| Recommendations | Strength rating |
|--|-----------------|
| Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of the infertile male, since this might determine decision-making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology (ART) versus surgical intervention). | Strong |

| | |
|---|--------|
| A complete medical history, physical examination and semen analysis are the essential components of male infertility evaluation. | Strong |
| Prader's orchidometer-derived testicular volume is a reliable surrogate of ultrasound (US)-measured testicular volume in everyday clinical practice. | Weak |
| Perform semen analyses according to the most recent WHO Laboratory Manual for the Examination and Processing of Human Semen (6 th edn.) indications and reference criteria or according to the previous version (5 th edn.) until a formal and complete adoption of the newly-released parameters is implemented. | Strong |
| Perform a full andrological assessment in all men with couple infertility, particularly when semen analysis is abnormal in at least two consecutive tests. | Strong |
| Include counselling for infertile men or men with abnormal semen parameters of the associated health risks. | Weak |
| In cases of oligozoospermia and azoospermia, a hormonal evaluation should be performed, including a serum total testosterone and Follicle Stimulating Hormone/Luteinising Hormone. | Weak |
| Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 10 ⁶ /mL) for diagnostic purposes. | Strong |

| | |
|--|--------|
| Do not test for Y-chromosome microdeletions in men with pure obstructive azoospermia as spermatogenesis will be normal. | Strong |
| Y-chromosome microdeletion testing may be offered in men with sperm concentrations of $< 5^6$ sperm/mL, but must be mandatory in men with sperm concentrations of $\leq 1^6$ sperm/mL. | Strong |
| Inform men with Yq microdeletion and their partners who wish to proceed with intracytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to their daughters. | Strong |
| Testicular sperm extraction (any type) should not be attempted in patients with complete deletions that include the aZFa and aZFb regions, since they are a poor prognostic indicator for retrieving sperm at surgery. | Strong |
| In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the man and his partner for cystic fibrosis transmembrane conductance regulator gene mutations, which should include common point mutations and the 5T allele. | Strong |
| Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease. | Strong |
| For men with Klinefelter syndrome, offer long-term endocrine follow-up and appropriate medical treatment. | Strong |

| | |
|--|--------|
| Do not routinely use reactive oxygen species testing in the diagnosis and management of the male partner of an infertile couple. | Weak |
| Sperm DNA fragmentation testing should be performed in the assessment of couples with recurrent pregnancy loss from natural conception and ART or men with unexplained infertility. | Strong |
| Perform scrotal ultrasound in patients with infertility, as there is a higher risk of testis cancer. | Weak |
| A multidisciplinary team discussion concerning invasive diagnostic modalities (e.g., US-guided testicular biopsy with frozen section versus radical orchidectomy versus surveillance) should be considered in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present. | Weak |
| Perform transrectal ultrasound if a partial or complete distal obstruction is suspected. | Strong |
| Consider imaging for renal abnormalities in men with structural abnormalities of the vas deferens and no evidence of cystic fibrosis transmembrane conductance regulator abnormalities. | Strong |

Special Conditions and Relevant Clinical Entities

Cryptorchidism

Cryptorchidism is the most common congenital abnormality of the male genitalia; at one year of age nearly 1% of all full-term male infants have cryptorchidism. Approximately 30% of undescended testes are non-palpable and may be located within the abdominal cavity.

| Recommendations | Strength rating |
|---|-----------------|
| Do not use hormonal treatment for cryptorchidism in post-pubertal men. | Strong |
| If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia <i>in situ</i> (formerly carcinoma <i>in situ</i>). | Strong |
| Men with unilateral undescended testis and normal hormonal function/spermatogenesis should be offered orchidectomy. | Strong |
| Men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (i.e., infertility) may be offered unilateral or bilateral orchidopexy, if technically feasible. | Weak |

Germ cell malignancy and male infertility

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years, and affects approximately 1% of sub-fertile men. Overall, sperm, cryopreservation is considered standard practice in all patients with cancer and not only those with testicular cancer. As such, it is important to stress that all men with cancer must be offered sperm cryopreservation prior to the

therapeutic use of gonadotoxic agents or ablative surgery which may impair spermatogenesis or ejaculation (i.e., chemotherapy; radiation therapy; retroperitoneal surgery). Men with TGCT have decreased semen quality, even before cancer treatment.

| Recommendations | Strength rating |
|---|-----------------|
| Men with testicular microcalcification (TM) should learn to perform self examination even without additional risk factors, as this may result in early detection of testicular germ cell tumour (TGCT). | Weak |
| Do not perform testicular biopsy, follow-up scrotal ultrasound (US), measure biochemical tumour markers, or abdominal or pelvic computed tomography, in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis). | Strong |
| Testicular biopsy may be offered in infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (< 12 mL), history of undescended testes and TGCT. | Weak |
| If there are suspicious findings on physical examination or US in patients with TM with associated lesions, perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multidisciplinary meeting and discussion with the patient. | Strong |

| | |
|---|------|
| Men treated for TGCT are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular risk. Men should be managed in a multi-disciplinary team setting with a dedicated late-effects clinic. | Weak |
| Sperm cryopreservation should be performed prior to planned orchidectomy, since men with testis cancer may have significant semen abnormalities (including azoospermia). | Weak |
| Men with testicular cancer and azoospermia or severe abnormalities in their semen parameters may be offered onco-testicular sperm extraction (onco-TESE) at the time of radical orchidectomy. | Weak |

Varicocele

Varicocele is a common genital abnormality, which may be associated with the following andrological conditions:

- male subfertility;
- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- hypogonadism.

| Recommendations | Strength rating |
|---|------------------------|
| Treat varicocele in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction. | Weak |
| Do not treat varicocele in infertile men who have normal semen analysis and in men with a sub-clinical varicocele. | Weak |

| | |
|--|--------|
| Treat infertile men with a clinical varicocele, abnormal semen parameters and otherwise unexplained infertility in a couple where the female partner has good ovarian reserve to improve fertility rates. | Strong |
| Varicocelectomy may be considered in men with raised DNA fragmentation with otherwise unexplained infertility or who have suffered from failed of assisted reproductive techniques, including recurrent pregnancy loss, failure of embryogenesis and implantation. | Weak |

Male accessory gland infections and infertility

Infections of the male urogenital tract are potentially curable causes of male infertility. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs). Semen analysis clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome.

| Recommendations | Strength rating |
|---|-----------------|
| Treating male accessory gland infections may improve sperm quality, although it does not necessarily improve the probability of increasing conception. | Weak |
| Data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia improve fertility outcomes. | Weak |

| | |
|---|--------|
| Refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment. | Strong |
|---|--------|

Non-Invasive Male Infertility Management

Idiopathic male infertility and OATS

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).

| Recommendations | Strength rating |
|--|-----------------|
| In men with idiopathic oligo-astheno-teratozoospermia, life-style changes including weight loss and increased physical activity, smoking cessation and alcohol intake reduction can improve sperm quality and the chances of conception. | Weak |
| No clear recommendation can be made for treatment of patients with idiopathic infertility using antioxidants, although antioxidant use may improve semen parameters. | Weak |
| No conclusive recommendations on the use of selective oestrogen receptor modulators in men with idiopathic infertility can be drawn. | Weak |

| | |
|--|------|
| No conclusive recommendations on the use of either steroidal (testolactone) or non-steroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility can be drawn, even before testis surgery. | Weak |
|--|------|

Hormonal therapy

| Recommendations | Strength rating |
|--|-----------------|
| Hypogonadotropic hypogonadism (secondary hypogonadism), including congenital causes, should be treated with combined human chorionic gonadotropin (hCG) and follicle-stimulating hormone (FSH) (recombinant FSH; highly purified FSH) or pulsed Gonadotropin-releasing hormone (GnRH) via pump therapy to stimulate spermatogenesis. | Strong |
| In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH). | Strong |
| The use of GnRH therapy is more expensive and does not offer any advantages when compared to gonadotropins for the treatment of hypogonadotropic hypogonadism. | Strong |
| In men with idiopathic oligozoospermia and FSH values within the normal range, FSH treatment may ameliorate spermatogenesis outcomes. | Weak |

| | |
|--|--------|
| No conclusive recommendations can be given on the use of high-dose FSH in men with idiopathic infertility and prior (m)TESE and therefore cannot be routinely advocated. | Weak |
| Do not use testosterone therapy for the treatment of male infertility. | Strong |
| Provide testosterone therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood. | Strong |
| In the presence of hyperprolactinaemia, dopamine agonist therapy may improve spermatogenesis. | Weak |

Invasive Male Infertility Management

Obstructive azoospermia

Obstructive azoospermia (OA) is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction. Obstructive azoospermia is less common than non-obstructive azoospermia (NOA) and occurs in 20-40% of men with azoospermia. Men with OA usually have a normal FSH, testes of normal size and epididymal enlargement or distension. Of clinical relevance, men with late maturation arrest may present with normal gonadotrophins and testis size and may be only be distinguished from OA at the time of surgical exploration. The vas deferens may be absent bilaterally (CBAVD) or unilaterally (CUAVD). Obstruction in primary infertile men is more frequently present at the epididymal level.

| Recommendations | Strength rating |
|---|-----------------|
| Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by epididymal or vasal obstruction in men with female partners of good ovarian reserve. | Strong |
| Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and percutaneous techniques (PESA and TESA) either as an adjunct to reconstructive surgery, or if the condition is not amenable to surgical repair, or when the ovarian reserve of the partner is limited or patient preference is not to undertake a surgical reconstruction and the couple prefer to proceed to ICSI treatment directly. | Strong |

Non-obstructive azoospermia

Non-obstructive azoospermia (NOA) is defined as the absence of sperm in semen analysis after centrifugation, with usually a normal ejaculate volume. This finding should be confirmed on at least two consecutive semen analyses. The severe deficit in spermatogenesis observed in NOA patients is often a consequence of primary testicular dysfunction or may be related to a dysfunction of the hypothalamus-pituitary-gonadal (HPG) axis.

| Recommendations | Strength rating |
|---|-----------------|
| <p>Patients with non-obstructive azoospermia (NOA) should undergo a comprehensive assessment, including detailed medical history, hormonal profile and genetic tests to investigate the underlying aetiology and associated co-morbidity. Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology protocols.</p> | Strong |
| <p>Surgery for sperm retrieval can be performed in men who are candidates for assisted reproductive technology (i.e., ICSI). In patients with complete AZFa and AZFb microdeletions, surgery is contraindicated since the chance of sperm retrieval is zero.</p> | Strong |
| <p>Fine needle aspiration (FNA) and testicular sperm aspiration (TESA) should not be considered the treatments of choice in patients with NOA, given the lower probability of positive sperm retrieval compared to cTESE and mTESE.</p> | Weak |
| <p>Fine needle aspiration mapping as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA is not recommended for use in routine clinical practice.</p> | Weak |
| <p>Microdissection TESE (mTESE) is the technique of choice for retrieving sperm in patients with NOA.</p> | Weak |
| <p>No pre-operative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA.</p> | Weak |

| | |
|--|------|
| No conclusive recommendations on the routine use of medical therapy (e.g., recombinant follicle-stimulating hormone (FSH); highly purified FSH; human chorionic gonadotrophin (hCG); aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA can be drawn and are not therefore currently recommended routinely before TESE. | Weak |
|--|------|

This short booklet is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-16-5), available to all members of the European Association of Urology at their website, <http://www.uroweb.org/guidelines/>.