Guidelines on Priapism

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1. INTRODUCTION

1.1 Aim

Priapism is a pathological condition representing a true disorder of penile erection that persists for more than 4 hours and is beyond, or is unrelated to, sexual interest or stimulation [1] (LE: 4). Overall, erections lasting up to 4 hours are by consensus defined as ‘prolonged’ (LE: 4).

Priapism may occur at all ages. The incidence rate of priapism in the general population is low (0.5-0.9 cases per 100,000 person-years) [2, 3]. In patients with sickle cell disease, the prevalence of priapism is up to 3.6% in patients < 18 years of age [4] increasing up to 42% in patients ≥ 18 years of age [5-8].

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients suffering from priapism.

1.2 Publication history

The EAU Guidelines on Priapism were first published in 2014 by the EAU Male Sexual Dysfunction Guidelines Panel.

This 2015 version has been updated and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

Alongside a scientific publication [9], a quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Priapism Guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of EAU Guidelines articles as well as translations produced by national urological associations: http://www.uroweb.org/guidelines/online-guidelines/.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The EAU Male Sexual Dysfunction Guidelines Panel consists of urologists. Members of this Panel have been selected based on their expertise to represent the professionals treating patients suffering from priapism.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

The EAU Guidelines on Priapism are based on a systematic literature search performed by the Panel members. The MedLine database was searched using the major Medical Subject Headings term ‘priapism’ with search cut-off date of October 2014. This search yielded 1,688 articles (192 review articles, 485 original articles and 911 case reports). The Panel also identified critical problems and knowledge gaps, enabling priorities to be established for future clinical research.
3. THE GUIDELINE

3A ISCHAEMIC (LOW-FLOW OR VENO-OCCLUSIVE) PRIAPISM

3A.1 Epidemiology/aetiology/pathophysiology

Ischaemic priapism is the most common form of priapism, accounting for more than 95% of all priapism episodes [10, 11]. It is usually painful, with a rigid erection characterised clinically by absent or reduced intracavernous arterial inflow. In ischaemic priapism, there are time-dependent modifications in the corporal metabolic environment, progressively leading to hypoxia, hypercapnia, and acidosis.

Ischaemic priapism beyond 4 hours is considered a compartment syndrome, characterised by supraphysiological pressure within the closed space of the corpora cavernosa, which severely compromises cavernous circulation. Emergency medical intervention is required to minimise potential irreversible consequences, such as corporal fibrosis and permanent erectile dysfunction (ED) [12, 13]. The duration of priapism represents the most significant predictor of the development of ED. In this context, interventions beyond 48-72 hours since onset may help to relieve erection and pain, but have little benefit in preventing ED.

Histologically, by 12 hours, corporal specimens show interstitial oedema, progressing to destruction of sinusoidal endothelium, exposure of the basement membrane and thrombocyte adherence at 24 hours. At 48 hours, thrombi can be found in the sinusoidal spaces and smooth muscle necrosis with fibroblast-like cell transformation is evident [13]. In terms of pathophysiology (Table 1), no specific cause can be identified in the majority of cases [11, 14]. However, ischaemic priapism can be associated with sickle cell disease, haematological dyscrasias, neoplastic syndromes, and with the use of several different medications. Ischaemic priapism may occur (0.4-35%) after intracavernous injections of erectogenic agents [11, 12, 15-17]. The risk is highest with papaverine-based combinations, while the risk of priapism is < 1% following prostaglandin E1 injection [17].

Since their introduction on the market, a few cases of priapism have been described in men who have taken phosphodiesterase type 5 inhibitors (PDE5Is) [11]. Most of these men however, had other risk factors for priapism, and it is unclear whether PDE5Is alone can cause ischaemic priapism [11]. Since most men who experienced priapism following PDE5I use had additional risk factors for ischaemic priapism, PDE5I use is usually not regarded a risk factor in itself.

Sickle cell disease is the most common cause in childhood, accounting for 63% of the cases. It is the primary aetiology in 23% of adult cases [18], with a lifetime probability of developing ischaemic priapism of 29-42% in men with sickle cell disease [11,18-20] (LE: 4). Mechanisms of sickle cell disease associated priapism may involve dysfunctional nitric oxide synthase and ROCK signaling, and increased oxidative stress associated with NADPH oxidase mediated signaling [21].

Priapism resulting from metastatic or regional infiltration is rare and usually reflects an infiltrative process [22]. As such, the recommendations for pharmacological treatment are unlikely to work and certainly all of these men should have a magnetic resonance imaging (MRI) scan and be offered supportive care for their primary cancer.

Priapism in children is extremely rare and is most commonly related to malignancy, haematological or otherwise. The investigative focus should be on identifying any underlying causes.

Partial priapism, or idiopathic partial thrombosis of the penis, is a very rare condition. It is a subtype of priapism limited to the crura. Its aetiology is unknown, but bicycle riding, trauma, drug usage, sexual intercourse, haematological diseases and α-blockers have been associated with partial priapism [23].
Table 1: Potential causative factors for ischaemic priapism

<table>
<thead>
<tr>
<th>Potential causative factors for ischaemic priapism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic</strong></td>
</tr>
<tr>
<td><strong>Haematological dyscrasias</strong> (sickle cell disease, thalassemia, leukaemia; multiple myeloma, Hb Olmsted variant, fat emboli during hyperalimentation, haemodialysis, glucose-6-phosphate dehydrogenase deficiency, Factor V Leiden mutation)</td>
</tr>
<tr>
<td><strong>Infections</strong> (toxin-mediated) (i.e. scorpion sting, spider bite, rables, malaria)</td>
</tr>
<tr>
<td><strong>Metabolic disorders</strong> (i.e. amyloidosis, Fabry’s disease, gout)</td>
</tr>
<tr>
<td><strong>Neurogenic disorders</strong> (i.e. syphilis, spinal cord injury, cauda equina syndrome, autonomic neuropathy, lumbar disc herniation, spinal stenosis, cerebrovascular accident, brain tumour, spinal anaesthesia)</td>
</tr>
<tr>
<td><strong>Neoplasms</strong> (metastatic or regional infiltration) (i.e. prostate, urethra, testis, bladder, rectal, lung, kidney)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
</tr>
<tr>
<td>o Vasoactive erectile agents (i.e. papaverine, phenolamine, prostaglandin E1/alprostadil, combination of intracavernous therapies)</td>
</tr>
<tr>
<td>o Alpha-adrenergic receptor antagonists (i.e. prazosin, terazosin, doxazosin, tamsulosin)</td>
</tr>
<tr>
<td>o Antianxiety agents (hydroxyzine)</td>
</tr>
<tr>
<td>o Anticoagulants (heparin, warfarin)</td>
</tr>
<tr>
<td>o Antidepressants and antipsychotics (i.e. trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thioridazine, phenothiazines)</td>
</tr>
<tr>
<td>o Antihypertensives (i.e. hydralazine, guanethidine, propranolol)</td>
</tr>
<tr>
<td>o Hormones (i.e. gonadotropin-releasing hormone, testosterone)</td>
</tr>
<tr>
<td>o Recreational drugs (i.e. alcohol, marijuana, cocaine [intranasal and topical], crack, cocaine)</td>
</tr>
</tbody>
</table>

3A.1.1 Conclusions on the epidemiology, aetiology and pathophysiology of ischaemic priapism

<table>
<thead>
<tr>
<th>Conclusions</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic priapism is most common, accounting for more than 95% of all cases.</td>
<td>1b</td>
</tr>
<tr>
<td>Ischaemic priapism is identified as idiopathic in the vast majority of patients, while sickle cell anemia is the most common cause in childhood.</td>
<td>1b</td>
</tr>
<tr>
<td>Ischaemic priapism occurs relatively often (up to 35%) after intracavernous injections of papaverine-based combinations, while it is rare (&lt; 1%) after prostaglandin E1 monotherapy.</td>
<td>2a</td>
</tr>
<tr>
<td>Priapism is rare in men who have taken PDE5Is with only sporadic cases reported.</td>
<td>1a</td>
</tr>
</tbody>
</table>

3A.1.2 Classification

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow [11]. The patient typically complains of penile pain and examination reveals a rigid erection. Resolution of ischaemic priapism is characterised by return to a flaccid non-painful state. However, in many cases, persistent penile oedema, ecchymosis and partial erections can occur and may mimic unresolved priapism. The partial erections may reflect reactive hyperaemia and are sometimes misdiagnosed as persistent priapism. When left untreated, resolution may take days and ED invariably results.
3A.1.3  **Diagnostic evaluation**

**Figure 1: Differential diagnosis of priapism**

- **Ischaemic priapism**
  - History
  - Penile blood gas analysis
  - Penile Doppler scan
  - Painful, rigid erection
  - Dark blood; hypoxia, hypercapnia and acidosis
  - Sluggish or non-existent blood flow

- **High-flow priapism**
  - History
  - Penile blood gas analysis
  - Penile Doppler scan
  - Bright red blood; arterial blood gas values
  - Normal arterial flow and may show turbulent flow at the site of a fistula

### 3A.1.3.1 History

A comprehensive history taking is the mainstay in priapism diagnosis [11, 24]. The medical history must include a history of sickle cell disease or any other haematological abnormality [8, 25] and a history of pelvic, genital or perineal trauma. The sexual history must include complete details of the duration of erection, the presence and degree of pain, prior medical drug use, any previous history of priapism and erectile function prior to the last priapism episode (Table 2). The history can help to determine the underlying type of priapism (Table 3). Ischaemic priapism is associated with progressive penile pain and the erection is rigid.

**Table 2: Key points in taking the history of priapism (adapted from Broderick et al [11])**

<table>
<thead>
<tr>
<th>Duration of erection</th>
<th>Presence and degree of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Previous episodes of priapism and method of treatment</td>
</tr>
<tr>
<td></td>
<td>Current erectile function, especially the use of any erectogenic therapies prescription or nutritional supplements</td>
</tr>
<tr>
<td></td>
<td>Medications and recreational drugs</td>
</tr>
<tr>
<td></td>
<td>Sickle cell disease, haemoglobinopathies, hypercoagulable states</td>
</tr>
<tr>
<td></td>
<td>Trauma to the pelvis, perineum, or penis</td>
</tr>
</tbody>
</table>

**Table 3: Key points in examining the penile blood gas analysis**

<table>
<thead>
<tr>
<th>Normal arterial flow and may show turbulent flow at the site of a fistula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood aspiration from the corpora cavernosa shows dark ischaemic blood (Table 3) (LE: 2b). Blood gas analysis is essential to differentiate between ischaemic and arterial priapism (Table 4).</td>
</tr>
</tbody>
</table>

Further laboratory testing should be directed by history, clinical and laboratory findings. These may include specific tests for the diagnosis of sickle cell anaemia or other haemoglobinopathies (e.g. haemoglobin electrophoresis) or urine and plasma toxicological studies when there is suspected use of recreational psychoactive drugs.
3A.1.3.4 Penile imaging

Colour Doppler ultrasound (US) of the penis and perineum is recommended and can differentiate ischaemic from arterial priapism as an alternative or adjunct to blood gas analysis [26-28] (LE: 2b). Scanning of the penis should be performed before aspiration in ischaemic priapism.

Examination of the penile shaft and perineum is recommended. In ischaemic priapism there will be an absence of blood flow in the cavernous arteries. The return of the cavernous artery waveform will result in successful detumescence [11, 28, 29]. After aspiration, a reactive hyperaemia may develop with a high arterial flow that may mislead the diagnosis as arterial priapism.

The role of MRI in the diagnostic evaluation of priapism is controversial. It may be helpful in cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In a prospective study in 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, as confirmed by corporal biopsy [30]. In this study, all patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up (LE: 3).

Table 3: Key findings in priapism (adapted from Broderick et al [11])

<table>
<thead>
<tr>
<th></th>
<th>Ischaemic priapism</th>
<th>Arterial priapism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corpora cavernosa</td>
<td>fully rigid</td>
<td>Usually</td>
</tr>
<tr>
<td>Penile pain</td>
<td>Usually</td>
<td>Seldom</td>
</tr>
<tr>
<td>Abnormal penile</td>
<td>blood gas</td>
<td>Usually</td>
</tr>
<tr>
<td>Haematological</td>
<td>abnormalities</td>
<td>Seldom</td>
</tr>
<tr>
<td>Recent intracorporeal</td>
<td>injection</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Perineal trauma</td>
<td>Seldom</td>
<td>Usually</td>
</tr>
</tbody>
</table>

Table 4: Typical blood gas values (adapted from Broderick et al [11])

<table>
<thead>
<tr>
<th>Source</th>
<th>pO₂ (mmHg)</th>
<th>pCO₂ (mmHg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal arterial blood (room air) [similar</td>
<td>&gt; 90</td>
<td>&lt; 40</td>
<td>7.40</td>
</tr>
<tr>
<td>values are found in arterial priapism]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal mixed venous blood (room air)</td>
<td>40</td>
<td>50</td>
<td>7.35</td>
</tr>
<tr>
<td>Ischaemic priapism (first corporal aspirate)</td>
<td>&lt; 30</td>
<td>&gt; 60</td>
<td>&lt; 7.25</td>
</tr>
</tbody>
</table>

3A.1.3.5 Recommendations for the diagnosis of ischaemic priapism

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<td>A comprehensive history is key for diagnosis and can help to determine the</td>
<td>B</td>
</tr>
<tr>
<td>underlying type of priapism.</td>
<td></td>
</tr>
<tr>
<td>Physical examination of the genitalia, the perineum and the abdomen must be</td>
<td>B</td>
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<tr>
<td>included in the diagnostic evaluation and may help to determine the</td>
<td></td>
</tr>
<tr>
<td>underlying type of priapism.</td>
<td></td>
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<tr>
<td>Laboratory testing should include complete blood count, white blood count</td>
<td>B</td>
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<tr>
<td>with blood cell differential, platelet count and coagulation profile. Further</td>
<td></td>
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<tr>
<td>laboratory testing should be directed by the history and clinical and</td>
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<tr>
<td>laboratory findings. Priapism in children requires a complete evaluation of</td>
<td></td>
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<td>all possible causes.</td>
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<tr>
<td>Blood gas analysis of blood aspirated from the penis is recommended for the</td>
<td>B</td>
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<td>differentiation between ischaemic and arterial priapism.</td>
<td></td>
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<tr>
<td>Colour duplex ultrasound of the penis and perineum is recommended for the</td>
<td>B</td>
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<tr>
<td>differentiation between ischaemic and arterial priapism as an alternative or</td>
<td></td>
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<tr>
<td>adjunct to blood gas analysis. It can also be helpful in localisation of the</td>
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<td>site and extend of fistula in arterial priapism as well as in the determination</td>
<td></td>
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<td>of successful resolution of ischaemic priapism.</td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance imaging of the penis can predict smooth muscle viability</td>
<td>B</td>
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<tr>
<td>and erectile function restoration.</td>
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<tr>
<td>Selected pudendal arteriogram should be reserved for the management of</td>
<td>B</td>
</tr>
<tr>
<td>arterial priapism when embolisation is undertaken.</td>
<td></td>
</tr>
</tbody>
</table>
3A.1.4 Disease management
Acute ischaemic priapism is an emergency condition. Rapid intervention is compulsory (LE: 4), and should follow a stepwise approach. The aim of any treatment is to restore penile flaccidity, without pain, in order to prevent damage to the corpora cavernosa.

Figure 2: Treatment of ischaemic priapism
The treatment is sequential and the physician should move on to the next stage if the treatment fails.

Initial conservative measures
- Local anaesthesia of the penis
- Insert wide bore butterfly (16-18G)
- Aspiration cavernosal blood until bright red arterial blood is obtained

Cavernosal irrigation
- Irrigate with 0.90% w/v saline solution

Intracavernosal therapy
- Inject intracavernosal adrenoceptor agonist
- Current first-line therapy is phenylephrine (*) with aliquots of 200 micrograms being injected every 5-10 minutes until detumescence is achieved [Maximum dose of phenylephrine is 1mg within 1 hour(*)]

Surgical therapy
- Surgical shunting
- Consider primary penile implantation if priapism has been present for more than 36 hours

(*) The 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 and monitoring of pulse, blood pressure and electrocardiogram (ECG) is advisable in all patients during administration and for 60 minutes afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

3A.1.4.1 First-line treatments
First-line treatments in ischaemic priapism of > 4 hours duration are strongly recommended before any surgical treatment (LE: 4). Conversely, first-line treatments initiated beyond 72 hours while relieving the priapism have little documented benefit in terms of potency preservation (LE: 4).

Historically, several first-line treatments have been described including exercise, ejaculation, ice packs, cold baths, and cold water enemas [11]. However, there is lack of evidence of benefit for such measures.

Partial priapism usually resolves spontaneously with analgesic treatment while surgical intervention is rarely needed [31].

3A.1.4.1.1 Penile anaesthesia/systemic analgesia
It is possible to perform blood aspiration and intracavernosal injection of a sympathomimetic agent without any anaesthesia. However, anaesthesia may be necessary when there is severe penile pain. While it is recognised that the anaesthesia may not alleviate the ischaemic pain, cutaneous anaesthesia will facilitate subsequent therapies. The treatment options for penile anaesthesia/systemic analgesia include:
- dorsal nerve block;
- circumferential penile block;
- subcutaneous local penile shaft block;
- oral conscious sedation (for paediatric patients).

3A.1.4.1.2 Aspiration ± irrigation with 0.90% w/v saline solution
The first intervention for an episode of priapism lasting > 4 hours consists of corporal aspiration (LE: 4) to
drain stagnant blood from the corporal bodies, making it possible to relieve the compartment syndrome-like condition of the penis. Blood aspiration may be performed with intracorporeal access either through the glans or via percutaneous needle access on the lateral aspect of the proximal penile shaft, using a 16G or 18G angiocatheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain the corpus cavernosum (LE: 4).

Some clinicians use two angiocatheters or butterfly needles at the same time to accelerate drainage, as well as aspirating and irrigating simultaneously with a saline solution [19] (LE: 4). Aspiration should be continued until fresh red, oxygenated, blood is aspirated (LE: 4).

This approach has up to a 30% chance of terminating the priapism. There are insufficient data to determine whether aspiration followed by saline intracorporeal irrigation is more effective than aspiration alone (LE: 4).

3A.1.4.1.3 Aspiration ± irrigation with 0.90% w/v saline solution in combination with intracavernosal injection of pharmacological agents

This combination is currently considered the standard of care in the treatment of ischaemic priapism [1, 11, 32] (LE: 4). Pharmacological agents include sympathomimetic drugs or alpha-adrenergic agonists. Options for intracavernosal sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80%. [11, 32-40] (LE: 2b). The use of intracavernosal adrenalin injection alone has also been sporadically reported [41].

3A.1.4.1.3.1 Phenylephrine

Phenylephrine is currently the drug of choice due to its high selectivity for the alpha-1-adrenergic receptor, without concomitant beta-mediated inotropic and chronotropic cardiac effects [33, 37, 38] (LE: 4).

Phenylephrine is diluted in normal saline to a concentration of 100-500 µg/mL. Usually 200 µg are given every 3-5 minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within 1 hour (LE: 4). A lower concentration or volume is applicable for children and patients with severe cardiovascular disease (LE: 4).

Phenylephrine use has potential cardiovascular side-effects [11, 32-34, 37, 38] and it is recommended that blood pressure and pulse are monitored every 15 minutes for an hour after the injection. This is particularly important in older men with existing cardiovascular diseases. After injection, the puncture site should be compressed and the corpora cavernosa massaged to facilitate drug distribution.

The potential treatment-related side-effects of intracavernous phenylephrine (and other sympathomimetic agents) include headache, dizziness, hypertension, reflex bradycardia, tachycardia and palpitations, irregular cardiac rhythms and sporadic subarachnoid haemorrhage [34]. Monitoring of blood pressure and pulse with ECG should be performed during intracavernous administration of sympathomimetic agents.

Overall, the administration of intracavernosal sympathomimetic agents is contraindicated in patients suffering from malignant or poorly controlled hypertension and in those who are concurrently taking monoamine oxidase inhibitors (LE: 4).

3A.1.4.1.3.2 Etilerine

Etilerine is the second most widely used sympathomimetic agent, administered by intracavernosal injection at a concentration of 2.5 mg in 1-2 ml normal saline [34] (LE: 3).

3A.1.4.1.3.3 Methylene blue

Methylene blue is a guanylate cyclase inhibitor, which may be a potential inhibitor of endothelial-mediated cavernous relaxation. It has therefore been suggested for treating short-term pharmacologically induced priapism [42, 43] (LE: 3). Methylene blue, 50-100 mg [42], should be injected intracavernously and left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes [43]. Treatment-related side-effects include a transient burning sensation and blue discoloration of the penis.

3A.1.4.1.3.4 Adrenaline

Intracavernosal adrenaline (dosage of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period [41]), has been used in patients with ischaemic priapism due to an intracavernosal injection of vasoactive agents. Success rate of over 50% after a single injection, with an overall success rate of 95% with repeated injections is achieved (LE: 3).
3A.1.4.1.3.5 Oral terbutaline
Oral terbutaline is a beta-2-agonist with minor beta-1 effects and some alpha-agonist activity. A dose of 5 mg has been suggested to treat prolonged erections lasting more than 2.5 hours, after intracavernosal injection of vasoactive agents, although the mechanism of action is not yet fully understood [44-46] (LE: 1b). Its main use is in the prevention of recurrent episodes of prolonged erection. Terbutaline should be given cautiously in patients with coronary artery disease, increased intravascular fluid volume, oedema and hypokalaemia [46].

Table 5: Medical treatment of ischaemic priapism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage/Instructions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>- Intracavernous injection of 200 µg every 3-5 minutes.</td>
</tr>
<tr>
<td></td>
<td>- Maximum dosage is 1 mg within 1 hour.</td>
</tr>
<tr>
<td></td>
<td>- The lower doses are recommended in children and patients with severe cardiovascular disease.</td>
</tr>
<tr>
<td>Etilenephrine</td>
<td>- Intracavernosal injection at a concentration of 2.5 mg in 1-2 ml normal saline.</td>
</tr>
<tr>
<td>Methylen blue</td>
<td>- Intracavernous injection of 50-100 mg, left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes.</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>- Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period.</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>- Oral administration of 5 mg for prolonged erections lasting more than 2.5 hours, after intracavernosal injection of vasoactive agents.</td>
</tr>
</tbody>
</table>

3A.1.4.1.4 Management of sickle cell disease related priapism
Rapid intervention is essential (LE: 4) and the general approach is similar to that described in other cases of ischaemic priapism [47-49] (LE: 4).

However, as with other haematological disorders, other therapeutic practices may also need to be implemented [47, 49, 50]. Specific measures for sickle cell disease related priapism include intravenous hydration and parental narcotic analgesia while preparing the patient for aspiration and irrigation. In addition, supplemental oxygen administration and alkalinisation with bicarbonate can be helpful [20, 48].

Exchange blood transfusion has also been proposed, with the aim of increasing the tissue delivery of oxygen. The transfused blood should be HbS negative, Rh and Kell antigen matched [51]. However, the evidence is inconclusive as to whether exchange transfusion itself helps to resolve the priapism in these men. It should also be noted that several reports suggest that this treatment may result in serious neurological sequelae [52]. Because of these considerations, the routine use of this therapy is not recommended (LE: 4).

3A.1.4.2 Second-line treatments
Second-line intervention typically refers to surgical intervention in the form of penile shunt surgery and should only be considered when conservative management options fail (LE: 4). There is no evidence detailing the amount of time allowed for first-line treatment before moving on to surgery. Consensus recommendations suggest a period of at least 1 hour of first-line therapy prior to moving to surgery (LE: 4). A number of clinical indicators suggest failure of first-line treatment including continuing corporal rigidity, cavernosal acidosis and anoxia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressures by pressure monitoring (LE: 4).

3A.1.4.2.1 Penile shunt surgery
Penile shunt surgery aims to produce an exit for ischaemic blood from the corpora cavernosa thereby allowing the restoration of normal circulation within these structures. Accordingly, any shunt creates an opening in the tunic albuginea, which may communicate with either the glans, the corpus spongiosum or a vein for blood drainage [11, 32, 53].

In general, the type of shunt procedure chosen is according to the surgeon’s preference and procedure familiarity (LE: 4). It is conventional for distal shunt procedures to be tried before proximal shunting is considered (LE: 4). Cavernous biopsy has been used to identify muscle necrosis (which, if present, would suggest that shunting is likely to fail) although this has mainly a medico-legal role.

It is important to assess the success of surgery by either direct observation or by investigation (e.g. cavernous blood gas testing, penile colour duplex US) (LE: 4) [11, 32].
The recovery rates of erectile function in men undergoing shunt surgery for prolonged erections are low and directly relate to the duration of the priapism [54, 55]. Priapism for more than 36 hours appears to irreversibly impair erectile tissue both structurally and functionally [54]. In general, shunt procedure undertaken after this time period may only serve to limit pain without any benefit for erectile function (LE: 4).

Four categories of shunt procedures have been reported [1, 11, 53]. The limited available data preclude any recommendation for one procedure over another based on outcome (LE: 4).

**Percutaneous distal (corpora-glanular) shunts**

Winter's procedure: this procedure uses a Trucut biopsy needle to create a fistula between the glans penis and each corpora cavernosa body [1, 11, 18, 56, 57] (LE: 3). Postoperative sequelae are uncommon [58]. Winter’s shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [55].

Ebbehoj's technique: this technique involves the execution of multiple tunical incision windows between the glans and each tip of the corpus cavernosum by means of a size 11 blade scalpel passed several times percutaneously [1, 11, 56, 59, 60] (LE: 3).

T-Shunt: this technique involves performing a bilateral procedure using a size 10 blade scalpel placed vertically through the glans until fully within the corpus cavernosum. The blade is then rotated 90 degrees away from the urethra and pulled out [1, 11, 56, 61] (LE: 3). The whole tunneling procedure could be performed using ultrasound for guidance, mainly in order to avoid urethral injury [61].

**Open distal (corpora-glanular) shunts**

Al-Ghorab’s procedure: this procedure consists of an open bilateral excision of circular cone segments of the distal tunica albuginea via the glans penis, along with a subsequent glans closure by means of a running suture with absorbable material [1, 11, 56, 62, 63] (LE: 3).

Burnett’s technique: a modification of the Al-Ghorab corpora-glanular shunt surgery involves the retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glanular excision. After removal of the dilator from the corpus cavernosum, blood evacuation is facilitated by manual compression of the penis sequentially from a proximal to distal direction. After detumescence, the glans penis skin is closed as in the Al-Ghorab procedure [1, 11, 56, 64, 65] (LE: 3). Reported complications included wound infection, penile skin necrosis and a urethrocutaneous fistula [65].

**Open proximal (corporospongiosal) shunts**

Quackles’s technique: through a trans-scrotal or perineal approach, a proximal open shunt technique creates a communication between the corpus cavernosum and the corpus spongiosum. The most frequent complications include an unwanted urethra-cavernous fistula and urethral stricture or the development of cavernositis [1, 11, 53, 66]. The risk of urethral injury is less with a perineal approach to the bulb of the corpus spongiosum (LE: 3).

**Vein anastomoses/shunts**

Grayhack’s procedure: this mobilises the saphenous vein below the junction of the femoral vein and anastomoses the vein end-to-side onto the corpus cavernosum. Venous shunts may be complicated by saphenofemoral thrombus formation and by pulmonary embolism [1, 11, 67-69] (LE: 3).

**Immediate surgical prosthesis implantation**

Intractable, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48-72 hours usually result in complete ED, possibly along with major penile deformity. In these cases, immediate penile prosthesis surgery has been suggested [70-73] (LE: 3).

The immediate insertion of a penile prosthesis has been recommended to avoid the difficulty and complications of delayed surgery in the presence of corporal fibrosis. Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and cavernositis [70, 72], along with a mild rate of revision surgery [70]. Early surgery also offers the opportunity to maintain penile size, which is inevitably compromised by delay.

Currently, there are no clear indications for immediately implanting a penile prosthesis in a man with acute ischaemic priapism [32]. Relative indications include [11] (LE: 4):

- ischaemia that has been presented for more than 36 hours [73];
- failure of aspiration and sympathomimetic intracavernous injections;
• failure of distal and proximal shunting (although in delayed cases, implantation might be considered ahead of shunt surgery).
• MRI or corporal biopsy evidence of corporal smooth muscle necrosis [11, 70] (LE: 4).

3A.1.4.3 Surgery for non-acute sequelae after ischaemic priapism
Structural changes may occur after ischaemic priapism including cavernosal tissue necrosis and fibrosis with consequent penile scarring, megalophallic deformities, penile shortening, and occasional penile loss, [53, 70, 74, 75]. Erectile dysfunction is also often observed [11, 76]. Unfortunately, these outcomes can still occur despite apparently successful first-line or second-line treatment.

Prosthesis implantation is occasionally indicated in sickle cell patients with severe ED since other therapeutic options such as PDE5Is and intracavernosal injections are avoided as they may provoke a further priapism event [11, 32]. In severe corporal fibrosis, semi-rigid prosthetic devices are preferable to inflatable implants [70, 77] (LE: 3). Following severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, penile reconstruction and concomitant prosthesis implant may be considered [78] (LE: 3).

3A.1.5 Recommendations for the treatment of ischaemic priapism

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic priapism is an emergency condition and rapid intervention is compulsory.</td>
<td>B</td>
</tr>
<tr>
<td>The specific aim is to restore painless penile flaccidity, in order to prevent chronic damage to the corpora cavernosa.</td>
<td>C</td>
</tr>
<tr>
<td>Management of ischaemic priapism should start as early as possible (within 4-6 hours) and should follow a stepwise approach. Erectile function preservation is directly related to the duration of priapism.</td>
<td>B</td>
</tr>
<tr>
<td>Initial management is decompression of the corpora cavernosa by penile aspiration until fresh red blood is obtained.</td>
<td>C</td>
</tr>
<tr>
<td>In priapism secondary to intracavernous injections of vasoactive agents blood aspiration can be replaced by intracavernous injection of a sympathomimetic drug as the first step.</td>
<td>C</td>
</tr>
<tr>
<td>In priapism that persists despite aspiration, the next step is intracavernous injection of a sympathomimetic drug. Phenylephrine is the recommended drug due to its favourable safety profile on the cardiovascular system compared to other drugs. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 µg/mL and given in 200 µg doses every 3-5 minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within 1 hour. Patients at high cardiovascular risk should be given lower doses. Patient monitoring is highly recommended.</td>
<td>B</td>
</tr>
<tr>
<td>In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, these steps should be repeated several times before considering surgical intervention.</td>
<td>C</td>
</tr>
<tr>
<td>Ischaemic priapism due to sickle cell anaemia is treated in the same fashion as idiopathic ischaemic priapism. Other supportive measures are recommended (intravenous hydration, oxygen administration with alkalisation with bicarbonates, blood exchange transfusions), but these should not delay initial treatment to the penis.</td>
<td>B</td>
</tr>
<tr>
<td>Surgical treatment is recommended only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed or for priapism events lasting ≤ 72 hours.</td>
<td>C</td>
</tr>
<tr>
<td>Distal shunt surgical procedures should be performed first followed by proximal procedures in case of failure. The efficacy of these procedures is questionable and cavernous biopsy may be considered to diagnose muscle necrosis. No clear recommendation on one type of shunt over another can be given.</td>
<td>C</td>
</tr>
<tr>
<td>In cases of priapism presenting &gt; 36 hours after onset, or in cases for which all interventions have failed, erectile dysfunction is inevitable and the immediate implantation of a penile prosthesis should be discussed with the patient. Implantation of penile prosthesis at a later stage can be difficult due to severe corporal fibrosis.</td>
<td>B</td>
</tr>
</tbody>
</table>

3A.1.6 Follow-up
Follow-up of ischaemic priapism after successful treatment should include modification of risk factors (if any) in order to avoid a new event and assessment of erectile function since it may be severely compromised especially after surgical treatment with a shunt. Penile fibrosis is usually easily identified with clinical examination of the penis.
3B ARTERIAL (HIGH-FLOW OR NON-ISCHAEMIC) PRIAPISM

3B.1 Epidemiology/aetiology/pathophysiology
Epidemiological data on arterial priapism are almost exclusively derived from small case series [11, 28, 29, 79, 80]. The most frequent cause of high-flow priapism is blunt perineal or penile trauma [81]. The injury results in a laceration in the cavernosal artery leading to a high-flow fistula between the artery and the lacunar spaces of the sinusoidal tissue [80]. This unregulated flow results in a persistent erection, and has been proposed to occur via a mechanism that involves stimulation of endothelial nitric oxide synthase by the turbulent blood flow [82]. Partial erections are enhanced after sexual stimulation, as the trabecular smooth muscle fully relaxes, activating the corporal veno-occlusive mechanism [80, 83].

There is often a delay between the injury and the development of the priapism that may be up to 2-3 weeks [83]. This has been suggested to reflect either spasm or ischaemic necrosis of the injured artery, with the fistula only developing as the spasm resolves or when the ischaemic segment blows out.

Occasional cases are associated with metastatic malignancy to the penis [84, 85], with acute spinal cord injury [86] and occasionally following intracavernosal injections or aspiration due to a lacerated cavernous artery or branch [87, 88]. Under these circumstances, it may complicate low-flow priapism. It has also been reported to occur following internal urethrotomy [89] and a Nesbit procedure [90]. Although sickle cell disease is usually associated with low-flow priapism, occasional cases of high-flow priapism have been reported [91].

3B.1.1 Conclusion on the epidemiology, aetiology and pathophysiology of arterial priapism

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial priapism usually occurs after blunt perineal or penile trauma.</td>
<td>2</td>
</tr>
</tbody>
</table>

3B.1.2 Classification
Arterial priapism is a persistent erection caused by unregulated cavernous arterial inflow [11]. The patient typically reports an erection that is not fully rigid and is not associated with pain although fully rigid erections may occur with sexual stimulation.

3B.1.3 Diagnostic evaluation

3B.1.3.1 History
A comprehensive history is also mandatory in arterial priapism diagnosis and follows the same principles as described in Table 2. Arterial priapism is suspected when there is no pain and erections are not fully rigid (Table 3). It can be associated with full erections under sexual stimulation and when there is a history of coital trauma or blunt trauma to the penis. The onset of post-traumatic high-flow priapism in adults and children may be delayed by hours to days following the initial injury. Sexual intercourse is usually not compromised.

3B.1.3.2 Physical examination
In arterial priapism, the corpora are tumescent but not fully rigid (Table 3). Abdominal, penile and perineal examination may reveal evidence of trauma.

3B.1.3.3 Laboratory testing
Blood aspiration from the corpora cavernosa shows bright red arterial blood in arterial priapism, while blood is dark in ischaemic priapism (Table 3) (LE: 2b). Blood gas analysis is essential to differentiate between arterial and ischaemic priapism (Table 4).

3B.1.3.4 Penile imaging
Colour duplex US of the penis and perineum is recommended and can differentiate arterial from ischaemic priapism as an alternative or adjunct to blood gas analysis [26-28] (LE: 2b). Examination of the penile shaft and perineum is recommended. In arterial priapism US will show turbulent flow at the fistula, which helps to localise the site of trauma since patients with arterial priapism have normal to high blood velocities in the cavernous arteries.

A selective pudendal arteriogram can reveal a characteristic blush at the site of the injury to the cavernosal artery in arterial priapism [92, 93]. However, due to its invasiveness it should be reserved for the management of arterial priapism, when embolisation is being considered [11, 24] (LE: 3).
The role of MRI in the diagnostic evaluation of priapism is controversial. In arterial priapism, its role is limited since the small penile vessels and arteriovenous fistulae cannot be easily demonstrated [94].

3B.1.3.5 **Recommendations for the diagnosis of arterial priapism**
The same recommendations as in section 3A.1.3.5 apply.

3B.1.4 **Disease management**
The management of high-flow priapism is not an emergency because the penis is not ischaemic. Definitive management can therefore be considered and should be discussed with the patient so that they understand the risks and complications of treatment [11, 24] (LE: 3).

3B.1.4.1 **Conservative management**
This may include applying ice to the perineum or site-specific perineal compression [28, 79, 95, 96]. It is an option in all cases, particularly children [97] (LE: 3). The fistula occasionally closes spontaneously. Even in those cases when it does not, the response to a sexual stimulus does allow for intercourse. Androgen deprivation therapy (leuprolide injections, bicalutamide and ketoconazole) has been reported in case series to enable closure of the fistula reducing spontaneous and sleep-related erections [98]. However, sexual dysfunction due to these treatments must be considered.

Blood aspiration is not helpful for the treatment of arterial priapism and the use of alpha-adrenergic antagonists is not recommended due to potential severe adverse effects, e.g. transfer of the drug into the systemic circulation.

3B.1.4.2 **Selective arterial embolisation**
Selective arterial embolisation can be performed using either an autologous clot [99-101], gel foam or sponge [100, 102], or more permanent substances, such as coils [100, 102-104] or acrylic glue [105] (LE: 3). Success rates of up to 89% have been reported [106] in relatively small, non-randomised studies. There are no robust data to demonstrate the relative merits of the different substances. At least theoretically, the use of an autologous clot has some attractions. It temporarily seals the fistula, but when the clot is lysed, the arterial damage has usually resolved and the blood flow of the penis can return to normal. The use of a permanent device, such as a coil, would permanently block an artery and may lead to adverse effects upon spontaneous sexual function. Other potential complications include penile gangrene, gluteal ischaemia, cavernositis and perineal abscess [11, 107].

Following percutaneous embolisation, a follow-up is appropriate within 1-2 weeks. Assessment by clinical examination and by colour duplex US can determine whether the embolisation has been successful [27]. If there is doubt, a repeat arteriogram is required. Recurrence rates of 7-27% after a single treatment of embolisation have been reported [100, 101, 108] (LE: 3). In a few cases, repeat embolisation is necessary. Sexual function following embolisation can be adversely affected although there is full restoration of potency in around 80% of men [108, 109] (LE: 3).

Embolisation in children, although reportedly successful, is technically challenging and requires treatment within a specialist paediatric vascular radiology department [36, 110].

3B.1.4.3 **Surgical management**
Selective ligation of the fistula through a transcorporeal approach under the guidance of colour duplex US is possible [1, 25, 111]. Surgery is technically challenging and may pose significant risks, mainly ED due to accidental ligation of the cavernous artery instead of the fistula. It is rarely performed and should only be considered when there are contraindications for selective embolisation, no availability of the technique or embolisation failure (LE: 4).
### 3B.4.4 Recommendations for the treatment of arterial priapism

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The management of high-flow priapism is not an emergency and definitive management can therefore be considered.</td>
<td>B</td>
</tr>
<tr>
<td>Conservative management includes the use of ice applied to the perineum or site-specific perineal compression. It may be successful particularly in children. Androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.</td>
<td>C</td>
</tr>
<tr>
<td>Selective artery embolisation, using temporary or permanent substances, is the suggested treatment modality and has high success rates. No definitive statement can be made on the best substance for embolisation in terms of sexual function preservation.</td>
<td>B</td>
</tr>
<tr>
<td>The recurrence of arterial priapism following selective artery embolisation requires the procedure to be repeated.</td>
<td>B</td>
</tr>
<tr>
<td>The preservation rate of sexual function is about 80%.</td>
<td>C</td>
</tr>
<tr>
<td>Selective surgical ligation of the fistula should be reserved as a last treatment option when embolisation has failed.</td>
<td>C</td>
</tr>
</tbody>
</table>

### 3B.5 Follow-up

Follow-up after successful treatment of arterial priapism should include assessment of erectile function and clinical examination to identify signs of recurrence especially after embolisation.

## 3C STUTTERING (RECURRENT OR INTERMITTENT) PRIAPISM

### 3C.1 Epidemiology/aetiology/pathophysiology

Robust epidemiological studies of stuttering priapism are lacking [5, 112]. However, recurrent priapism episodes are common in men with sickle cell disease (42-64%) [113, 114] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [5].

The aetiology of stuttering priapism is similar to that of ischaemic priapism. While sickle cell disease is the most common cause, idiopathic cases and cases due to a neurological disorder have been reported. Moreover, men who have suffered from an acute ischaemic priapic event, especially one which has been prolonged (more than 4 hours) are at risk for developing stuttering priapism [76].

Recently, several studies have proposed alternative mechanisms including inflammation, cellular adhesion, nitric oxide metabolism, vascular reactivity and coagulation [11, 21, 48, 115, 116].

### 3C.1.1 Conclusion on the epidemiology, aetiology and pathophysiology of stuttering priapism

Stuttering priapism is similar to ischaemic priapism in that it is low flow, ischaemic and if left untreated would result in significant penile damage, with sickle cell disease being the most common cause. But the cause can also be idiopathic and in rare cases may be due to a neurological disorder.

### 3C.1.2 Classification

Stuttering priapism, also termed intermittent or recurrent priapism, is a distinct condition that is characterised by repetitive and painful episodes of prolonged erections. Erections are self-limited with intervening periods of detumescence [48, 115]. These are analogous to repeated episodes of low flow (or ischaemic) priapism. The duration of the erectile episodes is generally shorter than in ischaemic priapism [1]. The frequency and/or duration of these episodes is variable and a single episode can sometimes progress into a major ischaemic priapic episode.

### 3C.1.3 Diagnostic evaluation

#### 3C.1.3.1 History

A comprehensive history is mandatory and follows the same principles as described in Table 2. There is a
history of recurrent episodes of prolonged erections. The onset of the priapic episodes usually occurs during sleep and detumescence does not occur upon waking. Many of these priapic episodes are painful and may be the reason that the patient seeks medical help.

3C.1.3.2 Physical examination
Erections are painful and the penis is rigid as in ischaemic priapism, but the duration of events is usually shorter. Between erections the penis is usually normal, but in some cases signs of fibrosis can be found. Rarely, the penis may become enlarged, a condition known as megalophallus.

3C.1.3.3 Laboratory testing
Laboratory testing follows the same principles as in the two other types of priapism. It is recommended to identify possible causes and should be directed by history, clinical and laboratory findings.

3C.1.3.4 Penile imaging
There are no specific findings for stuttering priapism. Colour duplex ultrasound of the penis and perineum and MRI are recommended and can differentiate arterial from ischaemic type of priapism.

3C.1.3.5 Recommendations for the diagnosis of stuttering priapism
The same recommendations as described in section 3A.1.3.5 apply. Stuttering priapism is actually a recurrent or intermittent type of ischaemic priapism.

3C.1.4 Disease management
The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can usually be achieved pharmacologically. The management of each acute episode is similar to that for ischaemic priapism; aspiration/irrigation in combination with intracavernous injections of alpha-adrenergic agonists. Unfortunately, the efficacy and safety of the various treatment modalities reported in the medical literature are poorly characterised. Specifically, most reports are from small case series and the Expert Panel is not aware of any published, well-designed, controlled studies on the efficacy and safety of these treatments [20, 48, 115].

3C.1.4.1 Alpha-adrenergic agonists
Studies of oral alpha-adrenergic agonists have suggested some benefit for daily dosing of these agents as effective prevention [117]. Side-effects include tachycardia and palpitations. Pseudoephedrine, widely used as an oral decongestant, can also be used as a first-line treatment [45]. However, its effect on corporal smooth muscle is not fully understood. Etilefrine has been used successfully to prevent stuttering priapism due to sickle cell anaemia. It is taken orally at doses of 50-100 mg daily, with response rates of up to 72% [7, 118, 119]. In one randomized, placebo-controlled, clinical study looking at medical prophylaxis with etilefrine and ephedrine, there was no difference in efficacy between the two drugs.

3C.1.4.2 Hormonal manipulations of circulating testosterone
The aim of hormonal manipulation is to down-regulate circulating testosterone levels to suppress the action of androgens on penile erection [20, 48, 120]. This can be done through the use of gonadotropin-releasing hormone (GnRH) agonists or antagonists, antiandrogens or oestrogens [121] (LE: 4). Potential side-effects may include hot flushes, gynaecomastia, impaired erectile function, loss of libido and asthenia. All approaches have a similar efficacy profile (LE: 4) while the potential cardiovascular toxicity of oestrogens limits their clinical use. Alternative endocrine approaches that have been used with some success include 5-alpha-reductase inhibitors [122] (LE: 3) and Ketoconazole, an antifungal agent that reduces adrenal and testicular androgen production [120, 123] (LE: 4).

Of the hormonal agents suggested for preventing priapism, GnRH agonists and anti-androgens appear to be the most efficacious and safe. They are recommended as primary treatments for the management of stuttering priapism in adult men (LE: 4).

The duration of hormonal treatment for effective suppression of recurrent priapic events is problematic. It is not possible to make any conclusions on the efficacy, dose and the duration of treatment. Moreover, hormonal agents have a contraceptive effect and interfere with normal sexual maturation. Caution is therefore strongly advised when prescribing hormonal treatments to prepubertal boys, adolescents or men who are trying for their female partner to conceive. Castrate levels of testosterone, which have a contraceptive effect, interfere with growth, and significantly affect sexual function.
3C.1.4.3  **Digoxin**

Digoxin (a cardiac glycoside and a positive inotrope) is used to treat patients with congestive heart failure. Digoxin regulates smooth muscle tone through a number of different pathways leading to penile detumescence [20, 48, 124]. The use of maintenance digoxin doses (0.25-0.5 mg daily) in idiopathic stuttering priapism has been proven to reduce the number of hospital visits and to improve QoL [48]. A small, clinical, double-blind, placebo-controlled study, using digoxin, produced a decrease in sexual desire and excitement with a concomitant reduction in penile rigidity, regardless of any significant change in plasma levels of testosterone, oestrogens and luteinising hormone [124] (LE: 2b). Side-effects may include a decreased libido, anorexia, nausea, vomiting, confusion, blurred vision, headache, gynaecomastia, rash and arrhythmia.

3C.1.4.4  **Terbutaline**

Terbutaline is a beta-agonist that causes vasodilation, resulting in smooth muscle relaxation of the vasculature [20, 48] and has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [45] (LE: 3). The only randomised, placebo-controlled study (n = 68) in patients with pharmacologically-induced priapism, showed detumescence in 42% of the terbutaline-treated group compared to only 15% in the placebo-treated group [46] (LE: 1b). Side-effects include nervousness, shakiness, drowsiness, heart palpitations, headache, dizziness, hot flashes, nausea and weakness.

3C.1.4.5  **Gabapentin**

Gabapentin has anticonvulsant, antinociceptive and anxiolytic properties and is widely used as an analgesic and antiepileptic agent. Its proposed mechanism of action is to inhibit voltage-gated calcium channels, which attenuates synaptic transmission [120], and reduces testosterone- and follicle-stimulating hormone levels [125]. It is given at a dose of 400 mg, four times a day, up to 2400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of gabapentin, 300 mg daily [126] (LE: 4). Side-effects include anorgasmia and impaired erectile function.

3C.1.4.6  **Baclofen**

Baclofen is a gamma-aminobutyric acid (GABA) derivative that acts as a muscle relaxant and anti-muscle spasm agent. It can inhibit penile erection and ejaculation through GABA activity and prevents recurrent reflexogonic erections or prolonged erections from neurological diseases [20]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal baclofen dosing is more effective [48, 127-129] (LE: 4). Side-effects include drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension and nausea.

3C.1.4.7  **Hydroxyurea**

Hydroxyurea blocks the synthesis of DNA by inhibiting ribonucleotide reductase, which has the effect of arresting cells in the S-phase [120, 130]. It is an established treatment for ameliorating sickle cell disease and improving their life expectancy [47, 131]. For such patients with recurrent priapism there is limited evidence to suggest a medical prophylactic role (LE: 3) [120, 130, 132]. Side-effects include oligozoospermia and leg ulcers.

3C.1.4.8  **Phosphodiesterase type 5 inhibitors (PDE5Is)**

Low doses of PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism [20, 48, 133-137] (LE: 3). It is important to remember that therapy should be started when the penis is in its flaccid state and not during an acute episode. There is a delay of one week before treatment is effective. There are no reported impairments in male sexual function (LE: 3). PDE5Is probably act in priapism by increasing the concentration of cGMP in the smooth muscle in a nitric oxide dysfunctional state. This can occur in priapism and may result in a change in the nitric oxide pathway, with down-regulation of cavernosal PDE5 thereby preventing the complete degradation of cGMP in the corpora cavernosa [20, 48, 133, 136].

3C.1.4.9  **Intracavernosal injections**

Some patients with stuttering priapism, who have been started on systemic treatments to prevent recurrence of unwanted erections, may not see therapeutic benefits immediately and may temporarily require intracavernous self-injections at home with sympathomimetic agents [20, 48]. The most commonly used drugs are phenylephrine and etilephrine (as described in the treatment of ischaemic priapism) [1, 11, 112, 119] (LE: 3). Side-effects include hypertension, coronary ischaemia and cardiac arrhythmias.

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the proenzyme plasminogen to plasmin, which acts as a fibrinolytic enzyme. Limited clinical data have suggested that a single intracavernosal injection of TPA can successfully treat patients with recalcitrant priapism [120, 138] (LE: 3). Mild bleeding is the
most commonly observed side-effect.

3C.1.5  **Recommendations for the treatment of stuttering priapism**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
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<tbody>
<tr>
<td>The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can generally be achieved pharmacologically.</td>
<td>B</td>
</tr>
<tr>
<td>The management of each acute episode is similar to that for ischaemic priapism.</td>
<td>B</td>
</tr>
<tr>
<td>Hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or antiandrogens may be used for the prevention of future episodes. They should not be used before sexual maturation is reached.</td>
<td>C</td>
</tr>
<tr>
<td>Phosphodiesterase type 5 inhibitors (PDE5Is) have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease associated priapism. Treatment should be initiated only when the penis is in its flaccid state.</td>
<td>C</td>
</tr>
<tr>
<td>Other systemic drugs (digoxin, alpha-adrenergic agonists, baclofen, gabapentin, terbutaline) can be considered, but data are even more limited.</td>
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</tr>
<tr>
<td>Intracavernosal self-injections at home of sympathomimetic drugs can be considered for the treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.</td>
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</tr>
</tbody>
</table>

3C.1.6  **Follow-up**

Follow-up for stuttering priapism include history and clinical examination to assess the efficacy of treatments in preventing or alleviating erectile events as well as assessing erectile function and penile fibrosis.

4. REFERENCES


http://www.ncbi.nlm.nih.gov/pubmed/10789908


http://www.ncbi.nlm.nih.gov/pubmed/8753749


5. CONFLICT OF INTEREST

All members of the EAU Male Sexual Dysfunction Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.