Guidelines

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Guideline of guidelines: priapism

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Introduction

Priapism is defined as a prolonged penile erection lasting for >4 h in the absence of sexual stimulation and remains despite orgasm. Current guidelines for priapism have been published after a comprehensive literature review and expert consensus by the AUA and by an evidence review according to the Oxford Centre for Evidence-Based Medicine (OCEBM) by the European Association of Urology (EAU). Although there are both local and regional guidelines available throughout the UK, these tend to be adaptations of guidelines from larger urology organisations and there are currently no guidelines available from the BAUS. However, in the UK the management of complex cases is increasingly undertaken in specialist centres with the basic management following existing guidelines.

As priapism is a urological emergency, which requires immediate detumescence, the condition does not lend itself to randomised controlled trials and the EAU guidelines are based, at best, on Level 3 evidence.

Methodology

The AUA guidelines [1], first published in 2003 with a further validation in 2010, are a set of recommendations from a selected panel of experts in priapism who arrive at a consensus based on the available literature. A peer-review process is used with the final consensus submitted to the board of directors at the AUA. The report is based on the current literature, expert opinion, and clinical experience.

The EAU guidelines [2] use a systematic literature search (1 688 articles, a combination of original papers and case reports) to grade the level of evidence according to the OCEBM classification. Again, the guidelines are peer reviewed before publication.

As there are no peer-reviewed UK guidelines, current practice is based on these available guidelines, as well as expert opinion from research and clinical studies published from specialist UK units. These will be used to compare the variation in practice in the UK.

Aetiology of Priapism

The three main subtypes are ischaemic, non-ischaemic, and stuttering priapism, although the terminology does vary in different guidelines. In ischaemic priapism the underlying pathophysiology is still not completely understood, but the initiating mechanisms are likely to be multifactorial involving central neuronal pathways, alterations in the corpus cavernosum microenvironment, modulation of the smooth muscle contractile machinery, and aberrant neurotransmitter regulation in the corpus cavernosum leading to dysregulation of the smooth muscle.

Obstruction of the penile venous outflow, which leads to stasis of blood within the corpus cavernosum akin to a compartment syndrome, results in the development of hypoxia, acidosis, and glucopenia that results in smooth muscle dysfunction the longer the duration of ischaemia [3].

Although a specific aetiology cannot be found in up to one-third of cases, vasoactive intracavernosal injections, psychotropic medications, recreational drugs, alcohol abuse, and direct infiltration of the corpora by pelvic malignancies, are the common causes of ischaemic priapism.

Furthermore, conditions associated with increased blood viscosity such as parenteral nutrition and haemoglobinopathies, such as sickle cell disease, thalassaemia, and haematological malignancies, can potentially cause ischaemic priapism secondary to the obliteration of the small emissary veins in the subtunical space.

Ischaemic priapism is a medical emergency as the progressive ischaemia within the cavernosal tissue is associated with time-dependent changes in the corporal metabolic environment, which eventually leads to smooth muscle necrosis. As the duration of the penile erection

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becomes pathologically prolonged, as in the case of low-flow priapism, the partial pressure of oxygen (pO_2) progressively falls as the closed compartment prevents replenishment of stagnant blood with freshly oxygenated arterial blood. Broderick and Harkaway [4] analysed the change in cavernosal blood gas parameters in patients presenting with prolonged penile erections following pharmacologically induced erections. There were time-dependent alterations in the pO_2, pH, and partial pressure of carbon dioxide (pCO_2) during the erection, and after 240 min the cavernosal tissue was no longer perfused by highly oxygenated blood. Persistent blood stasis for >2 days is associated with infiltration of the trabecular tissue with inflammatory cells and the smooth muscle cells undergo necrosis or phenotypic change into fibroblast-like cells [5].

Comparison of Guidelines

Definition of Priapism

Both the AUA and EAU stipulate a 4-h time-frame for the duration of the erection in order to classify it as a priapism. Pre-clinical studies in the UK using *in vitro* models have also consistently used a 4-h window, as these models show that irreversible smooth muscle dysfunction starts at 4 h after the onset of ischaemia [3].

The classification of priapism is conventionally divided into three main groups. The commonest classification is into non-ischaemic (high flow), ischaemic (low flow), and stuttering (recurrent) subtypes [6,7]. The EAU guidelines refer to the subtypes as ischaemic (low flow, veno-occlusive) and arterial (high flow, non-ischaemic). Of these ischaemic priapism is the commonest, with refractory cases at risk of smooth muscle necrosis in the corpus cavernosum leading to a sequelae of corporal fibrosis and erectile dysfunction (ED).

The AUA guidelines use the terms ischaemic (veno-occlusive, low flow), non-ischaemic (arterial, high flow), and stuttering (intermittent). These definitions are clearer to clinicians and ensure that urgent intervention occurs when faced with an ischaemic priapism, as the long-term smooth muscle recovery and ultimately erectile function is time dependent. In the UK, using the terms ischaemic and non-ischaemic is common place and should be incorporated into local guidelines.

Diagnosis and Investigation of Priapism Episodes

Both the EAU and AUA guidelines are consistent in relation to the clinical pathway required to establish a diagnosis and undertake the appropriate investigations to establish a diagnosis and differentiate the different subtypes. A clinical history with a focus on possible risk factors including, haematological disorders (e.g. sickle cell disease), drug history (intracavernosal agents, antipsychotics), and a preceding history of genitourethral trauma (associated with non-ischaemic priapism), should be taken. Although both ischaemic and non-ischaemic priapism present with an erection, the distinct lack of pain in non-ischaemic priapism is attributed to the absence of an ischaemic microenvironment within the corpora. In ischaemic priapism, the progressive hypoxia and acidosis developing within a closed compartment results in activation of nociceptors.

One of the key considerations in the management of priapism is the duration of the erection at presentation. The AUA guidelines do not subdivide the time points into distinct intervals where specific pharmacological or surgical interventions are recommended. The EAU guidelines do differentiate the time periods such that the intervention varies accordingly, which is particularly important for prolonged episodes that are refractory to pharmacological interventions and allow a step-wise intervention. This is again highlighted in publications based on the incidence of ED after shunt surgery in a UK centre, which indicates a high incidence of ED such that an early penile prosthesis is recommended [8,9].

Investigations using corporal blood aspiration, that in itself can be a therapeutic intervention leading to partial or complete penile detumescence, helps to differentiate ischaemic from non-ischaemic priapism subtypes based on the pO_2, pCO_2 and pH levels. The AUA guidelines state that typically the blood gas analysis would give a pO_2 of <30 mmHg and pCO_2 of >60 mmHg and a pH of <7.25 in ischaemic priapism, whereas non-ischaemic blood gas analysis would show values similar to venous blood.

Stuttering priapism is often either self-limiting or resolves following oral medication or conservative therapeutic manoeuvres that patients themselves have developed, e.g. waking up and going up and down stairs or exercising. Where the stuttering priapism episodes are prolonged and without spontaneous resolution, corporal blood aspiration and blood gas analysis as for ischaemic priapism should be performed.

Imaging methods, such as Doppler ultrasonography, again help to differentiate between ischaemic and non-ischaemic priapism and imaging is included in the diagnostic evaluation in both the AUA and EAU guidelines. In refractory cases, penile MRI has been used to help diagnose corpus cavernosum smooth muscle necrosis, with one study showing an excellent correlation between the penile MRI and corporal biopsies in suspected smooth muscle necrosis secondary to refractory ischaemic priapism [10]. The AUA guidelines do not mention penile MRI as a diagnostic test, although it is mentioned as an imaging method for priapism in the EAU guidelines. For non-ischaemic cases, arteriography is mentioned in both guidelines in order to identify an arterio-lacunar fistula and allow subsequent therapeutic embolisation.

Management of Priapism According to Subtypes

Ischaemic Priapism

Once the diagnosis of priapism has been made, the initial management involves corporal blood aspiration followed by instillation of α-agonists directly into the corpus cavernosum. The AUA guidelines give a choice of sympathomimetic agents as follows:

- Epinephrine (adrenaline).
- Norepinephrine (noradrenaline).
- Metaraminol.
- Phenylephrine.

The EAU guidelines recommend a number of possible agents for intracavernosal injection, as well as oral terbutaline after intracavernosal injection.

- Phenylephrine – 200 μg every 3–5 min to a maximum of 1 mg within 1 h.
- Etilephrine – 2.5 mg diluted in 1–2 mL saline.
- Adrenaline – 2 mL of 1/100 000 solution given up to 5 times in a 20-min period.
- Methylene blue – 50–100 mg intracavernosal injection followed by aspiration and compression.

The AUA guidelines recommend phenylephrine injections at a dose of 100–500 μg every 3–5 min. In comparison, within the UK, the commonest agent based on referrals and drug usage in the largest specialist centres managing priapism is phenylephrine, which is normally available in a 10-mg vial and diluted such that between 200 and 500 μg aliquots can be injected intracavernosally to achieve complete detumescence.

Non-Ischaemic Priapism

Pharmacological agents are unlikely to be effective due to the aberrant blood flow in a suspected fistula. As the blood within the corpus cavernosum is well oxygenated the risk of smooth muscle necrosis and subsequent fibrosis is low, and therefore a period of conservative treatment is recommended in both the AUA and EAU guidelines. If this fails then arteriography followed by superselective embolisation of the fistula can be performed using absorbable material. Although this is also common practice in the UK, the suggested period of conservative treatment has yet to be defined. A recently published UK case series has reported the development of distal corporal fibrosis following non-ischaemic priapism, despite the presence of oxygenated blood within the corpora, which manifests as ED or distal flaccidity [11]. Therefore, in some specialist centres, there is a shift towards early embolisation if there are clinical signs of progressive distal flaccidity developing or if repeat imaging using penile MRI indicates that distal fibrosis of the corpora is developing.

Stuttering Priapism

Patients with sickle cell disease and haematological conditions are the commonest group of patients presenting with stuttering priapism. However, idiopathic stuttering priapism comprises a distinct group of patients with no obvious underlying risk factors but they often present with self-limiting painful nocturnal prolonged erections.

The AUA guidelines state that patients presenting with haematological disorders should still follow the same treatment algorithm for ischaemic priapism, as well as simultaneously undergoing treatment for the underlying haematological disorder. There is no overall consensus about the role of exchange transfusions etc. for patients with sickle cell disease but there are specific sickle cell disease guidelines that provide details on recognising conditions such as priapism in patients with sickle cell disease.

There is a paucity of published literature relating to stuttering priapism due to the rarity of the condition. In the UK, therapeutic interventions have been reviewed in the largest published series and suggest that anti-androgens are effective as first-line treatment [12,13].

Surgical Interventions for Priapism

Shunt surgery allows diversion of blood from the corpus cavernosum into another area such as the corpus spongiosum (glans or urethra) or the venous system (saphenous vein). Both the EAU and AUA guidelines recommend surgical intervention using firstly distal shunts and then proximal shunts in cases where aspiration and instillation of pharmacological agents fails to achieve penile detumescence. The EAU guidelines recommend that distal shunts should be attempted before proximal shunts, although the specific technique is left to the individual surgeon's preference. The EAU guidelines also define a time point (36 h) when shunt surgery is likely to be ineffective in maintaining long-term erectile function and may serve to reduce pain only. This is an important consideration when contemplating early penile prosthesis placement. The shunts described in the EAU and AUA guidelines are shown in Table 1.

Table 1 Various shunts described in the AUA and EAU guidelines.

EAU guidelines	AUA guidelines
Winter shunt	Winter shunt
Ebbehoj technique	Ebbehoj technique
T shunt	Al-Ghorab procedure
Al-Ghorab procedure	Quackles technique
Burnett technique	Grayhack shunt
Quackles technique	
Grayhack shunt	

Table 2 Various materials used for superselective embolisation.

Absorbable	Non-absorbable
Autologous blood clot	Coils
Gelatine sponge	Ethanol
	Polyvinyl alcohol
	Acrylic glue

Table 3 Treatment options for stuttering priapism.

AUA guidelines	EAU guidelines
Hormonal agents (GnRH agonists or anti-androgens, diethylstilboestrol)	Pseudoephedrine
Digoxin	Etilefrine
Baclofen	Hormonal agents (GnRH agonists or anti-androgens, oestrogens)
Terbutaline	5-α reductase inhibitors
Intracavernosal self-injection with phenylephrine	Ketoconazole
	Digoxin
	Terbutaline
	Gabapentin
	Baclofen
	Hydroxyurea
	Phosphodiesterase type 5 inhibitors
	Intracavernosal injections

The long-term outcomes after shunt surgery appear to be variable amongst all the guidelines. In the AUA guidelines, the rate of ED is quoted as <25% for distal shunts and 50% for proximal shunts. Again, this is based on the panel consensus and poor levels of evidence. In contrast, the EAU does not mention the individual risk of ED after proximal or distal shunt surgery. In the largest published UK series, a follow-up of patients undergoing a distal shunt (T shunt or corporal 'snake' manoeuvre) indicated that even if there was successful detumescence after a priapism lasting <24 h, ~50% of patients would develop ED. If the duration was ≥48 h then 100% develop ED [14].

Refractory cases that do not resolve after aspiration, pharmacological treatment or shunt surgery are a difficult group of patients to manage. The evidence from clinical and pre-clinical studies show that irreversible corpus cavernosum smooth muscle dysfunction as a result of prolonged ischaemia occurs and the rate of long-term ED is high [15,16]. The AUA guidelines do not mention a treatment algorithm for refractory cases and limit the details of the treatment pathway up to shunt surgery. However, the EAU guidelines state that cases lasting for >36 h may be considered for an acute penile prosthesis implantation. This proposal has been deemed controversial since a UK series was published in 2002 [8]. Subsequently, the largest series of acute malleable penile prostheses for ischaemic priapism has been published in the UK and demonstrates a 96% patient satisfaction rate, as it allows patients to maintain their penile length and rigidity with the option later of an exchange to an inflatable penile prosthesis and upsizing to a larger implant [17]. This is recommended as a primary treatment for cases presenting with ischaemic priapism lasting for >72 h, as well as those who have a duration of 24–48 h but have failed to detumesce after distal shunt surgery provided that there is image verification that there is no blood flow and features of cavernosal smooth muscle necrosis by using penile Doppler studies and penile MRI.

Management of Non-Ischaemic Priapism

Non-ischaemic priapism occurs secondary to unregulated arterial inflow, commonly after a traumatic laceration of the cavernosal artery and the development of an arterio-sinusoidal fistula. The AUA guidelines suggest that 62% will spontaneously resolve but one-third will subsequently report erectile difficulties. The explanation for this is not clear. These guidelines also state that aspiration of blood from the corpus cavernosum is solely for diagnostic purposes. They also state that the time interval from sustaining the injury to resolution does not have an impact on the long-term outcomes. Selective embolisation is recommended if patients request it but the AUA does not propose a specific time period before embolisation should be performed. However, it does make it clear that absorbable materials are the preferred option rather than non-absorbable coils. The resolution rate using absorbable material is 74% with a 5% ED rate compared to 78% for non-absorbable material that also carries a 39% risk of ED. Table 2 lists the materials proposed by the AUA guidelines.

The EAU guidelines propose a similar diagnostic pathway and recommend either absorbable or non-absorbable material as a Grade B recommendation. More conservative options such as ice packs, compression on the perineum, and anti-androgen treatment to reduce spontaneous erections and allow closure of the fistula are also proposed in the guidelines. It is recommended that refractory cases should be offered surgical ligation. The preservation of sexual function is reported in 80% of cases (Grade C).

Stuttering (Intermittent or Recurrent Priapism)

The AUA guidelines use the terms stuttering and recurrent priapism interchangeably. They propose that each episode should be managed as for an episode of ischaemic priapism but the long-term management plan involves a strategy to reduce the number of episodes using either systemic treatment or surgery.

Table 3 lists the various treatment options mentioned in both guidelines for comparison, but it should be noted that these are based on small case series or anecdotal reports. The use of a phosphodiesterase type 5 inhibitor shows a paradoxical effect in patients with stuttering priapism and is used as a preventative therapy for recurrent attacks when the penis is in the flaccid state as opposed to during an acute ischaemic

episode. In some cases patient self-injection therapy with sympathomimetics has also been used. This is to prevent hospitalisation of patients with acute episodes and both the AUA and EAU guidelines include the use of self-injection as an option for individuals who develop prolonged erections despite systemic treatment. Patients should be taught the technique and also warned about the side-effects.

Conclusions

Of the two highly cited guidelines on priapism, the EAU guidelines have used an evidence-based approach, whereas the AUA guidelines have been developed based on a literature review and consensus statement. With the lack of randomised controlled trials in this subject area, the EAU guidelines are generally Grade B and C recommendations, and are based on case series and case reports. The guidelines do differ, with the EAU guidelines offering a more extensive pathway for the management of refractory ischaemic priapism patients. At present, there are no published UK guidelines, although the practice generally reflects the management pathway developed in an andrology specialist centre and published in a paper investigating the outcomes following shunt surgery [16].

Key points

- Priapism is divided into three main subtypes: ischaemic, non-ischaemic, and stuttering
- Differentiating between ischaemic and non-ischaemic subtypes is important to prevent irreversible smooth muscle dysfunction
- Ischaemic priapism requires prompt management with aspiration and adrenergic agonists
- Refractory cases should be offered shunt surgery if within a reasonable time frame
- Failure of treatment signifies smooth muscle necrosis and therefore an early penile prosthesis can be offered

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Conflict of Interest

None.

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Abbreviations: EAU, European Association of Urology; ED, erectile dysfunction; NIHR, National Institute for Health Research; OCEBM, Oxford Centre for Evidence-Based Medicine; pCO_2, partial pressure of carbon dioxide; pO2, partial pressure of oxygen.