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EAU Guidelines

# Comparison of EAU and UK guidelines on priapism

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## Abstract

Priapism is a rare condition defined as a prolonged penile erection lasting for more than four hours in the absence of sexual stimulation and remains despite orgasm. Priapism guidelines have been published following an evidence review by the European Association of Urology (EAU). Within the UK, local guidelines are sometimes available and these tend to be adaptations of guidelines from the American Urological Association or the EAU together with input from the local haematology department since sickle cell patients represent a high-risk group. As yet there are no guidelines available from the British Association of Urological Surgeons.

## Keywords

European, ischaemic, non-ischaemic, priapism, shunts

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## Introduction

Priapism is a rare condition defined as a prolonged penile erection lasting for more than four hours in the absence of sexual stimulation and remains despite orgasm.<sup>1</sup> Priapism guidelines have been published following an evidence review according to the Oxford Centre for Evidence-Based Medicine by the European Association of Urology (EAU).<sup>2</sup> Within the United Kingdom (UK), local guidelines are sometimes available within urology departments and these tend to be adaptations of guidelines from the American Urological Association (AUA) or EAU together with input from the haematology department as sickle cell patients represent a high-risk group. As yet there are currently no published guidelines available from the British Association of Urological Surgeons (BAUS). However, in the UK the management of complex cases is increasingly undertaken in specialist andrology centres with the option of referring complex or refractory cases to tertiary centres if initial management fails. Priapism is a urological emergency which requires urgent intervention to ensure immediate detumescence and therefore the condition does not lend itself to good quality randomised controlled trials (RCTs)

and therefore the EAU guidelines are based at best on Level 3 evidence.

## Methodology

The EAU guidelines use a systematic literature search (1688 articles – combination of original papers and case reports) to grade the level of evidence according to the Oxford Centre for Evidence-Based Medicine classification. The guidelines are peer reviewed before publication.

As there are currently no peer-reviewed UK guidelines, the practice in the UK is based on a combination of

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AUA and EAU guidelines as well as expert opinion from research and clinical studies published from specialist UK units. With the development of priapism databases at a local level which allow a larger number of patients to be incorporated into case series, best practice UK guidelines can now be developed from these published data.

## 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 (IP) the underlying pathophysiology is still not completely understood although the initiating mechanisms are likely to be multifactorial involving central neuronal pathways, alterations in the corpus cavernosum micro-environment, 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, which results in smooth muscle dysfunction as the duration of ischaemia increases.<sup>3</sup>

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 common causes of IP.

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 IP secondary to the obliteration of the small emissary veins in the subtunical space.

IP is a medical emergency as the progressive ischemia within the cavernosal tissue is associated with time-dependent changes in the corporal metabolic environment, which leads to smooth muscle necrosis. As the duration of the penile erection becomes pathologically prolonged as in the case of IP, the  $pO_2$  progressively falls as the closed compartment prevents replenishment of stagnant blood with freshly oxygenated arterial blood. Broderick and Harkaway analysed the change in the cavernous 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  $pCO_2$  during the erection and after 240 minutes the cavernous tissue is no longer perfused by highly oxygenated blood.<sup>4</sup> Persistent blood stasis for longer than two days is associated with infiltration of the trabecular tissue with inflammatory cells and the smooth muscle cells undergoing necrosis or phenotypic change into fibroblast-like cells.<sup>5</sup>

## Definitions

The EAU guidelines stipulate a four-hour 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 utilised a four-hour window as these models show that irreversible smooth muscle dysfunction starts at four hours following ischaemia.<sup>3</sup>

The classification of priapism is conventionally divided into three main groups. The commonest classification uses the terms non-ischaemic (high-flow), ischaemic (low-flow) and stuttering (recurrent) subtypes.<sup>6,7</sup> The EAU guidelines refer to priapism subtypes as ischaemic (low-flow, veno-occlusive) and arterial (high-flow, non-ischaemic).<sup>2</sup> Of these IP is by far 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).

Definitions should be clear for non-urological clinicians as they may range from haematologists to emergency physicians and it ensures that urgent medical intervention is performed when faced with a patient presenting with an IP. This is important as long-term corpus cavernosum smooth muscle recovery and ultimately erectile function is time dependent. In the UK using the terms ischaemic and non-ischaemic is commonplace both in clinical practice and publications and should be incorporated into local guidelines.

## Diagnosis and investigation

The EAU guidelines are consistent in relation to the clinical pathway required to establish a diagnosis and undertake the appropriate investigations to establish and differentiate the 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 high-flow/non-ischaemic priapism) is required. Although both ischaemic and non-ischaemic priapism present with a prolonged erection, the distinct lack of pain in non-ischaemic priapism is attributed to the absence of an ischaemic micro-environment within the corpora. In IP, the development of progressive hypoxia and acidosis within a closed compartment results in activation of nociceptors resulting in penile pain.

One of the key considerations in the management of priapism is the duration of the erection at presentation. The EAU guidelines differentiate the time periods such that the type of intervention varies depending on the duration of the priapism episode, which is particularly important for prolonged episodes which are refractory to pharmacological interventions and allows a step-wise management protocol. This is again highlighted in

publications based on the high incidence of long-term ED following shunt surgery published from a tertiary UK centre proposing early penile prosthesis insertion for refractory cases.<sup>8,9</sup>

Investigations using corporal blood aspiration, which in itself can be a therapeutic intervention leading to partial or complete penile detumescence, help to differentiate ischaemic from non-ischaemic priapism subtypes based on the  $pO_2$ ,  $pCO_2$  and pH levels.

The rarer subtype, 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 IP should be performed.

Imaging modalities such as Doppler ultrasonography again help to differentiate between ischaemic and non-ischaemic priapism and are included in the diagnostic workup in the EAU guidelines. In refractory cases, penile magnetic resonance imaging (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 IP.<sup>10</sup> For non-ischaemic cases, arteriography is suggested in the EAU guidelines in order to identify an arterio-lacunar fistula and allow subsequent therapeutic embolisation.

## Management of priapism

### IP

Once the diagnosis is made, the initial management involves corporal blood aspiration followed by instillation of alpha agonists into the corpus cavernosum.

The EAU guidelines recommend a number of possible agents for intracavernosal injection as well as oral terbutaline following intracavernosal injection. The intracavernosal agents recommended for injection are:

- Phenylephrine – 200 µg every three to five minutes to a maximum of 1 mg within one hour
- Etilephrine – 2.5 mg diluted in 1–2 ml saline
- Adrenaline – 2 ml of 1/100,000 solution given up to five times in a 20-minute period
- Methylene Blue – 50–100 mg intracavernosal injection followed by aspiration and compression

In comparison, within the UK the commonest agent based on referrals and drug usage in the largest centres is phenylephrine, which is normally available in a 10 mg vial and diluted such that between 200 and 500 microgram aliquots can be injected intracavernosally in order 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 in the corpus cavernosum is well oxygenated, the risk of smooth muscle necrosis and corporal fibrosis is low and therefore a period of conservative treatment is recommended in the EAU guidelines. If this fails then arteriography followed by superselective embolisation 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 recent UK case series which has reported the development of distal corporal fibrosis following non-ischaemic priapism shows that despite the presence of oxygenated blood within the corpora, ED can still occur.<sup>11</sup> Therefore, in some specialist centres, early embolisation is undertaken if there are clinical signs of progressive distal flaccidity developing or if repeat imaging using penile MRI indicates the presence of distal fibrosis 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, often nocturnal, prolonged erections.

There is no overall consensus regarding the role of exchange transfusion etc. in sickle cell disease but there are specific sickle cell disease guidelines which provide details on recognising conditions in patients with sickle cell disease.

There is a paucity of published literature relating to stuttering priapism due to the rarity of the condition. A number of different pharmacological interventions have been suggested in the EAU guidelines (Table 1). In the UK, therapeutic interventions have been reviewed in the largest published series and suggest that anti-androgens are effective for first-line treatment.<sup>12,13</sup>

Table 1 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 phosphodiesterase type 5 (PDE-5) inhibitors shows a paradoxical effect in patients with stuttering priapism and are 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 the 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.

**Table 1.** Treatment options for stuttering priapism.

EAU Guidelines
Pseudoephedrine
Etilefrine
Hormonal agents (GnRH agonists or anti-androgens, oestrogens)
5-Alpha reductase inhibitors
Ketoconazole
Digoxin
Terbutiline
Gabapentin
Baclofen
Hydroxyurea
PDE-5 inhibitors
Intracavernosal injections

EAU: European Association of Urology; GnRH: gonadotropin-releasing; PDE-5: phosphodiesterase type 5.

### Surgical interventions

Shunt surgery allows diversion of blood from the corpus cavernosum into another area such as the corpus spongiosum or the venous system. The EAU guidelines recommend surgical intervention using distal shunts and proximal shunts in situations where aspiration and instillation of pharmacological agents fail to achieve 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 hours) when shunt surgery is likely to be ineffective in maintaining long-term erectile function and may serve to reduce pain only. The shunts described in the EAU guidelines are shown in Table 2.

The EAU guidelines do not mention the individual risk of ED following proximal or distal shunt surgery. In the largest published UK series, a follow-up of patients undergoing a distal shunt (T shunt or Snake manoeuvre) indicated that even if there was successful detumescence following a priapism episode lasting less than 24 hours, approximately 50% of patients would develop ED. If the duration was 48 hours or more, then 100% develop ED.<sup>14</sup>

Refractory cases which do not resolve following 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

**Table 2.** Surgical interventions for priapism.

EAU
Winter shunt
Ebbehoj technique
T shunt
Al-Ghorab
Burnett technique
Quakle's technique
Grayhack's procedure

EAU: European Association of Urology.

is high.<sup>15,16</sup> The EAU guidelines state that cases lasting over 36 hours may be considered for an acute penile prosthesis implantation. This proposal has been deemed controversial since a UK series was published in 2002.<sup>8</sup> Subsequently the largest series of acute penile prostheses for IP 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 later option of an exchange to an inflatable penile prosthesis and upsizing to a larger implant.<sup>9,17</sup> This is recommended as a primary treatment for cases presenting with IP lasting for over 72 hours as well as those which have a duration of 24–48 hours but have failed to achieve detumescence following 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 EAU guidelines propose a diagnostic pathway for non-ischaemic priapism 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).

### Conclusions

The EAU guidelines use an evidence-based approach to develop guidelines and treatment pathways. Priapism

presents a difficult disease group to perform randomised trials due to the urgent intervention required to manage the condition. With the lack of RCTs in this subject area, the EAU guidelines are generally Grade B,C and are based on cases series and case reports. At present there are no published UK guidelines on priapism *per se* although the practice generally reflects the management pathway developed in large tertiary centres with one pathway published in a UK paper investigating the outcomes following shunt surgery.<sup>14</sup>

### Conflicting interests

The Authors declare that there is no conflict of interest.

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### Ethical approval

Not applicable.

### Informed consent

Not applicable.

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