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REVIEW

An update on the management algorithms of priapism during the last decade

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Summary ***Priapism is a persistent penile erection lasting longer than 4 hours, that needs emergency management. This disorder can induce irreversible erectile dysfunction. There are three subtypes of priapism: ischemic, non-ischemic, and stuttering priapism. If the patient has ischemic priapism (IP) of less than 24-hours (h) duration, the initial management should be a corporal blood aspiration followed by instillation of phenylephrine into the corpus cavernosum. If sympathomimetic fails or the patient has IP from 24 to 48h, surgical shunts should be performed. It is recommended that distal shunts should be attempted first. If distal shunt failed, proximal, venous shunt, or T-shunt with tunneling could be performed. If the patient had IP for 48 to 72h, proximal and venous shunt or T-shunt with tunneling is indicated, if those therapies failed, a penile prosthesis should be inserted. Non-ischemic priapism (NIP) is not a medical emergency and many patients will recover spontaneously. If the NIP does not resolve spontaneously within six months or the patient requests therapy, selective arterial embolization is indicated. The goal of the management of a patient with stuttering priapism (SP) is the prevention of future episodes. Phosphodiesterase type 5 (PDE5) inhibitor therapy is considered an effective tool to prevent stuttering episodes but it is not validated yet. The management of priapism should follow the guidelines as the future erectile function is dependent on its quick resolution. This review briefly discusses the types, pathophysiology, and diagnosis of priapism. It will discuss an updated approach to treat each type of priapism.***

KEY WORDS: Priapism; Ischemic priapism; Non-ischemic priapism; Stuttering priapism.

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INTRODUCTION

Priapism is defined as a persistent erection due to abnormal mechanisms regulating penile tumescence, rigidity, and flaccidity. The rapid diagnosis and management of priapism are necessary to spare patients ineffective interventions and maintain erectile function outcomes (1). The use of intracavernous injections of papaverine rapidly increases the number of men seeking attention for priapism, a previously rare disease. The use of recreational drugs (cocaine) and perineal trauma leading to presentations of priapism seem to be rising in incidence (2). There are essentially two main types of priapism: high flow and low flow. Low flow priapism is more common, and it is associated with a decrease in venous outflow and vascular stasis that, in turn, cause tissue hypoxia and acidosis. High flow priapism is usually due to trauma, although, on rare occasions, it has been idiopathic. The hallmark of this type of priapism is an increase in arterial inflow in the setting of normal venous outflow (3). A general overview of the types of priapism is summarized in Table 1.

The primary goals of medical therapy for *ischemic priapism* (IP) are to decompress the corporal bodies and restore arterial blood flow. Management of IP should progress in an aggressive and stepwise fashion.

Management of acute IP starts with the aspiration of blood and the irrigation of the corpora cavernosa, in combination with the use of intracavernous α-agonist injection therapy. Phenylephrine is the preferred sympathomimetic agent, but other α-adrenergic agonists may be used, such as ephedrine, epinephrine, norepinephrine, or metaraminol. Caution should be taken when using those agents based on the patient's cardiovascular profile and time used for injection (4). If conservative therapies failed to resolve IP, it is recommended to perform distal shunting first (5). *European Urology Association* (EAU) guidelines currently recommended that if priapism persists despite the use of first-line treatments including shunting procedures, ED is inevitable. Immediate PP insertion is recommended to avoid the corporal fibrosis associated with later insertion (6). It is crucial to prevent future episodes of IP due to its high morbidity. Many drugs have been used for this purpose such as oral use of terbutaline, digoxin, baclofen, estrogens, *gonadotropin-releasing hormone agonists* (GnRH), antiandrogens, and PDE5 inhibitors (7). Table 2 summarizes the advantages and the disadvantages of each type of therapy used in priapism.

It is reasonable to presume that patients diagnosed to have *non-ischemic priapism* (NIP) can undergo observation and conservative management, then pursue embolization if possible with temporary agents (8). Angiography with super-selective embolization is the treatment of choice if

No conflict of interest declared.

Table 1.
Overview of each type of priapism.

Characteristics of each type	Ischemic priapism	Non Ischemic priapism	Stuttering priapism
Etiologies	· Iatrogenic · Medications · Intracavernous injection · Idiopathic	· Traumatic rupture of the cavernous artery or its branches	· Similar to the causes of ischemic priapism · Sickle cell disease is the common cause
Symptoms	· Penile pain · Rigid corpora	· Erection without full rigidity · No pain · Penile trauma	· Same as ischemic type · Multiple recurrent episodes are usually noted
Corporal blood aspirate	· Blood is dark · Acidity (pH < 7.25) · High PCO2 (> 60 mmHg) · Low PO2 (< 30 mmHg)	· Blood is bright red · PO2 > 90 · PCO2 < 40 · PH of 7.4	· Same as ischemic type
Color Doppler findings	· Lack of cavernous artery blood flow · Very high-resistance flow pattern in the cavernous artery	· Doppler waveforms with peak systolic velocity > 50 cm/s, and end-diastolic velocity that is 0 or negative	· Low peripheral resistance waveform · Elevated, variable cavernosal artery velocity

Table 2.
Advantages and disadvantages of each type of therapy used in priapism.

Type of therapy	Advantages	Disadvantages
Penile aspiration and irrigation used in IP	· Easy to learn · Minimally invasive	· High failure rate · Contraindicated in patients with bleeding disorders or using anticoagulation
Intracavernosal injections of pharmacological agents used in IP	· Easy to learn · Minimally invasive	· Cardiac side effects · Require cardiovascular monitoring · Less than 60% efficacy
Shunt surgery used in IP	· Usually, proximal shunt procedures are easy to learn · Can be used in patients whose intracavernous injections are contraindicated	· Usually, proximal shunt procedures are difficult to learn · Invasive procedures · Duration of priapism affects resolution rates
Penile prosthesis used in IP	· Allow recovery of sexual function	· Increased risk of prosthetic infection · In chronic cases, penile prosthesis surgery is difficult due to fibrosis
Hormonal therapy used in SP	· Allow fistula to heal more easily	· It may cause erectile dysfunction · Multiple side effects such as hot flashes, fatigue, decreased libido
Selective arterial embolization used in SP cases	· Minimally invasive	· It may cause erectile dysfunction · High failure rate · Can cause penile gangrene · Can cause perineal abscess

IP: Ischemic priapism; NIP: non ischemic priapism; SP: Stuttering priapism

prompt definitive management of NIP is desired. Cavernosal artery ligation is another option reserved in case of failures of embolization (9). We performed a narrative review to discuss briefly the types, pathophysiology, and diagnosis of priapism. This review will focus on updates in the treatment of each type of priapism.

Materials and methods

We searched electronic databases including PubMed and the Scopus database for published studies that analyzed the role of the following *Medical Subject Headings* (MeSH) terms: 'priapism' (AND) 'erectile dysfunction' (OR) 'ischemic priapism' (AND) 'management' (OR) 'non-ischemic priapism' (AND) 'management' (OR) 'stuttering priapism' (AND) 'management'.
This was done in order to ensure the comprehensive inclusion of articles related to the management of priapism. The initial search resulted in 250 articles. After review, we initially excluded papers that were not relevant: 96 articles. At the completion of the review, 154 articles were selected based on their clinical relevance related to the aim. Data extraction was performed by all authors. Table 3 resumes the research summary.

Overview of priapism

Types of priapism

There are three different types of priapism: low-flow or ischemic; high-flow or non-ischemic priapism; and recurrent or stuttering priapism (10). *Stuttering priapism* (SP) manifests in recurring episodes of IP incidents of varying duration and should be distinguished from the persistence or rapid recurrence of a single episode of acute priapism. Although many of these episodes are self-limited, they can increase in duration and incidence, leading to acute major IP events requiring emergency medical management (11).

Table 3.
Search summary used in our review.

Section of our review	Number of articles screened related to the topic	Number of articles excluded from the review process	Number of articles that were relevant to the review aims	Reasons to exclude articles from our review
Priapism definition	10	5	5	Not relevant to the aims Repetitive content
Priapism types	15	9	6	Not relevant to the aims Repetitive content
Priapism etiologies	9	4	5	Not relevant to the aims Repetitive content
Priapism diagnosis	30	14	16	Not relevant to the aims Repetitive content Editorials/comments
Treatment of IP	70	18	52	Not relevant to the aims Repetitive content Preclinical studies Pilot studies Editorials/comments Same intervention, different outcomes
Treatment of NIP	56	18	38	Not relevant to the aims Repetitive content Preclinical studies No relevant outcomes No comparison group
Treatment of SP	60	28	32	Not relevant to the aims Repetitive content Preclinical studies No outcomes Editorials/comments Studies from the same author(s)

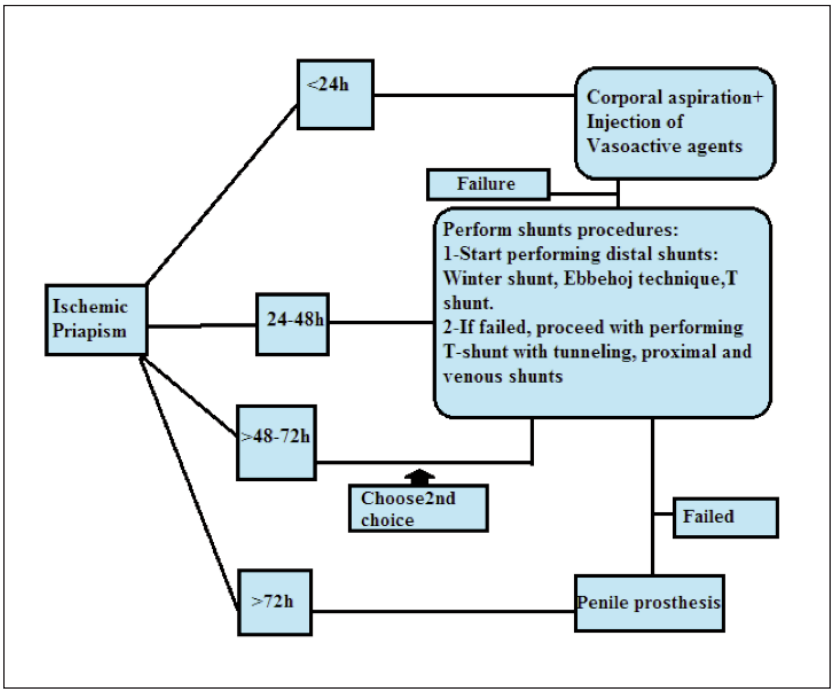
IP: Ischemic priapism; NIP: non ischemic priapism; SP: Stuttering priapism.

Epidemiology of priapism
Epidemiologic studies reported an overall incidence rate of 1.5 per 100,000 man-years. The incidence rate in men 40 years old and older was 2.9 per 100,000 person-years (12). *Roghmann et al.* reported 32,462 visits to the emergency department for priapism between 2006 and 2009 in the United States, which represents a national incidence of 5.34 per 100,000 male subjects per year (13). *Kulmala et al.* reviewed all cases of priapism in Finland during the years 1975-90. When cases due to intracorporal injections were excluded, the incidence of priapism was stable and varies from 0.34 to 0.52/100000 males per year. Most cases of priapism were seen during the lighter half of the year, between March and August (14).
The incidence of priapism among patients with *sickle-cell disease* (SCD) is high (35%). The implications of priapism for erectile and sexual function are significant (15). 30% of males with SCD under the age of 20 years reported at least one episode of priapism, whereas frequencies of 30% to 45% are estimated for adult men (16).

Etiology of priapism
Numerous etiologies of priapism are considered.
The excess release of contractile neurotransmitters, obstruction of draining venules, prolonged relaxation of intracavernosal smooth muscle may lead to an abnormal detumescence (17). Various possible etiologies for IP have been described in the literature including hemoglobinopathies (SCD), iatrogenic causes like intracavernosal injections, *phosphodiesterase 5* (PDE5) inhibitors, psychiatric medications (such as risperidone and clozapine), and alpha-1 blockers (18). Veno-occlusive crisis can occur in the penis of SCD patients, that is often due to stasis and low blood flow rates within the sinusoids of the erectile tissue. In SCD patients, there is abnormal signaling of the *nitric oxide* (NO) pathway. This can be the main pathophysiology of priapism in those patients (19).
NIP is mostly due to the traumatic rupture of the cavernous artery or its branches. Most of the time, the venous channels remain open, and the penis is partially erect. NIP is usually caused by perineal or penile trauma and can occur after shunt procedures for the management of IP (20).

Diagnosis of priapism
The diagnosis of IP is based on the history and physical examination and may be done by penile blood gas analysis and penile ultrasound (21).
A physical examination of the penis should be performed to ascertain whether it is fully erect (as in IP) or partially erect (as in NIP) (22). A perineal examination may reveal evidence of trauma in NIP cases (8). A recent penile injection site is sometimes found in IP cases examination (23).
The diagnosis of IP can be made by a cavernous blood gas analysis to confirm the storage of venous blood within the corpora cavernosa manifesting as a lower partial oxygen pressure (pO_2 < 30 mmHg), higher partial carbon dioxide pressure (pCO_2 > 60 mmHg), and a decline of pH (<

Figure 1.
Algorithm used for the management of ischemic priapism.



7.25) (24). A penile Doppler study is the key radiological tool in the assessment of a patient with priapism. In the ischemic subgroup, cavernosal blood flow typically will be absent, with a high-resistance, low-velocity trace. The diastolic flow will be low or absent. In NIP, the Doppler study demonstrates normal or elevated cavernosal artery velocities with a high diastolic flow (25). In all patients with priapism, blood count, coagulation tests, sickle cell screen, and hemoglobin electrophoresis with reticulocyte counts should be performed (26).
Men with SP had a unique baseline Doppler ultrasound waveform, with a low peripheral resistance waveform and an elevated, variable cavernosal artery velocity. As proposed by *Patel et al.*, this may be the sonographic manifestation of a reduced, fluctuating smooth muscle tone (27). There are two main indications for MRI in priapism. In IP, the degree of corporal infarction may influence the decision to intervene. In NIP, a fistula can be suspected in the dynamic post-contrast images (28). Arteriography may be utilized to precisely localized arterial fistulae in NIP; typically this is only undertaken in the context of attempted treatment with super-selective embolization of the affected vessel (29).

Management of ischemic priapism

A duration-directed therapy for IP is crucial. Management of IP should progress in a stepwise fashion to achieve resolution as urgent as possible. When the priapism episodes are lasting more than 24 to 36 hours, patients are less likely to respond to corporal blood aspiration and instillation of α-adrenergic agonists because of the presence of irreversible smooth muscle damage. If IP is reversed within 24 hours, there is usually a recovery of erectile function in approximately 50% of patients (30). If based on history, the duration of erection is between 1-2 hours, hypoxic damage to the muscle has been occurred leading to poor muscle response to α-adrenergic agonists. Previous studies have concluded that priapism episodes of greater than 24 h were associated with a 90% rate of erectile dysfunction (31). Cavernous smooth muscle will not respond to alpha-adrenergic agonists if the episodes last more than 48h because of impaired intracavernous circulation and tissue swelling. T-shunt or T-shunt with tunneling should be performed first because doing aspiration and irrigation could delay the therapy (32). A duration-directed therapy for IP is crucial. The treatment algorithm of IP is summarized in Figure 1.

Non surgical options

• Corporal aspiration

The first step in the management of IP is doing corporal aspiration with or without corporal irrigation. This should be performed with a 18 or 19 gauge needle placed at the base of the penis in the 3 o'clock and/or 9 o'clock position. Saline solution 0.9% is used for irrigation. An important trick is to continue aspiration till oxygenated blood appeared (33). Corporal aspiration and irrigation with 10 degrees C saline for patients with prolonged penile erection were tested. The complete detumescence rate is improved after the cold saline usage (34). An easily constructed priapism task trainer was developed and tested. It is was found that is realistic and useful for resident education. The use of the model in a simulation session can improve resident comfort in performing corpus cavernosa aspiration and phenylephrine injection (35).

• Intracavernosal injections of pharmacological agents

Phenylephrine is considered the drug of choice for intracavernosal injection due to its high selectivity for the alpha-1-adrenergic receptor, without concomitant beta-mediated inotropic and chronotropic cardiac effects. Phenylephrine is injected after adequate dilution in normal saline at a concentration of 100-500 µg/mL. Usually, 200 µg is given every three to five minutes directly into the corpora.
The maximum dosage is 1 mg within one hour. It is recommended that blood pressure and pulse are monitored every 15 minutes for an hour after phenylephrine injection to monitor any serious cardiovascular side effects (36). According to some studies, patients with IP that fail to respond to conventional doses of an alpha-agonist cannot benefit from continual or high-dose phenylephrine injection, as the cavernosal smooth muscle is damaged and cannot contract (37). *Wen et al.* assessed the efficacy of high-dose phenylephrine in treating patients with acute IP. Injection of high-dose phenylephrine (1.000 mg q 5 minutes) was given for 17 consecutive cases of iatrogenic IP that occurred after vascular assessment. Intracavernosal therapy with high-dose phenylephrine was effective in all cases. Phenylephrine at doses higher than previously

reported may be necessary to overcome the effect of acidosis on ligand dissociation from adrenergic receptors (38).
Sympathomimetic drugs include epinephrine, ephedrine, norepinephrine, and metaraminol. There are no published data that compare the efficacy of these drugs. The summary data developed by the expert panel showed that for all patients with IP, the resolution occurred in 81% of cases treated with epinephrine, 70% with metaraminol, 43% with norepinephrine, and 65% with phenylephrine (39).
Other options for pharmacologic agents include *methylene blue* (MB). Intracavernosal injection of adrenergic agents can rarely cause systemic toxicity. In rare cases, intracavernosal phenylephrine was associated with subarachnoid hemorrhage and intracavernosal epinephrine injection resulted in severe hypertension and angina pectoris (40).
Intracavernosal adrenalin was used for patients with IP due to intracavernosal vasoactive agent use. A 2 ml adrenalin (1/100 000) was injected in each cavernosal body. In the patients who did not respond to the first injection, repeated adrenalin injections were performed at 20 min intervals, up to 5 times. Intracavernosal adrenalin injection alone had shown to be an effective therapy for the treatment of IP with a short duration of erection (41).
Etilefrine is an α1-selective agonist that has been used by intracavernous injection for the management of acute priapic episodes showing fewer cardiovascular effects than other drugs (42). MB, a guanylate cyclase inhibitor, is considered a potent inhibitor of endothelial-mediated cavernous relaxation. Five ml of MB were injected within the corpora cavernosa and left for 5 minutes. MB is a safe and highly effective treatment agent for short-term pharmacologically induced priapism (43). Intracorporal injection of MB is free of complications and as effective as a sympathomimetics treatment for priapism (44).

• Oral agents

Terbutaline, a beta-agonist, can be used in the management of priapism. A placebo-controlled study was implemented to study the efficacy of oral medical therapy in the treatment of priapism. A total of 75 patients with pharmacologically induced (prostaglandin E1) prolonged erections were randomized to receive terbutaline, pseudoephedrine, or placebo.
Detumescence occurred in 36 percent, 28 percent, and 12 percent, respectively. Terbutaline was significantly better than placebo ($p < 0.05$) in achieving detumescence (45). In another study, terbutaline was used in a prolonged erection. The dosage was 5 mg and its effect was observed for 15 min. An additional dosage of 5 mg was given if detumescence did not occur after 15 min and 30 min. Results showed that oral terbutaline can be used to treat pharmacologically induced prolonged erection. Terbutaline is given cautiously in patients with coronary artery disease, pulmonary edema, and hypokalemia (46). Midodrine administered orally is a simple and efficient treatment for the priapism induced by intracavernous injection of prostaglandin E1 in spinal cord injured patients (47).

Criteria to move to 2nd line therapy for ischemic priapism

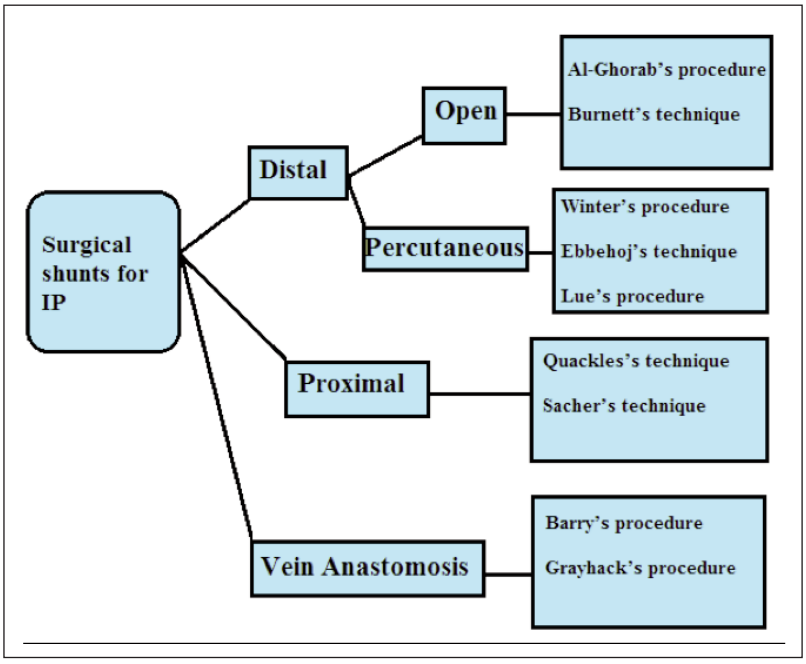
Surgery for IP should be considered only when conservative management options fail. However, there is no experimental evidence detailing the amount of time allowed for first-line treatment before moving on to second-line therapy (36). In the early stages of priapism (< 24-36 hours), conservative measures and aspiration, with or without intracorporeal instillation of α-adrenergic agonists, are usually successful. The shunt surgery is less effective if the duration of priapism is > 48 hours (48).

Surgical intervention

• Surgical shunts

Shunt surgery for priapism diverts 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 using firstly distal shunts and then proximal shunts in cases where aspiration and instillation of pharmacological agents failed (49). Surgical shunts are divided into four anatomical subcategories: percutaneous distal, open distal, open proximal (corporospongiosal) shunts, and vein anastomosis/shunts (50). Their types are summarized in Figure 2.
Winter shunt consists of the insertion of a large-bore needle from the glans to the distal side of the corpus cavernosum. The *Ebbehoj* procedure consists of creating a shunt from the glans to the distal corpora using a small incision with the number 10 scalpel (30). T shunt involves passing a number 10 blade vertically through the glans into the corporal bodies bilaterally, rotating the

Figure 2.
Surgical shunts used for ischemic priapism.



blade laterally 90° (to avoid urethral injury), and then removing (4). In IP of > 3 days duration and/or when the penis is quite firm after repeated '*milking*', bilateral T-shunts followed by intracavernous tunneling using a straight urethral sound or dilator are indicated. To create tunneling of the corpora cavernosa, a straight 20-24 F straight urethral sound or dilator is inserted through each glans incision and advanced to the penile crura (51). Although a T-shaped shunt operation has the advantages of simple operation, and fewer complications, it is not used in case of tumor-induced IP (52). An open distal shunt may be performed if the previous shunt failed to achieve detumescence.
The *Al-Ghorab* shunt involves a transversal incision that was made on the penile glans, 1 cm distal of the coronal sulcus. Two 5-mm circular cone segments of the tunica albuginea create a corporoglandular shunt (53). This shunt procedure can incise the dorsal nerve of the penis and thereby denervate the glans penis. A novel modification to the *Al-Ghorab* shunt in which incisions are made on the ventral aspect of the glans in an effort to prevent destruction and preserve the sensations of the glans penis (54). *Burnett* and *Pierorazio* described the corporal "*snake*" procedure as a modification of the *Al-Ghorab* shunt (55). The modified *Al-Ghorab* corporoglanular shunt using the *Burnett* snake maneuver is successful in resolving IP, particularly in cases refractory to first-line therapy (56). A shunt cuts a new wound through the collagen-rich tunica albuginea. To prevent the collagen-activated platelets and fibrin phenomena begin to form a clot within minutes to seal off the shun, a perioperative anticoagulant should always be administered in this type of surgery (57).
When distal shunts failed, other treatment options included proceeding to open proximal shunts and venous shunts, namely the *Quackels* (unilateral corporospongiosal) or *Sacher* (bilaterally staggered corporospongiosal) shunts (4). The creation of a venous shunt requires microsurgical skills. Saphenous vein shunt (*Greyhack*), and dorsal vein graft (*Barry*) has been often used (32).

• Penile prosthesis

More than 90% of patients with priapism lasting > 24 h complain of subsequent erectile dysfunction. The choice of an early penile prosthesis insertion has many advantages. It allows the recovery of sexual function, it may prevent penile shortening, and it is easier to implant a penile prosthesis in the acute setting, with fewer complications (58). Early penile prosthesis insertion for acute IP is simple and successful even though distal cylinder can protrude through a defective corpora due to previous shunt surgery. Nonabsorbable sling suture of the cylinder to the tunica albuginea is an effective, simple, and safe treatment for this complication (59).
Immediate insertion of a penile prosthesis for acute refractory IP can treat the acute episode and the erectile dysfunction that will occur with the preservation of penile length (60). No RCT assess the use of penile prosthesis in IP. The best type of prosthesis and the timing of its placement is not determined yet. An increased risk of prosthetic infection occurred if a penile prosthesis procedure is performed during the acute phase of priapism. Delayed procedure could have technical challenges due to corporal fibrosis (33). The implantation of penile prosthesis in chronic priapism is technically much more challenging and often requires the use of downsized shorter cylinders (61). *Palmisano et al.* used a *soft penile prosthesis* (sPP) for patients with refractory IP in the acute phase. They found that sPP insertion can lead to immediate pain relief, preservation of sexual function, and penile size, with a higher surgery reproducibility in an emergency situation (62).
The EAU recommends that penile prosthesis (either malleable or a three-piece inflatable prosthesis) at the time of presentation could be taken into consideration if ischemia has been presented for more than 36 hours (mainly in sickle cell disease patients), aspiration and sympathomimetic intracavernous injections have failed and distal and proximal shunting have also failed (36).

Management of non-Ischemic Priapism

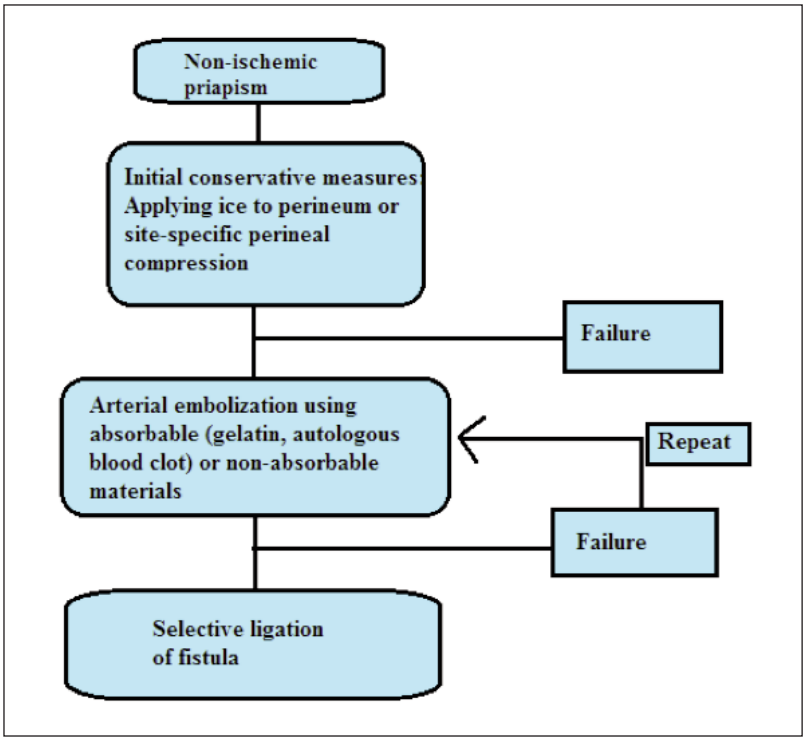
NIP is not an emergency and will often resolve without treatment. Acute conservative treatment, such as ice and site-specific compression to the injury, may be used. However, there are no data that can demonstrate the benefit of those conservative measures (39). Super-selective transcatheter embolization of the proximal artery supplying arterial-lacunar fistula should be the present treatment of choice in these cases of high-flow priapism refractory to conservative treatment. Autologous clots and gelatine sponge have been used as the embolic agent. More recently, platinum microcoils have been proposed to achieve more precise and selective embolization (63). Microcoils are permanent occlusive agents. Hence, there are theoretically increased risks of permanent vascular occlusion and subsequent erectile dysfunction with their use (64). Temporary materials are initially preferred in most cases of NIP. However, cases with arterial embolism using absorbable materials often have a recurrence of priapism, with the recurrence rate reported to be 30% to 40% (24).
Super-selective transcatheter embolization and transient occlusion of the fistula with an autologous blood clot is an effective therapy for the treatment of NIP. *Numan et al.* reviewed their experience with super-selective transcatheter embolization in the treatment of NIP. In three (27.2%) of 11 cases, a second embolization was required due to recurrence of priapism. In all patients, erectile function was restored within 6 weeks of the procedure (65). *Kim et al.* reported the effectiveness and safety of super-selective transcatheter embolization in the treatment of NIP at nine university hospitals. 27 patients were included in the study. In 24 of 27 patients (89%), a single embolization was sufficient for the complete resolution of priapism. Repeat embolization was required in two patients (7%), and in the remaining patient (4%), shunt surgery was performed after embolization (66). Using angioembolisation to treat NIP, reduced sexual function is the primary adverse effect of interest, with small sample observational studies reporting 19-20% had reduced erection quality after the procedure. Preliminary estimates of recurrence rates are between 30 and 40% (67).
The type of vessels that are involved in refilling the fistula after embolization is of concern for the outcome of the

patients. The fistulas supplied only by cavernosal-spongiosal communications closed spontaneously within 1 month. Watchful waiting should be preferred to repeated embolization to avoid the risk of unnecessary procedures (68). Color Doppler ultrasound allows the confirmation of successful embolization by demonstrating disappearance or size reduction of the fistula (69).

Surgical treatment consists of selective ligation of the fistula through a transcorporal approach under the guidance of color duplex ultrasound. Although surgery has been successful in treating arterial priapism, it is technically challenging and may pose significant risks, mainly erectile dysfunction due to accidental ligation of the cavernous artery instead of the fistula (36). Two surgical approaches are used for NIP, one extracorporal, and the other transcorporal. Despite that transcorporal dissection is a risky procedure, it is appropriate for arterial priapism of prolonged duration, especially if a well-formed vascular pseudocapsule is identified (70).

Androgen blockade (AB) to suppress nocturnal erections is an alternative treatment for NIP. *Mwamukonda et al.* reported the outcomes of 7 patients with NIP that were treated with AB. Priapism resulted from trauma in three patients and a persistent high-flow state after shunt procedures in four. Therapy consisted primarily of 7.5 mg intramuscular monthly leuprolide injections, although bicalutamide and ketoconazole were also utilized as adjunct treatments. Therapy duration ranged from 2 months to 6 months. One patient discontinued daily ketoconazole after 1 week because of severe hot flashes. The remaining six patients reported complete resolution of NIP (71). The management algorithm of NIP is summarized in Figure 3.

Figure 3.
Algorithm used for the management of non-ischemic priapism.



Management of stuttering priapism

SP is a variant of the ischemic type that is characterized by repetitive, transient, painful, self-limiting episodes of priapism. It is associated with various hematological disorders, including sickle cell disease and pharmacological treatments (72). Typically, the priapic events in SP are self-limited, resolving in under 3 h, some lasting for only minutes before spontaneous resolution. It has been reported that 77% of the transitory attacks are sleep-related, 17% are associated with sexual activity (11). If these episodes are not treated, it may evolve into a classic IP and eventually lead to irreversible corporal fibrosis with permanent erectile dysfunction. The goal of the management of a patient with SP is the prevention of future episodes, while the management of each episode should follow the specific treatment recommendations for acute IP (73).

Hormonal therapy

The use of hormonal therapy for the prevention of SP has been a successful medical management option for some patients. Caution is strongly advised in using hormonal treatments for prepubertal or adolescent men who have not reached sexual maturation and or in those desiring children, as side effects often result in castrate levels of testosterone creating a contraceptive effect, interfere with closure of the epiphyseal plates and have significant impairments on sexual function (42).

Hormonal therapy using *gonadotropin-releasing hormone analogues* (GnRH) has been successful in treating episodes of priapism refractory to classic drugs. It is associated with significant adverse effects, in particular the loss of libido and erectile dysfunction (74). Patient with sickle cell disease and recurrent priapism was treated successfully for more than a year with monthly GnRH analogue therapy after failure of standard medical management (75).

The use of low-dose estrogen shows is considered an effective and relatively rapid treatment option for some cases of idiopathic SP (76).

Baker et al. reviewed their 12-year experience with the 5-α reductase inhibitor dutasteride as a potential long-term treatment option for SP. Patients were started on a dose of 0.5 mg daily and tapered to a more infrequent dosing schedule, ranging from 0.5 mg every other day to once weekly: 85% of men treated with dutasteride had some degree of improvement, 38% had complete resolution of their symptoms. Side effects were minimal and included gynecomastia (8%), decreased libido (8%), and fatigue (8%) (77). *Rachid-Filho et al.* demonstrating that the use of finasteride could decrease and control the number of priapism recurrences in patients with sickle cell anemia (78).

Oral ketoconazole reversibly inhibits testosterone production and has been used to decrease postoperative erections (79). *Abern et al.* used ketoconazole and prednisone with dosing titrated according to

serum testosterone levels to prevent recurrent priapism episodes. Eight patients with recurrent IP were treated with ketoconazole and prednisone. Patients were seen monthly and therapy was withdrawn after 6 months. One patient had 2 recurrent IP episodes while on ketoconazole and prednisone treatment. Another patient had an increase in testosterone from 361 to 432 ng/dl after initiation of therapy, and 3 recurrent IP episodes requiring emergency corporal irrigation. After dose titration testosterone was 184 ng/dl and the patient had no subsequent episodes (80). *Hoeh et al.* reported their experience to prevent recurrent IP using ketoconazole, 16 of 17 patients (94%) had complete resolution of priapism while on ketoconazole. After 6 months, it was recommended to stop the medication (81).
The duration of hormonal treatment for effective suppression of recurrent priapic events is still unknown. Of the hormonal agents suggested for preventing priapism, GnRH agonists, and anti-androgens appear to be the most efficacious and safe (37).

Non hormonal therapies
Baclofen is a centrally acting *gamma-amino-butyric acid B* (GABAB) agonist used to treat spasticity. As baclofen inhibits penile reflex responses. Sexual side effects of intrathecal baclofen including the decrease or loss of penile erections (82). Oral baclofen, starting with a daily dose of 10 mg that was increased to 30 mg can achieve control of priapism (83). Oral baclofen 10 mg, three times a day can be used to treat prolonged erections. After 24 h of therapy, the erection of penis occurred less frequently and each episode lasted for a shorter duration (84).
Digoxin is a known inhibitor of sodium/potassium adenosine triphosphatase (sodium pump), a plasma membrane enzyme that has a role in the regulation of smooth muscle tone. *Gupta et al*. investigated the effects of digoxin on human corpus cavernosum smooth muscle contractility and overall erectile function. *In vitro* digoxin caused inhibition of contraction of corporal smooth muscle. *In vivo* digoxin diminished the penile rigidity during visual sexual stimulation and nocturnal penile tumescence testing compared to placebo without influencing libido or serum testosterone, estrogen, or luteinizing hormone levels (85).
Oral gabapentin was used to treat refractory idiopathic priapism in three patients.
They responded to treatment within 48 h. Two men continue not to experience prolonged erections while treated with lower doses of gabapentin for 16 and 24 months, respectively. The third, after successful treatment for 6 months, stopped gabapentin and priapism recurred (86). The rationale for the treatment of priapism with this medication was based on the reported sexual dysfunction possibly caused by gabapentin. Although the molecular targets of gabapentin remain unknown, the inhibition of Ca^{2+} efflux from muscle cells in the corpora, with consequent inhibition of smooth muscle relaxation, may explain the effectiveness of gabapentin in the management of refractory priapism (87). Also, gabapentin can reduce both testosterone and FSH levels (88).
Hydroxyurea (HU) has been reported to decrease the number of stuttering priapism episodes in patients who retained erectile function. The beneficial effects may stem from its role as an NO donor, as HU has been shown to interact with hemoglobin to form NO (89). In a study HU has been used for preventing priapism in patients with SP, HU was introduced at the initial dose of 10 mg/kg, and as the HU dosage increased, the number or length of priapism episodes decreased. The data suggests that HU may prevent priapism attacks in SCD (90).

Phosphodiesterase type 5 (PDE5) inhibitors
The molecular mechanism of priapism is not clear. *Champion et al.* suggested aberrant downstream signaling of the NO pathway based on the finding that mice lacking the gene for endothelial nitric oxide synthase tend to have more a priapic activity (91). Dysregulation of the NO/cGMP signaling pathway in the penis is thought to be the primary molecular mechanism of recurrent IP. Studies identified transcriptional and translational down-regulation of PDE5, owing to basally decreased cGMP (92).
In a study done by *Burnett et al.* to test the use of PDE5 inhibitors to treat recurrent priapism, 13 patients with SCD reporting priapism recurrences at least twice weekly were randomized to receive sildenafil 50 mg or placebo daily for 8 weeks. Priapism frequency reduction by 50% did not differ between sildenafil and placebo groups by intention-to-treat or per-protocol analyses ($p = 1.0$) (93).
In another study, PDE5 inhibitors were used as a long-term therapeutic regimen in seven men with recurrent priapism. Six men had idiopathic priapism recurrences and one man had sickle cell disease-associated priapism recurrences. Tadalafil 5 mg was administered daily. Daily long-term oral PDE5 inhibitor therapy alleviated priapism recurrences in all patients. Five (71.4%) had no episodes of priapism and two (28.6%) referred decrease in their episodes of priapism (94).
PDE5 inhibitors should be first used under conditions of full detumescence and their efficacy is obtained after 2-4 weeks of use (11).

Self-injection of intracavernosal sympathomimetics
The AUA recommends that intracavernosal self-injection of phenylephrine should be considered in patients who either fail or reject the systemic treatment of SP (39).

Conclusions
Priapism must be determined as ischemic or non-ischemic because the treatments and the prognosis for these two types are different. As priapism is a rare urological emergency, multicenter randomized clinical trials are needed to recommend the best treatment options.

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