Penile Priapism, Clitoral Priapism, and Persistent Genital Arousal Disorder: A Contemporary Review

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ABSTRACT

Introduction. Priapism is a persistent erection that arises from a dysfunction of the normal regulatory mechanisms of penile tumescence, rigidity, and flaccidity. It is defined as an erection lasting longer than 6 hours that is not related to sexual stimulation. There are three types of priapism: ischemic, non-ischemic, and stuttering. Similarly, clitoral priapism may occur in females manifested by symptoms such as engorgement with pain and swelling of the clitoris and surrounding tissue. Persistent genital arousal disorder (PGAD) is uncontrollable genital arousal in females, with or without orgasms, that occurs spontaneously and without any sexual feelings.
Aim. The aim of this article is to review the available literature on priapism, clitoral priapism, and PGAD.
Methods. A literature review was performed through PubMed regarding priapism, clitoral priapism, and PGAD.
Main Outcome Measures. The main outcome is an assessment of the potential etiologies, pathophysiology, diagnostic tools, and management options (medical and surgical) for these conditions.
Results. Initial workup of priapism should include a thorough history, physical examination, and cavernous arterial blood gas measurement. Findings should guide further management depending on the etiology of priapism (ischemic vs. non-ischemic). For ischemic priapism, a widely used therapeutic algorithm has been described. For patients with stuttering priapism, multiple oral therapies are currently available. Most reported cases of clitoral priapism appear to be drug-induced, and the primary treatment is stopping the offending agent. Medications like phenylpropanolamine and phenylephrine can also be utilized. PGAD may be associated with anatomical abnormalities, such as Tarlov cysts for which an epidural anesthesia block may be considered.
Conclusions. Early recognition and diagnosis of priapism is paramount to preserving erectile function. Current treatment regimens for ischemic priapism have room for innovation in both pharmacological and surgical therapies. Further investigation into the etiologies and treatment options for clitoral priapism and PGAD are required. **Yafi FA, April D, Powers MK, Sangkum P, and Hellstrom WJG. Penile priapism, clitoral priapism, and persistent genital arousal disorder: A contemporary review. Sex Med Rev 2015;3:145–159.**

Key Words. Priapism; Clitoral Priapism; Persistent Genital Arousal Disorder

Priapism

Introduction

Priapism is a persistent erection that arises from a dysfunction of the normal regulatory mechanisms of penile tumescence, rigidity, and flaccidity. It is defined as an erection lasting longer than 6 hours that is not related to sexual stimulation. There are three types of priapism: ischemic, non-ischemic, and stuttering. Both the American Urological Association (AUA) (www.auanet.org.com) and the International Society for Sexual Medicine (www.issm.info) have noted that the literature on priapism is mostly based on individual case reports and small case series. Standardized definitions and methodologies have been inconsistent, and long-term data for best practices have also been lacking. The diagnostic and

management recommendations presented in this work are based on a combination of the available literature, expert opinion, and our personal experience.

Ischemic priapism is a persistent erection that results from occlusion of the venous outflow while there is little or no arterial inflow into the rigid corpora cavernosa. Pain is usually present and physical examination demonstrates a rigid erection. This ischemic condition leads to time-dependent changes in the sinusoidal smooth muscle cells of the penis in which there is progressive hypercarbia, hypoxia, and acidosis.

Stuttering priapism is defined as recurrent self-limiting episodes of ischemic priapism [1]. Episodes are usually less than 4 hours long and arise nocturnally or following sexual stimulation [2]. A patient's quality of life can be negatively affected as episodes may increase in frequency and intensity, eventually becoming a major episode of ischemic priapism with irreversible damage to corporal tissue [3]. Stuttering priapism is recognized as a classic manifestation of sickle-cell disease (SCD) in male patients [4].

Non-ischemic priapism describes a persistent erection caused by continuous flow of arterial blood into the cavernosa, but without occlusion of venous outflow. Although the cavernosa remains tumescent, pain and rigidity are not usually present, and normal erectile function usually returns after tumescence dissipates.

Etiology/Epidemiology

Much of the existing epidemiological data are sparse and based on studies with small sample sizes and little diversity. Thus, the epidemiology of the condition remains relatively poorly characterized. Recent data from U.S. emergency departments found that priapism accounted for 5–8 per 100,000 visits [5,6]. The mean age of these patients was 36 years, and 21% had a concurrent diagnosis of SCD. They also noted that only 13% of these visits for priapism resulted in hospital admission, and visits were more common in summer than winter [7–9].

A variety of broad disease categories associated with priapism include hematologic dyscrasias, neurologic conditions, non-hematologic malignancies, erectile dysfunction therapy, trauma, and idiopathic factors (Table 1). Pohl et al. reported on 230 cases and observed that the etiology in most cases of priapism was idiopathic. Other causes were alcohol or drug abuse (21%), perineal trauma (12%), and SCD (11%) [10]. Idiopathic priapism has been associated with prolonged periods of sexual activity and involuntary nocturnal erections [11].

Table 1 Etiologies of priapism

α-Adrenergic receptor antagonists
Antianxiety agents
Anticoagulants
Antidepressants and antipsychotics
Antihypertensives
Drugs (illicit)
Genitourinary injury
Hematologic abnormalities
Hormones
Infectious (toxin-mediated)
Metabolic
Neoplastic (metastatic or regional infiltration)
Neurogenic
Vasoactive erectile agents

Etiology of Ischemic Priapism

Erectile Dysfunction Pharmacotherapy

Kulmala et al. observed that 21% of 207 patients presenting with priapism had used an intracavernosal injection of a vasoactive drug [12]. These patients were more likely to abuse alcohol, to use psychopharmaceuticals, antihypertensives, and anticoagulants, and to have lumbar back pain and chronic prostatitis. Fifty-eight percent of those affected were reported to be smokers. The incidence of priapism with vasoactive injection depends upon the pharmacotherapy used. Papaverine and prostaglandin E1 are the most common culprits, with associated risks of 5% and <1%, respectively [13,14].

Hemoglobinopathies

Priapism is closely associated with most hyperviscosity syndromes, with SCD ranking as the most common cause. The exact mechanism is unclear, but it is postulated that a normal erection leads to a decrease in oxygen tension and sickling of erythrocytes [15]. Sickled erythrocytes induce venous occlusion, stasis, and obstruction of the deep dorsal penile vein [15]. In a study of 52 patients with SCD, 20 (38%) reported having at least one incidence of priapism [16].

More recently, in a 2002 multicenter study, Adeyoju et al. reported that of 130 patients with SCD, 46 (35%) reported a history of priapism, and of this group 33 (72%) reported a history of stuttering priapism and 24 (52%) reported having an acute ischemic episode of priapism. The mean age of onset of priapism in this SCD group was 15 years, with 75% having their first episode before

the age of 20. Of the 46 patients with priapism, 10 reported having subsequent erectile dysfunction [8]. Other hemoglobinopathies that have been associated with priapism include thrombophilia, hemoglobin Hb Olmsted, protein C and S deficiencies, and thrombotic thrombocytopenic purpura [17–21].

Neurologic Causes

Priapism can also occur as a result of neurologic disease and injury. Cansever et al. reported on a case of a priapism in a patient with symptomatic lumbar stenosis [22]. Similarly, acute spinal cord injury has been reported in a number of cases as the precipitating factor in ischemic priapism [23]. A case has even been reported of a ruptured intracranial aneurysm causing priapism in a man for 22 days with subsequent development of organic impotence [24].

Malignancies

Priapism has been associated with some solid tumors involving the genitourinary system, including prostate, bladder, and rectal cancer [25–28]. Malignant infiltration of tumor cells may obstruct venous outflow leading to subsequent stasis. Leukemia has also been cited as a causative factor in case studies of priapism [29,30]. A low-flow veno-occlusive state is achieved in the corpora cavernosa due to hyperviscosity of leukemic blood.

Pharmacological

Many classes of drugs have been implicated in the etiology of priapism. The anticoagulants—most often heparin and warfarin—have been associated with priapism [31]. Cessation of anticoagulants and resultant hypercoagulability has been the proposed mechanism. A variety of centrally acting agents, such as trazodone and other atypical antipsychotics, have also been reported to cause priapism [32,33]. Trazodone has often been implicated and has been thought to have synergistic effects with cocaine in causing ischemic priapism [34]. Priapic episodes have also been observed in patients receiving treatment with the antihypertensive medications hydralazine and guanethidine [35].

Idiopathic

The etiology of priapism has been identified as idiopathic in as many as 50% of patients [10]. A myriad of conditions, such as rabies [36], appendicitis [37], and total parenteral nutrition [38], among others, have been suggested as potential causes of priapism. Although these are very rare, they should be considered when evaluating a patient with a diagnosis of priapism of unknown etiology.

Etiology of Non-Ischemic Priapism

High-flow priapism is a less urgent condition, and is associated with persistent tumescence due to unregulated arterial inflow that is usually associated with perineal, pelvic, or penile trauma. Most commonly, blunt trauma or an iatrogenic needle injury leads to an arteriolar-sinusoidal fistula and unregulated arteriolar inflow to the corpora cavernosa. In non-ischemic priapism, the cavernosal environment does not become hypoxic or acidotic and does not represent a true emergency [39]. Blunt or penetrating injury to the crura or corporal bodies can lacerate the cavernous artery or its branches and lead to increased vascular flow within the corpora cavernosa. Since the outflow remains unobstructed, a compartment-like syndrome with hypoxia and acidosis does not occur. Implicated causes include sexual trauma, pelvic fractures, needle lacerations, metastatic infiltration of the corpora, kicks to the penis or perineum, straddle injury, and birth trauma to the newborn male [40–42]. Cases of high-flow priapism have even been reported in mountain biking accidents and penile tattooing [43,44]. Delayed onset of high-flow priapism is typical after penile or perineal trauma, but sustained erection will usually occur within 24 hours [45]. A proposed mechanism is that the nocturnal erection disrupts the thrombosed, damaged artery, and the necrotic tissue and clot are cleared leading to fistula formation.

Priapism in Children

Priapism in adolescents and children is usually caused by SCD and is typically ischemic in nature. Reported rates of priapism in boys with SCD are 18–27% [46]. The mean age at presentation is 12 years, and the average number of episodes in a lifetime is 15 per patient. Episodes most commonly occur around 4:00 AM, and 75% of the patients report having episodes during sleep or upon awakening.

Pathophysiology of Priapism

Research into the molecular basis of priapism derives mostly from animal models. An imbalance between constrictive and relaxatory mechanisms in corporal vessels leads to the hypoxia and acidosis associated with ischemic priapism. In vitro studies

have shown that apoptosis occurs as a result of hypoxic conditions, as demonstrated on isolated strips of rabbit cavernosal smooth muscle cells [47–50]. This results in failure of alpha-adrenergic stimulation to elicit trabecular cavernosal smooth muscle contraction. Eventual smooth muscle death occurs as a result of prolonged tissue hypoxia with subsequent fibrosis of corporal smooth muscle. Further animal model studies have demonstrated the role of reactive oxygen species in inducing lipid peroxidation and hemo-oxygenase expression in ischemic erectile tissue [51,52]. Growth factor-induced fibrosis has also been described as an important factor in the progression of ischemic priapism. An important cytokine involved in this pathway is transforming growth factor-beta (TGF-β). Although TGF-β is vital to tissue repair, severe hypoxia leads to excess amounts and overt fibrosis in corporal tissue [52,53].

The use of transgenic mice has laid the groundwork to our understanding of priapic mechanisms [54,55]. Normal endothelial cells respond to mechanical and neurohumoral signals to actively regulate vascular tone by releasing a multitude of vasoactive mediators. NO and adenosine have been identified as vasorelaxatory mediators in the penile vascular endothelium, while RhoA/Rho-kinase acts as a vasoconstricting mediator. Aberrant adenosine, NO, and RhoA/Rho-kinase signaling have been identified as possible contributors to ischemic priapism [56–58]. Destruction of the endothelial vascular tissue leads to dysregulation of these pathways and further exacerbation of smooth muscle relaxation.

Transgenic SCD mice have shown abnormal expressions of NO/cGMP, RhoA/Rho-kinase, and adenosine signaling mechanisms, manifesting as increased sensitivity to erectile stimuli and subsequent priapism [56].

Diagnosis

Evaluation and Diagnosis

Priapism is generally a straightforward diagnosis owing to the salient nature of an erect penis in the absence of sexual stimulation. Key to the evaluation is distinguishing between ischemic and non-ischemic priapism because of the emergent treatment required for the former. Depending on the scenario, it may be necessary to initiate initial treatment while awaiting confirmatory laboratory and radiologic results if ischemic priapism is suspected.

History and Physical Examination

The clinical history should elucidate information about the presence of pain, duration and prior history of priapism, pharmacological or manual attempts at relief, etiologic factors, and erectile function status before presentation. Ischemic priapism is associated with progressive pain, drug use, history of blood dyscrasia, and neurologic conditions associated with the central nervous system. Lack of pain and a history of penile or perineal trauma are suggestive of non-ischemic priapism.

The penis should be inspected and palpated to determine the extent of tumescence, corporal body involvement, and presence of tenderness. Evaluating the surrounding abdomen, perineum, and rectum is necessary to rule out trauma or malignancy.

Laboratory Testing

Routine evaluation of a patient with priapism should include a complete blood count, white blood cell differential, platelet count, and coagulation profile. These will help test for the presence of an infection and hematologic disorders, and to insure that the patient is a candidate for medical and surgical interventions. It is important to note the hemoglobinopathies are not just limited to men of African descent. Urine and plasma toxicology can help determine whether recreational narcotics or prescription drugs are the cause. Blood gas aspiration of corporal tissue is recommended, as it is the optimal test to differentiate ischemic and non-ischemic priapism (Table 2).

Imaging

Penile duplex Doppler ultrasonography (PDDU) of the penis and perineum may be used as an adjunct to cavernosal blood gas measurement to differentiate ischemic from non-ischemic priapism. PDDU will show an absence of blood flow in the cavernous arteries in ischemic priapism, and successful therapy will show a return of PDDU waveform. In non-ischemic priapism, PDDU will show normal to high cavernosal blood inflow and

Table 2 Typical arterial blood gas values

Source	PO_2 (mm Hg)	PCO_2 (mm Hg)	pH
Normal arterial blood	>90	<40	7.4
Normal mixed venous blood	40	50	7.35
Ischemic priapism (cavernous)	<30	>60	<7.25

Modified from AUA Guidelines on the management of priapism [2].

can also help in localizing the site of trauma. PDDU can be used for confirmatory evaluation of a persistent erection following treatment for ischemic priapism, as persistent tumescence can be due to penile edema, persistent ischemia, or conversion to non-ischemic priapism.

Although not routine, magnetic resonance imaging (MRI) has recently been offered as an alternative, non-invasive imaging technique in evaluating priapism. Ralph et al. have shown that gadolinium-enhanced MRI can be used to assess for non-viable tissue and predict long-term outcomes in cases of prolonged priapism (>72 hours) [59]. Unilateral corporal body thrombosis does occur, albeit rarely, and is difficult to differentiate from bilateral thromboses. MRI, however, is particularly useful in determining whether thrombosis is unilateral or bilateral. Additionally, MRI has also been useful in imaging arteriolar-sinusoidal fistulas and evaluating corporal metastasis causing priapism [60].

Medical Management

Ischemic Priapism

Ischemic priapism is a urologic emergency that mandates immediate treatment. The AUA Guidelines Panel (2003) recommends that treatment should begin with either therapeutic aspiration or intracavernous injection (ICI) of an alpha-adrenergic sympathomimetic agent [61]. This can be performed with or without irrigation. Resolution of priapism with sympathomimetic injection (43–81%) is higher than aspiration alone (24–36%). Recurrence rates with sympathomimetic injection are 58% alone, and following a prior surgical aspiration a 77% resolution rate can be achieved with the sympathomimetic injection. In practice, aspiration is usually done first with a butterfly needle (19–21 gauge) into the corpus cavernosum with subsequent reduction of intracavernosal pressure. This can be done with a dorsal penile nerve block or a local penile shaft block.

Sympathomimetic injection causes relief of tumescence by causing cavernous smooth muscle contraction. Possible agents used include phenylephrine, etilefrine, ephedrine, norepinephrine, and metaraminol. Although no direct comparison of the efficacy of each drug has been published, the AUA Panel recommends phenylephrine as the agent of choice in ICI, with resolution rates of 81% with epinephrine vs. 65% with phenylephrine. Epinephrine is not recommended as the agent of choice because it is a direct systemic activator of both alpha- and beta-adrenergic receptors with significant cardiovascular and peripheral vascular side effects. Phenylephrine, on the other hand, is an alpha1-selective adrenergic agonist with no indirect neurotransmitter-releasing action, thus minimizing adverse cardiovascular side effects. It is recommended that phenylephrine be diluted with normal saline to a concentration of 100–500 mcg/mL, with 1-mL injections performed every 3–5 minutes for 1 hour until detumescence. Caution should be given to children and patients with cardiovascular disease where lower concentrations should be used. Patients should be monitored carefully after sympathomimetic injection for signs and symptoms of systemic side effects.

Additionally, the β-agonist terbutaline has shown efficacy in some trials in the treatment of pharmacologically induced priapism [62–64].

Relief of hemoglobinopathy-induced priapism had traditionally been attempted with hydration, analgesics, oxygen, bicarbonate, and blood transfusion. None of these approaches have been shown to be overtly beneficial and may actually delay the effective treatment of priapism [65].

Stuttering Priapism

Although not usually an emergency, episodes of stuttering priapism often increase in frequency and can lead to a major episode of ischemic priapism. Studies have shown that oral use of etilefrine and self-injection of intracavernosal α-adrenergic agents may help reverse episodes lasting more than 1 hour [66,67]. Etilefrine is an α-agonist with a short half-life. Other described treatment options that have been used in the prevention and treatment of stuttering priapism include terbutaline, digoxin, gonadotropin-releasing hormone analogues, α-adrenergic agents, hydroxycarbamide, baclofen, gabapentin, and recently phosphodiesterase-5 (PDE5) inhibitors [68]. Many of these agents have been shown to be effective, but only in small case series. Normally used as an oral antifungal, ketoconazole's (KTZ) antiandrogen effects have been shown to be effective in preventing recurrent cases of priapism [69]. Hoeh and Levine demonstrated a 94% resolution rate for men taking KTZ, with no reported sexual side effects. With the concurrent use of prednisone, they found that a tapered dose regimen of KTZ over a course of 6 months was very effective.

PDE5 Inhibitors in Stuttering Priapism

PDE5 inhibitors are widely used in the management of erectile dysfunction as they are erectogenic, which makes them counterintuitive for use in persistent erections. Bialecki and Bridges first reported this paradoxical effect in treating stuttering priapism with on-demand PDE5 inhibitors in three patients with SCD [70]. The rationale behind their use in such a fashion is, however, perplexing and lacks scientific reason.

When used in long-term rigorously implemented clinical management program dosing regimens, PDE5 inhibitors have been shown to relieve stuttering priapism episodes associated with both SCD-associated and idiopathic priapism without altering normal erectile function [55,71]. Bivalacqua et al. proposed a mechanism by which PDE5 inhibitors, used long-term, exert their detumescent effects. They observed that the priapic activity in mouse models was associated with the dysregulation of PDE5 and subsequent altered downstream signaling of NO and cGMP [72]. This altered pathway allows for the unregulated generation of cGMP in corporal endothelial tissue resulting in unrestrained penile smooth muscle relaxation. In SCD, increased oxidative stress leads to decreased endothelial NO availability and decreased production of cGMP. They showed that continuous PDE5 inhibitor therapy restored the cGMP/PKG/PDE5 regulatory balance, resulting in proper degradation of periodically produced cGMP and detumescence.

Non-Ischemic Priapism

Non-ischemic priapism may spontaneously resolve in up to 62% of patients with little to no adverse effects on erectile function [61]. Although corporal aspiration is used in the diagnosis of priapism, it serves no role in the treatment of non-ischemic priapism. Also, given the pathophysiology of unregulated arterial inflow and increased venous outflow, the use of intracorporal sympathomimetic injection is not recommended.

Observation with or without concomitant ice and compression directly on the erectile tissue represents the initial management. Selective arterial embolization can be employed in long-standing cases where the patient desires immediate relief. There is, however, no data comparing the long-term outcomes of observation and interventional therapy. Arteriographic studies can demonstrate the connection of a lacerated cavernous artery or branch to the lacunar spaces, deemed an arterial-lacunar fistula. Selective arterial embolization may be performed using a number of methods, including polyvinyl alcohol, n-Butyl cyanoacrylate, gel-foam, microcoils, and autologous blood clot [73–76]. The use of temporary embolic agents is preferred due to its decreased rate of postprocedural impotence [76].

In children with high-flow priapism due to trauma, manual compression of the penile tissues alone may relieve the erection. This simple intervention often works in children only, because the perineum has much less subcutaneous fat than in adults, and compression of the crural bodies is more easily accomplished [77].

Surgical Management

Ischemic Priapism

Surgical treatment is recommended after repeated failure of non-surgical interventions. ICI of sympathomimetics is unlikely to be effective after a prolonged interval. Phenylephrine becomes less efficient 48 hours after onset, as the acidic environment impairs cavernosal tissue response to adrenergic agents [47]. Due to a lack of adequate data, there is no agreed upon timing for when to initiate surgical management. Data suggest that priapism lasting longer than 24 hours is associated with a 90% rate of erectile dysfunction [78]. Early surgical management may be an optimal approach in patients with concurrent cardiovascular issues because of the systemic effects of adrenergic treatment.

The objective of shunting is to allow oxygenation of ischemic cavernosal smooth muscle by establishing an alternative outflow tract to the glans, corpus spongiosum, or a vein. Surgical management usually begins with a distal penile shunt to allow extravasation of cavernosal blood, as distal shunting carries lower complication rates [61]. In any procedure, it is important to fully discuss and document baseline erectile function, risks, and benefits of the surgery. Specifically, it is crucial to document the chances of permanent erectile dysfunction (ED) irrespective of which intervention is chosen. Distal shunts can be either percutaneous [79,80] or open [81–83]. Three techniques for percutaneous shunts have been described: the Winter shunt, the Ebbehøj shunt, and the T-shunt [84]. The Winter shunt involves passing a large biopsy needle several times through the glans to the tip of the corpus cavernosum [79] (Figure 1A). The Ebbehøj involves passing a #11 blade several times through the glans into the tip of the corpus cavernosum [80] (Figure 1B). The T-shunt is a modification of the Ebbehøj where a #10 blade

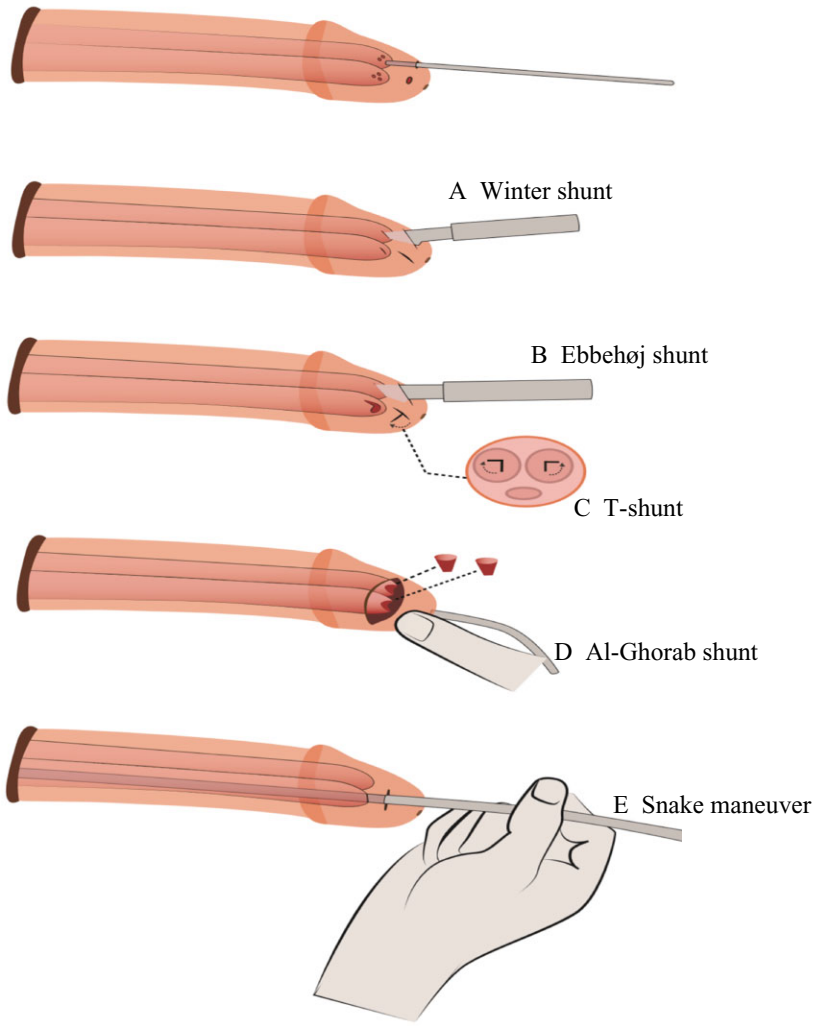

Figure 1 Illustrations of the various distal shunting surgical techniques used for the management of acute ischemic priapism (A) Winter shunt, (B) Ebbehøj shunt, (C) T-shunt, (D) Al-Ghorab shunt, and (E) Snake maneuver.

scalpel is inserted vertically fully into the corpus cavernosum, at which point the blade is rotated 90 degrees laterally and then removed [81] (Figure 1C). The advantage of the T-shunt procedure is that it makes a larger window for effective drainage. Dark blood is milked out until red oxygenated arterial blood is identified. Failed percutaneous shunting can be followed by an open cavernosum-glans shunt under direct vision [82,83] (Al-Ghorab) (Figure 1D). This procedure involves making a 2-cm transverse incision in the dorsum of the glans. The incision is deepened until the distal tips of the corpora cavernosa are identified and retraction sutures are placed in the tunica. A circular 5 × 5 mm cone segment of tunica albuginea with underlying cavernosal tissue is excised. Gentle compression is employed until bright red blood is observed. In most cases, the cavernosum-glans shunt will close with time, but secondary closure may be required to close the tunica in the future.

Burnett and Pierorazio described a modification of the Al-Ghorab procedure called the corporal "snake" maneuver [85]. It entails the retrograde insertion of a 7/8 Hegar dilator into each corporal body through the window made the by the Al-Ghorab procedure. The instrument is gently twisted to help release coagulated, viscous blood. After removing the instrument, manual compression in a proximal to distal direction facilitates blood evacuation. If detumescence occurs, the glans is closed with a 4-0 suture with a urethral catheter (Figure 1E).

In rare cases where distal shunting is unsuccessful (edematous distal penis), a proximal shunt may be necessary to relieve the compartment syndrome and reestablish blood flow. The two types of proximal shunting are open proximal (corpospongiosal)

[86,87] and vein anastomoses/shunts (i.e., saphenous or dorsal) [88,89]. The unilateral shunt, described by Quackles, is the most commonly used [86]. Through a transscrotal or transperineal approach, a cavernosum to spongiosum (CC-CS) shunt involves establishing a communication between the corpus spongiosum and the corpus cavernosum. Its inherent complications are the creation of an unwanted cavernous urethral fistula or a urethral stricture. Bilateral shunts are usually staggered to minimize the risk of urethral stricture. If proximal shunting fails, some have used a saphenous vein bypass or deep dorsal vein (DDV) shunting technique [88,89]. With the Grayhack shunt, a wedge of tunica albuginea is removed and the saphenous vein is anastomosed to the corpus cavernosum. Venous shunting carries a significant risk of thrombus formation and pulmonary embolism [90]. DDV shunting involves ligating the distal DDV and anastomosing the proximal DDV to the corpus cavernosum.

Penile blood gas testing, PDDU, and intracorporal pressure monitoring can be performed for documentation and further assurance of success. In the case of recurrence, additional shunt attempts should be made serially for at least 24 hours. Penile shunting is usually a second-line treatment, and data on postprocedure erectile dysfunction are lacking. In settings where ischemia lasts for greater than 24–36 hours, shunting may only serve to relieve associated pain, while permanent tissue damage may have already occurred. A suggested algorithm for the management of acute priapism is shown in Figure 2.

Surgical Prosthesis

In circumstances where priapism is refractory to initial therapeutic attempts and/or treatment has been significantly delayed past 2–3 days, a penile prosthesis (PP) may be an excellent option, as erectile impairment and penile deformity may be inevitable. Zacharakis et al. compared early (median 7 days) and late implantation (median 7 months) of a PP in patients with refractory ischemic priapism. In follow-up interviews, patients with early prosthetic implantation had much higher rates of erectile function and satisfaction [91]. This is most likely due to the natural history of untreated priapism, which pertains to severe fibrosis, loss of length, and erectile dysfunction [92]. Sedigh et al. reported on a cohort of five patients who underwent early PP implantation for priapism [93]. They found that, long term, all five patients reported maintaining penile length and were able to participate in satisfactory sexual intercourse. Recently, Tausch et al. reported on their 6-year experience with acute insertion of malleable penile prostheses in 14 patients with refractory ischemic priapism and multiple emergency room visits, prolonged hospital admissions, and significant resource utilization [94]. They showed this intervention to be a rapid and cost-effective treatment modality.

Corporal fibrosis after priapism is usually distal and makes inflatable penile prosthesis insertion a surgical challenge. Many techniques have been described to overcome this problem, and these include excision or incision of the scar, corporotomies with or without grafting, use of cavernotomes, implant downsizing, and transcorporal excavation, among others [104]. A comparison of surgical procedures is detailed in Table 3.

Non-Ischemic Surgical Priapism

Non-ischemic priapism is not a urologic emergency and is usually painless, but reports exist describing partial erections lasting for years [105]. Often, in long-standing high-flow priapism, a pseudocapsule forms around the fistula following penile or perineal trauma. Prior to formation of this capsule, surgical exploration may be possible to ligate the cavernous artery rather than selective embolization. This procedure should only be performed in extenuating circumstances in patients who are poor candidates for embolization or where it is not available or has failed [2,106].

Clitoral Priapism

Similarly, a rare form of priapism, known as clitoral priapism, can take place in women [107]. Engorgement with pain and swelling of the clitoris and surrounding tissue are the typical presenting symptoms. This can be caused by multiple pharmacological agents, and a high index of suspicion is required for an accurate and expedited diagnosis.

Multiple case reports describe vulvar and clitoral pain with swelling and tenderness [108]. Medina described the case of a 47-year-old female who was taking trazodone, a heterocyclic antidepressant medication, who subsequently experienced clitoral priapism. These episodes occurred over the course of 3 years, each one lasting 3–8 hours in duration. Various other case reports describe treatment with imipramine, a tricyclic antidepressant, to help with resolution. In this particular patient, the withdrawal of both medications was the resolving factor.

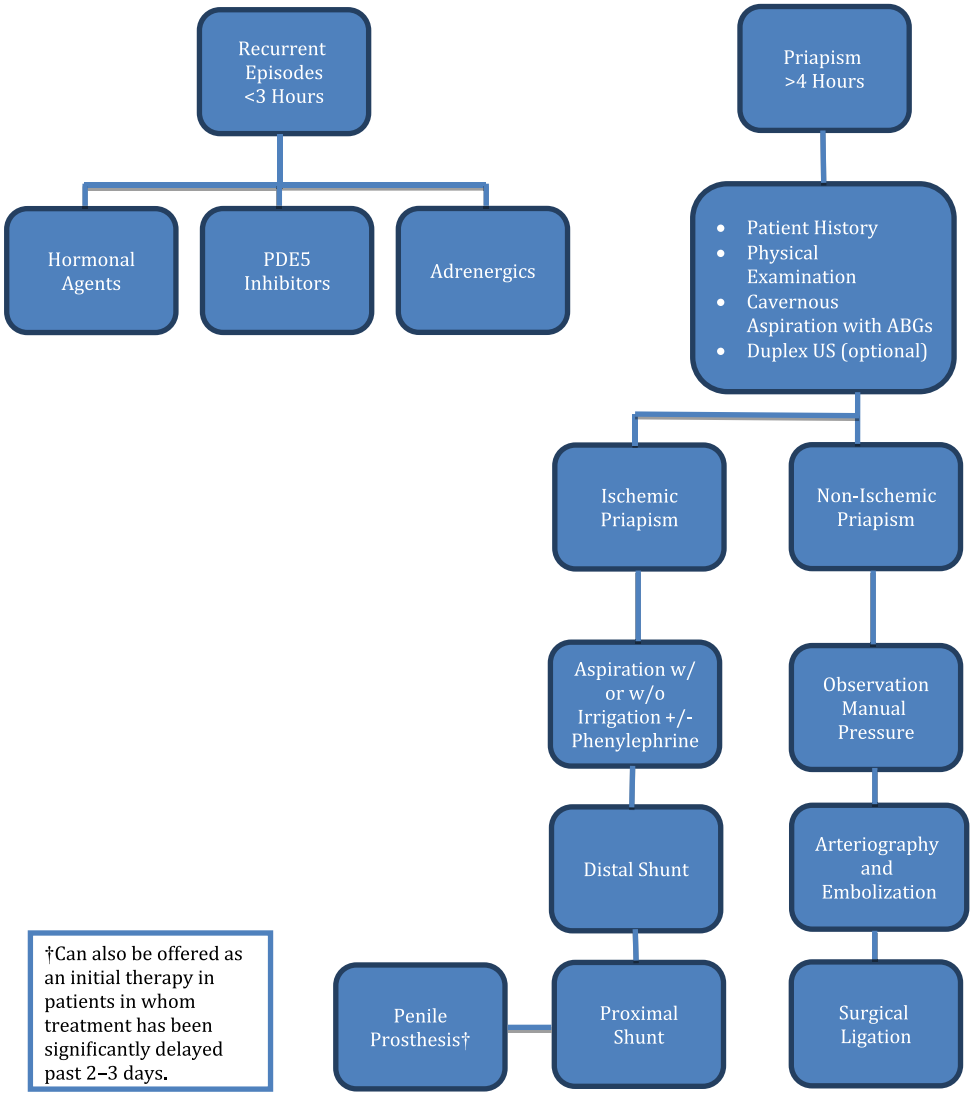

Figure 2 Suggested algorithm for the management of acute priapism.

The exact cause of clitoral priapism is not fully elucidated, but it is likely similar to male priapism. Comparable to ischemic priapism in males, a sequestration of blood obstructed from venous outflow tracts leads to increased clitoral intracavernosal pressures [108]. It is unlikely that there is an increase of arterial blood flow [109]. Corporeal smooth muscle relaxation caused by α sympathetic blockage may delineate why α-blocking medications can lead to priapism [107]. Other contributing factors include occlusion of venous channels from blood dyscrasias, like sickle cell anemia [110]. Physical obstruction from transitional cell carcinoma can lead to the rare side effect of venous outflow obstruction leading to clitoral priapism [111].

Most reported cases of clitoral priapism appear to be drug-induced. The most commonly cited drug is trazodone, with fluoxetine, bromocriptine, bupropion, and citalopram also being reported. Fluoxetine and citalopram are serotonin reuptake inhibitors and have moderate α-blockade. Bromocriptine stimulates the release of oxytocin and affects dopaminergic receptors. While the mechanism of action of how these medications lead to clitoral priapism is unclear at this time, there is likely some link between dopaminergic and serotonergic receptors [107].

The primary treatment for clitoral priapism is stopping the offending agent. Based on the biochemistry of the above medications and possible mechanism of clitoral priapism, medications like

Table 3 Comparison of surgical procedures

Procedure	Number of patients	Median duration of priapism (hours)	Resolved (%)	Erectile dysfunction (%)
Distal shunts				
Winter [12]	57	NA	54	NA
Ebbehøj [95]	18	NA	61	NA
T-shunt [80]	13	64	92	2
Al-Ghorab [96]	13	44	92	NA
Al-Ghorab + tunneling [97]	12	NA	100	10
"Snake" maneuver [98]	10	60	80	2
T-shunt + dilation (snake) [99]	45	96	64	42
Proximal shunts				
Corpospongiosal [100]	17	NA	65	10
Cavernospongiosal [86]	12	70 hours–18 days	100	3
Penile prosthesis				
Inflatable penile prosthesis [101]	50	209	100	2
Inflatable penile prosthesis [102]	8	91	100	1
Inflatable penile prosthesis [103]	12	120	100	0

NA, not available.

phenylpropanolamine and phenylephrine can be utilized for their α-adrenergic agonist effect [107,108].

Persistent Genital Arousal Disorder (PGAD)

PGAD is uncontrollable genital arousal with or without orgasms, which occurs spontaneously and without any sexual feelings [112]. Described by Leiblum and Nathan in 2001, five diagnostic criteria exist: persists for hours, days, and/or months, does not go away after orgasm/orgasms, unrelated to desire or sexual feelings, unwanted, and causes distress. There is poor understanding of the etiology of PGAD, although sensory neuropathy of the dorsal nerve of the clitoris appears to be involved [113]. The combination of PGAD with restless leg syndrome and/or overactive bladder syndrome and/or urethral hypersensitivity is cumulatively called restless genital syndrome [114].

While the exact cause of PGAD is not fully elucidated, multiple case reports exist, attributing medications and other anatomical abnormalities toward its cause. There appears to be a correlation with perineural or sacral nerve root cysts, or "Tarlov" cysts. These occur most commonly at S2 and S3 vertebral levels and can lead to radiculopathy or be completely asymptomatic. Case reports from Ebiye and Jensen describe a 30-year-old female who experienced PGAD after stopping paroxetine and was found to have a 1-cm S2-S3 Tarlov cyst [115]. She underwent electroconvulsive therapy and after five treatment sessions her symptoms slowly abated. Komisaruk and Lee presented a study of 18 women with PGAD who had undergone sacral MRI for evaluation of Tarlov cysts [116]. Twelve of the women had clearly visualized cysts, some with multiple cysts present. The general population experiences Tarlov cysts at a prevalence of 9%, while this study demonstrated 66%. Other proposed theories include postsurgical, postinjury brain lesions, seizure disorder, pelvic nerve entrapment, vascular changes leading to pelvic congestion, or psychological factors [112].

Battaglia and Venturoli have demonstrated that the use of trazodone, while rare, can lead to PGAD. The cessation of the medication does not always improve the symptoms or frequency of unwanted orgasms, as demonstrated in case reports [115,117]. In some patients, withdrawal of the medication may in fact worsen or lead to PGAD. One theory suggests that serotonin receptor downregulation may lead to a vasodilator effect on the genital tissue vasculature, leading to recurrent episodes of clitoral priapism. Leiblum proposed that "stuttering clitoral priapism may masquerade as PGAD."

Recently, Carvalho et al. hypothesized that moral standards, as well as conservative beliefs regarding sexuality, may be involved in the etiology and maintenance of PGAD [118]. They, accordingly, conducted a worldwide survey of 43 women, 18 years and older, with PGAD and 42 controls. They successfully demonstrated that "women reporting PGAD symptoms presented significantly more dysfunctional sexual beliefs (e.g., sexual conservatism, sexual desire as a sin), as well as more negative thoughts (e.g., thoughts of sexual abuse and of lack of partner's affection) and

dysfunctional affective states (more negative and less positive affect) during sexual activity than non-PGAD women." These findings suggest a role for cognitive behavioral therapy for certain women with PGAD who, on interview, display some of these maladaptive sexual beliefs and thoughts.

Treatment options are not widely agreed upon, but various entities have been proposed. If a patient is taking any suspected agent, withdrawal of the offending medication should be undertaken. Patients who are experiencing PGAD from Tarlov cysts need to undergo epidural anesthesia block and will have resolution of their symptoms if caused by the cyst [116]. This would suggest surgical intervention as an option for these responsive patients. For patients with Tarlov cysts that are symptomatic, drainage of the cysts with injection of fibrin glue can be performed. Recently, there is a growing consensus that spinal MRI would prove useful and diagnostic for PGAD in patients found to have Tarlov cysts on imaging.

Transcutaneous electrical nerve stimulation has been utilized in patients with PGAD and restless leg syndrome with good response [119]. Psychological education with social support has also been suggested for patients by using coping skills to help break the cycle of anxiety exacerbating the symptoms. Other therapies have included topical numbing agents and pelvic floor physical therapy with massage and stretching exercises. Medications such as mood-stabilizing or anti-seizure drugs, including valproate or selective norepinephrine reuptake inhibitors, have, however, been met with limited success [120,121]. Overall, PGAD is a complex, poorly understood disease entity that can stem from multiple etiologies, and treatment should be aimed toward the most likely source.

Conclusions

The time-dependent nature of priapism makes rapid diagnosis and treatment paramount to preserving erectile function and preventing further morbidity. Treating physicians must document prior baseline erectile function, duration of priapism, and associated comorbidities. Patients need to be thoroughly educated and informed about their condition, particularly patients with SCD.

Although not life-threatening, penile injury with erectile dysfunction as a consequence of priapism is a distressing condition with a strong social stigma. Current treatment regimens for ischemic priapism have room for innovation in both pharmacological and surgical therapies. Further basic and clinical research into the pathophysiology of ischemic and stuttering priapism is needed to better treat and prevent priapic episodes. Large, double-blind, placebo-controlled clinical studies will further elucidate the causes and best treatment options, and describe respective outcomes. Retrospective questionnaires have an important place in comparing clinical outcomes.

Further basic science research may allow researchers to better define the molecular basis of ischemic and stuttering priapism. Animal models have a potential role in expanding our understanding of these mechanisms. This will allow for the creation of novel pharmacological therapies as well as methods of predicting outcomes of those at risk. Of particular importance is early identification of patients with posttreatment conversion to a high-flow priapism. Similarly, further characterization of the molecular basis of stuttering priapism is crucial for SCD patients because of the associated risk for refractory ischemic episodes. Comparative trials need to be done on medical and surgical treatments, as well as comparing early and late prosthetic implantation, sexual satisfaction, infection rates, eventual need for revision, and overall cost analyses with conventional treatments.

Clitoral priapism and PGAD represent a spectrum of disease in females that is similar to male priapism. Difficulty in diagnosis can lead to a delay in recognition of the medical condition, and underreporting of this condition is likely. A variety of pharmacological medications have been reported to be a cause of PGAD and clitoral priapism along with malignant infiltration or Tarlov cysts. Treatment options include withdrawal of the offending agent, the use of α-adrenergic agonists, or surgical management (if a Tarlov cyst is present). Currently, the few reported cases make the disease process poorly understood. Further investigation into the etiologies and treatment options for clitoral priapism and PGAD is required.

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