Management of priapism: an update for clinicians

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***Abstract*:** Priapism is a prolonged erection that persists beyond or is unrelated to sexual stimulation. It is associated with significant morbidity: psychological, socioeconomic, and physical, including pain and potentially irreversible compromise of erectile function. There are three major types of priapism: ischemic, nonischemic, and stuttering. Establishing the type of priapism is paramount to safely and effectively treating these episodes. Ischemic priapism represents a urological emergency. Its treatment may involve aspiration/irrigation with sympathomimetic injections, surgical shunts, and as a last resort, penile prosthesis implantation. Nonischemic priapism results from continuous flow of arterial blood into the penis, most commonly related to penile trauma. This is not an emergency and may be managed conservatively initially, as most of these episodes are self-limiting. Stuttering priapism involves recurrent self-limiting episodes of ischemic priapism. The primary goal of therapy is prevention, but acute episodes should be managed in accordance with guidelines for ischemic priapism. In this paper we review the diagnosis and treatment of the three priapism variants, as well as discuss future targets of therapy and novel targets on the horizon.

Keywords: priapism, guidelines, ischemic, stuttering, recurrent, non-ischemic

Introduction

Priapism represents a great challenge in therapeutic management amongst erectile disorders and it carries with it significant risks of structural damage to the penis and permanent erectile dysfunction (ED) [Berger *et al.* 2001]. However, the disorder is a poorly recognized condition by many medical professionals [Burnett and Bivalacqua, 2007].

Priapism constitutes a true disorder of erection physiology and results from a combination of disturbances involving the regulatory mechanisms governing penile tumescence and initiation/maintenance of penile detumescence. First reported in 1845 by Tripe, priapism is defined as a prolonged and persistent penile erection, unassociated with sexual interest or stimulation, lasting longer than 4 h [Montague *et al.* 2003; Burnett and Bivalacqua, 2007]. It has further been divided into three main categories: ischemic, nonischemic, and stuttering priapism, based on the etiology and pathophysiology of the condition [Montague *et al.* 2003].

Ischemic priapism, also termed veno-occlusive or low flow priapism, is a persistent erection marked by rigidity of the corpora cavernosa and little or no cavernous arterial inflow [Montague *et al.* 2003]. It consists of an imbalance in vasoregulatory mechanisms, predisposing the penis to an ischemic environment. Mixed venous blood in the penis becomes trapped, creating venous congestion. The tissue ischemia and increased pressure generated within the corporal bodies lead to pain and rigidity, classically seen with ischemic priapism. Studies have shown that ischemic priapism lasting longer than 24 h results in ED rates as high as 90% [Pryor and Hehir, 1982]. Therefore, ischemic priapism constitutes a true emergency that must be treated in a time-sensitive manner.

Conversely, nonischemic priapism, also termed arterial or high-flow priapism, is a persistent erection caused by unregulated cavernous arterial inflow [Montague *et al.* 2003]. Nonischemic priapism generally occurs as a result of trauma, creating a disruption in the cavernous arterial anatomy, resulting in an arteriolar-sinusoidal fistula. Nonischemic priapism can also result from congenital arterial malformations, iatrogenic insults and as a persistent high-flow state after shunt procedures for ischemic priapism [Burnett and

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Sharlip, 2013]. The cavernous environment does not become ischemic secondary to the continuous influx of arterial blood [Montague *et al.* 2003]. In concordance, the corpora are tumescent but not rigid, and patients typically do not complain of pain with erection [Broderick *et al.* 2010]. For this reason, nonischemic priapism is not an emergency and does not require immediate intervention.

Stuttering priapism, also termed intermittent or recurrent priapism, is characterized by recurrent episodes of ischemic priapism. These episodes typically last under 4 h prior to remission [Emond *et al.* 1980; Broderick *et al.* 2010] Erections commonly arise during nocturnal sleep, or preceding or following sexual stimulation [Berger *et al.* 2001]. These episodes may increase in frequency and duration, however, compromising the patient's quality of life and potentially developing into major episodes of ischemic priapism [Burnett and Bivalacqua, 2007]. Both stuttering and ischemic priapism result in the same consequence, namely, ischemic damage to the corporal tissue. Delays in treatment and repetitive episodes of stuttering priapism lead to cellular, molecular and morphological changes in the corpus cavernosum, which over time result in tissue injury that accumulates and develops into permanent ED [Broderick and Harkaway, 1994; Kim *et al.* 1996; Saenz de Tejada *et al.* 1997; Liu *et al.* 1999; Moon *et al.* 1999]. Therefore, all episodes of recurrent priapism that progress to prolonged, painful erections should be treated promptly, according to the guidelines set for ischemic priapism [Burnett and Bivalacqua, 2007]. The ultimate goal of the treating urologist should be to prevent recurrent stuttering priapism by using pharmacotherapies which address the underlying pathophysiology of the disease state.

Epidemiology of priapism

The true incidence and prevalence of priapism is largely unknown. Epidemiologic reports suggest that the incidence rates of priapism range between 0.5 and 1 case per 100,000 person years [Kulmala *et al.* 1995; Eland *et al.* 2001; Earle *et al.* 2003; Montague *et al.* 2003]. However, this may in fact underestimate the true prevalence of priapism, because previous studies only included cases which sought medical intervention. In a recent study published by Roghmann and colleagues, the incidence of priapism in the USA between 2006 and 2009 was found to be 32,462 visits to the emergency department for priapism, representing a national incidence of 0.73 per 100,000 male subjects per year [Roghmann *et al.* 2013].

While priapism is a rare disorder, specific patient populations, namely those with sickle cell disease (SCD), are affected with greater frequency relative to the general population [Broderick *et al.* 2010]. In the USA, over 70,000 individuals live with SCD, and the worldwide number may be as high as 20–25 million [Van der Horst *et al.* 2003]. The lifetime probability for the development of priapism in these men is as high as 42% and the rate of ED following these episodes exceeds 30% [Kulmala *et al.* 1995; Mantadakis *et al.* 1999; Eland *et al.* 2001; Broderick *et al.* 2010]. Typically, there is a bimodal peak of incidence between 5–10 and 20–50 years of age. Up to 75% of men with stuttering priapism and SCD will experience their first priapic episode by their twenties. SCD is the most common etiology of priapism in childhood, and accounts for 63% of cases, and it is the primary etiology of ischemic priapism in 23% of adult cases [Bennett and Mulhall, 2008].

Ischemic priapism is the most common priapism variant and accounts for almost 95% of all diagnosed episodes. A significant proportion of these cases are iatrogenic, due to intracavernosal injections used to treat ED [Pohl *et al.* 1986; Broderick *et al.* 2010]. Priapism is associated with an assortment of disease states and several clinical contexts have risk associations for developing the disorder [Emond *et al.* 1980; Berger *et al.* 2001; Montague *et al.* 2003; Burnett and Sharlip, 2013]. Priapism is most often associated with hematologic dyscrasias, such as glucose-6-phosphate dehydrogenase deficiency, SCD/trait, thrombophilias, hyperviscosity states, anticoagulants, psychiatric medications (most notably the sedative trazodone, as well as selective serotonin reuptake inhibitors), antihypertensives (α-adrenergic antagonists), malignancy (most commonly bladder, prostate, kidney and colorectal), total parenteral nutrition, recreational drug use such as cocaine, heavy alcohol abuse and trauma [Emond *et al.* 1980; Berger *et al.* 2001; Montague *et al.* 2003; Burnett and Sharlip, 2013]. Understanding the risk factors for priapism and commonly associated disease states will assist the clinician in making an accurate and expedient diagnosis.

Diagnosis

Identification of the type of priapism variant a patient presents with is paramount (Table 1).

Table 1. Pathophysiologic criteria of priapism.

Variant	Penile blood appearance	Penile arterial blood gas findings	Color Duplex ultrasonography findings
Ischemic priapism	Corpus cavernosum testing: blood is hypoxic and dark in color	Blood gases: pO_2 <30 mmHg; pCO_2 >60 mmHg; and pH <7.25	Minimal or absent blood flow
Nonischemic priapism	Corpus cavernosum testing: blood is oxygenated and red	Blood gases: pO_2 >90 mmHg; pCO_2 <40 mmHg; and pH 7.40 (similar to normal arterial blood)	Blood flow is normal to high in velocity
Stuttering (recurrent) priapism	Corpus cavernosum testing: blood is hypoxic and dark in color	Blood gases: pO_2 <30 mmHg; pCO2 is >60 mmHg; and pH <7.25	Minimal or absent blood flow during acute priapism; normal blood flow otherwise

pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen.

Management must begin with a detailed history and physical examination. Diagnosis should focus on identifying any contributory/predisposing conditions, listed above [Berger *et al.* 2001; Montague *et al.* 2003]. The duration of priapism, any clinical treatments used, previous priapism episodes, presence of pain, and erectile function status prior to the priapism episode should be noted. In patients with known SCD, it is particularly important to determine the presence of any other systemic symptomatology associated with SCD, such as a sickle crisis. A physical examination involving inspection and palpation of the penis, to assess for the extent of tumescence or rigidity, degree of corporal body involvement, and presence and severity of tenderness, is essential [Bivalacqua and Burnett, 2006]. In ischemic priapism, the corpora cavernosa are typically rigid and tender to palpation. In contrast, the presentation of nontender, partially tumescent corpora cavernosa suggests a diagnosis of nonischemic priapism. Abdominal, perineal, and rectal examinations may reveal signs of trauma, pelvic infection or malignancy. A full neurologic exam may be indicated when a spinal cord injury or lesion is suspected. After a careful history and physical exam, a cavernous blood gas analysis will provide direct visualization and evaluation of penile blood, serving to provide immediate distinction between the different variants of priapism [Lue *et al.* 1986]. In patients with ischemic priapism, the aspirated blood is hypoxic and dark, and typical blood gas values show a partial pressure of oxygen (pO_2) of less than 30 mmHg, partial pressure of carbon dioxide (pCO_2) of greater than 60 mmHg, and a pH of less than 7.25. Conversely, in nonischemic priapism, the blood is oxygenated and bright red with cavernous blood gas values of a pO_2 greater than 90 mmHg, pCO_2 less than 40 mmHg, and pH 7.40, consistent with normal arterial blood at room air [Montague *et al.* 2003].

Laboratory testing should be incorporated into the diagnostic workup. These include a complete blood count, white blood cell differential, and platelet count which may reveal the presence of acute infections or hematologic abnormalities. Reticulocyte counts and hemoglobin electrophoresis may signify the presence of SCD/trait or other hemoglobinopathies [Montague *et al.* 2003]. These tests are recommended in all men unless the etiology of priapism is evident. Other hematologic tests, such as serum lactic dehydrogenase level, a marker of intravascular hemolysis, and glucose-6-phosphate dehydrogenase testing, may also be informative. Urine and plasma toxicology can screen for the potential pharmacologic influences of psychoactive medications and recreational drugs [Montague *et al.* 2003]. While these laboratory tests are useful for differentiating potential causes of priapism and for patient counseling, it is important to note that these tests should not preclude prompt treatment and may not influence management of the acute episode.

Radiologic evaluation

Penile imaging may assist in the diagnosis of otherwise equivocal priapism cases and may be used in follow up to verify treatment success. Color

duplex ultrasonography (CDU) of the perineum and penis can evaluate intracorporeal arterial blood flow in real time (Table 1). This serves in conjunction with penile blood gas sampling to further differentiate ischemic from nonischemic priapism. In ischemic priapism, minimal or absent blood flow is seen in the cavernosal arteries within the corpora cavernosa. Patients with nonischemic priapism, however, will show characteristic normal to high blood flow velocities in the cavernosal arteries [Feldstein, 1993; Montague *et al.* 2003; Burnett and Bivalacqua, 2007]. CDU should not be used as an alternative to arterial blood gas testing [Montague *et al.* 2003; Burnett and Bivalacqua, 2007].

Penile magnetic resonance imaging (MRI) has been shown to provide an accurate imaging method to assess smooth muscle viability in patients presenting with priapism. Potential benefits of this procedure include its ability to reliably predict nonviable smooth muscle within the corpora after episodes of priapism as well as detecting unusual conditions such as malignant infiltration and segmental cavernosal thrombosis. Drawbacks include the lack of uniform accessibility of MRI, costs and the time it takes to perform [Ralph *et al.* 2010].

Treatment of ischemic priapism

Medical management

The most common complication of priapism is ED, which can occur in as many as 59% of cases [Montague *et al.* 2003; Montorsi *et al.* 2010]. However, recovery of erectile function may be seen in up to 44% of patients who experience priapism for 24–36 h, therefore, 'time is erectile tissue', and timely treatment is crucial [Bennett and Mulhall, 2008]. The primary goals of medical therapy for ischemic priapism are to decompress the corporal bodies and restore arterial blood flow, thus reducing ischemia and the risk of tissue necrosis or injury, and ameliorating pain [Montague *et al.* 2003].

Management of ischemic priapism should progress in an aggressive and stepwise fashion to achieve prompt resolution [Montague *et al.* 2003]. First-line therapy for patients with episodes of acute ischemic priapism is aspiration of blood with irrigation of the corpora cavernosa, in combination with intracavernous α-agonist injection therapy. For anesthetic purposes, a preceding dorsal nerve block or local penile shaft block is usually performed [Berger *et al.* 2001].

The technique of penile blood aspiration involves using a transglanular intracorporal angiocatheter insertion or a proximal penile shaft needle access [Chung *et al.* 2003]. For proximal penile shaft access, a 16 or 18 gauge angiocatheter is placed percutaneously into the lateral aspect of the penile shaft entering the corpus cavernosum. With a syringe attached, aspiration and evacuation of blood from the corpora cavernosa is performed with irrigation of normal saline or in combination with intracavernous injection of an α-adrenergic sympathomimetic agent [Bivalacqua and Burnett, 2006; Burnett and Sharlip, 2013]. Two angiocatheters may be placed laterally on each side so injection and irrigation/aspiration can be done simultaneously. Evacuation of blood by corporal aspiration relieves the compartment syndrome of the penis and serves to counteract local acidotic and anoxic metabolic derangements [Bivalacqua and Burnett, 2006].

A greater resolution of ischemic priapism is obtained after injection of a sympathomimetic agent with or without irrigation (43–81%) than after aspiration with or without irrigation alone (24–36%). Further, the risk of post-priapism ED is lower when sympathomimetic agents are used [Montague *et al.* 2003].

Phenylephrine is the preferred sympathomimetic agent because of its lower risk profile for systemic cardiovascular adverse effects than other agents [Burnett and Bivalacqua, 2007]. However, if phenylephrine is unavailable, other α-adrenergic agonists may be used, such as ephedrine, epinephrine, norepinephrine, or metaraminol [Montague *et al.* 2003].

Phenylephrine should be diluted in normal saline to produce a concentration of 100–500 μg/ml. Then, injections of 1 ml aliquots should be performed intracavernosally every 3–5 min for up to 1 h or up to a dose escalation of 1000 μg of diluted phenylephrine [Montague *et al.* 2003]. All patients should be monitored for systemic complications associated with sympathomimetic administration. Patients with known hypertension, coronary artery disease, or other cardiac comorbidities should be placed on telemetry with blood pressure and electrocardiogram monitoring during and following intracavernous injection of any sympathomimetic agent. The patient should be monitored for known systemic adverse effects,

including hypertension, headache, reflex bradycardia, tachycardia, palpitations, and cardiac arrhythmia [Montague *et al.* 2003]. Caution should be taken when using phenylephrine, particularly after substantial effort has been made using injection therapy for a prolonged amount of time, without resolution of priapism: there has been a case report of subarachnoid hemorrhage following intracavernosal injection of phenylephrine for ischemic priapism [Davila *et al.* 2008]. Administration of α-adrenergic agonists is contraindicated in patients who have malignant or poorly controlled hypertension or are concurrently using monoamine oxidase inhibitors. In these patients, early surgical intervention may be necessary [Burnett and Sharlip, 2013].

Expert consensus suggests that repeated injections and aspiration should occur for at least up to 1 h prior to proceeding with second-line interventions in patients presenting with a priapism of less than 24 h [Montague *et al.* 2003; Burnett and Sharlip, 2013]. After this initial treatment, the penis may continue to feel tumescent secondary to postischemic hyperemia and residual edema of the intracorporal or extracorporal tissues, and it may be difficult to assess whether the priapism has been effectively treated. If uncertainty exists, a CDU or penile blood gas assessment should be obtained to evaluate the status of the cavernosal arterial flow in the penis. [Berger *et al.* 2001; Montague *et al.* 2003; Burnett and Bivalacqua, 2007] Clinical indicators that suggest failure of first-line intervention include corporal rigidity by exam, acidosis by cavernous blood gas testing, absence of cavernosal artery inflow by penile CDU, or elevated intracorporal pressures [Burnett and Sharlip, 2013].

For priapism specifically related to SCD, medical therapies such as intravenous hydration, oxygenation, alkalinization, and exchange transfusion may be performed. However, these interventions should never precede the first-line treatment for all episodes of ischemic priapism mentioned above [Mantadakis *et al.* 2000; Berger *et al.* 2001; Montague *et al.* 2003; Burnett and Bivalacqua, 2007; Broderick *et al.* 2010]

Ischemic priapism of extended durations (typically greater than 48 h) is unlikely to resolve with intracavernous injection/irrigation therapy alone, therefore these patients may be counseled to consider more immediate surgical shunting after a trial of intracavernous injection/irrigation [Berger *et al.* 2001; Montague *et al.* 2003; Zheng *et al.* 2013].

Surgical shunts

The goal of surgery is to create a channel or fistula that allows the deoxygenated blood to drain from the corpora cavernosa [Montague *et al.* 2003]. There are four subdivisions of shunts: percutaneous distal shunts, open distal shunts, open proximal shunts, and vein anastomoses/shunts [Burnett and Sharlip, 2013] (Table 2). For all shunt procedures, the patient should receive perioperative antibiotics covering skin flora. Guidelines advocate for an aggressive approach in treating patients with refractory priapism by proceeding in a serial fashion from distal to proximal shunts to vein shunting as quickly and safely as possible in order to achieve penile flaccidity [Broderick *et al.* 2010; Burnett and Sharlip, 2013].

A percutaneous distal corporoglanular shunt is typically attempted first, as most urologists are comfortable with the technique [Tabibi *et al.* 2010]. In a Winter shunt, a large-bore biopsy needle is passed percutaneously through the glans penis into the corpus cavernosum [Winter and McDowell, 1988]. This may be performed bilaterally or multiple times to achieve detumescence. Alternatives include the Ebbehoj shunt (similar to the Winter shunt, but employing a scalpel blade rather than a needle) and T shunt with or without intracavernous tunneling [Brant *et al.* 2009]. This involves passing a number 10 blade vertically through the glans into the corporal bodies bilaterally, rotating the blade laterally 90° (to avoid urethral injury) and then removing it. Intracavernous tunneling with a 20–24 F straight urethral sound may also be performed to facilitate drainage. This was shown to effectively drain blood from the corpora even in priapism of significant durations (> 3 days) when severe edema and tissue death has occurred [Garcia *et al.* 2008]. Brant and colleagues demonstrated that after this technique, six of 13 patients still reported normal postoperative erectile function with a Sexual Health Inventory for Men score greater than 22 [Brant *et al*. 2009].

If these attempts at distal shunting are ineffective, an open distal shunt may be performed. The Al-Ghorab shunt involves excising a piece of the tunica albuginea from the tip of the corpora cavernosa bilaterally. This enables effective drainage of blood from the penis, as well as minimizing the likelihood of spontaneous shunt closure. A modification of the Al-Ghorab shunt, the Burnett 'snake' maneuver has been described [Burnett and Pierorazio, 2009]. This involves tunneling

Table 2. Types of surgical shunt procedures for ischemic priapism.

Distal shunts	
Percutaneous distal shunts	
Winter (corporoglanular) shunt	Large biopsy needle is inserted through glans into corpora cavernosum several times creating multiple fistulae
Ebbehoj (corporoglanular) shunt	#11 blade scalpel is percutaneously passed multiple times through glans into corpus cavernosum creating openings in the tunica albugenia resulting in larger fistulae
T shunt (corporoglanular shunt)	Modified Ebbehoj using #10 blade scalpel and turning scalpel 90° when pulling out creating 'T-shaped' openings in tunica albugenia
Open distal shunt	
Al-Ghorab	A 1 cm incision is made distal to coronal sulcus with excision of 5 × 5 mm cone segment of distal tunica albuginea from each corporal body
Burnett 'snake' maneuver	Modification of Al-Ghorab shunt. A Hegar dilator is used to evacuate ischemic blood through a distal tunical window
Proximal shunts	
Open proximal shunt	
Quackels or Sacher (corporospongiosal) shunt	In lithotomy position, bulbocavernosus muscle is dissected from corpus spongiosum and 1 cm staggered ellipses of tissue are incised/excised from spongiosal/corporal bodies, and the defects anastomosed together
Corporosaphenous vein or superficial/deep dorsal vein shunts	
Grayhack shunt	The saphenous vein is ligated and anastomosed with corpora cavernosa
Barry shunt	The superficial or deep dorsal vein is ligated and anastomosed to the corpora cavernosa

the corporal bodies through the distal tunical defect with a Hegar dilator, further facilitating corporal drainage. This technique has been successfully used in men who had refractory priapism and who had previously undergone unsuccessful surgical attempts at priapism decompression. Long-term results from this technique have shown to not only resolve ischemic priapism refractory to first-line and often second-line management, but also to prevent further episodes of priapism [Segal *et al.* 2013]. Another modification of the Al-Ghorab shunt has been described, consisting of blunt cavernosotomy [Shiraishi and Matsuyama, 2013]. These modified distal shunt procedures, specifically the Burnett snake maneuver and the T shunt with or without tunneling, have proven to be highly effective monotherapies for priapism of extended durations (greater than 48 h). Long-term results from these procedures have been published and are encouraging as first-line interventions for priapism of extended durations or recurrence [Segal *et al.* 2013; Shiraishi and Matsuyama, 2013]. With the development of these new modified techniques and a mounting body of evidence in support of their efficacy, historical open proximal shunt procedures and vein anastomoses may become superfluous as treatment for refractory priapism.

For the sake of completeness, we will detail these historical shunt procedures which are rarely necessary in the treatment of refractory priapism. When distal shunts failed, other treatment options included proceeding to open proximal shunts, namely the Quackels (unilateral corporospongiosal) or Sacher (bilateral staggered corporospongiosal) shunts. Complications of these procedures may include urethral-cavernous fistula or iatrogenic urethral injury resulting in urethral stricture [Winter and McDowell, 1988; Nixon *et al.* 2003; Zheng *et al.* 2013]

Vein anastomoses employed as shunts have also been described for the treatment of refractory priapism. These include the Grayhack and Barry shunts, where a window is created in the corpus cavernosum, with a shunt created by anastomosing the saphenous vein or the deep dorsal vein respectively [Nixon *et al.* 2003; Tabibi *et al.* 2010; Zheng *et al.* 2013]. Vein shunts may be complicated by local thrombus formation and pulmonary embolism [Kandel *et al.* 1968].

Currently, limited data preclude a recommendation of greater efficacy for one shunt over another, based on accurate outcome estimates. The summary data generated by the American Urological Association panel for treatment of priapism shows resolution rates of 74% for Al- Ghorab, 73% for Ebbehoj, 66% for Winter, 77% for Quackels, and 76% for Grayhack procedures [Montague *et al.* 2003]. These data represent the outcomes of case reports and case series, and further conclusions cannot be reached given the absence of head-to-head comparisons that would be derived from a prospective, randomized clinical trial.

ED rates are higher for the proximal or vein shunts (Quackels and Grayhack, roughly 50%) than for the distal shunts (25% or less); however, patients frequently receive multiple modalities of treatment for priapism, therefore making it difficult to ascertain which treatment produced the adverse event [Montague *et al.* 2003]. In addition, the duration of priapism is critical to the development of ED, and therefore, many men presenting with prolonged priapism are at risk for subsequent ED irrespective of the treatment modality used.

For all surgical procedures, the urologist should have a thorough discussion with the patient detailing the indications, risks, and benefits of the procedure. As priapism can be a litigious issue, it is essential to give a clear explanation to the patient, informing him that the prolonged duration of priapism alone is a risk factor for ED, and that any shunt procedure or surgery itself might not modify that risk.

Penile prosthesis

There are no defined indications for implanting a penile prosthesis in patients with priapism. Acute priapism episodes may be definitively treated with penile prosthesis implantation, especially in the context of priapism duration exceeding 72 h, where complete ED is likely to ensue [Upadhyay *et al.* 1998; Ralph *et al.* 2009]. It may also be done in the nonacute setting to facilitate the resumption of sexual intercourse for individuals whose priapism has resulted in significant penile deformity or erection loss, although further discussion of this concept is beyond the scope of this article [Bertram *et al.* 1985; Douglas *et al.* 1990]. Some experts now advocate for the use of penile prostheses earlier in patients presenting with recurrent refractory episodes of priapism or those who have already undergone shunt procedures in the past [Monga *et al.* 1996; Rees *et al.* 2002; Bivalacqua and Burnett, 2006; Montague and Angermeier, 2006; Tausch *et al.* 2007; Ralph *et al.* 2009]. Practically speaking, it may prove difficult obtaining an appropriate informed consent in a patient in the midst of an acute painful priapism episode, as well as the insurance implications that may arise regarding the cost coverage for the procedure without prior insurance approval.

In men who undergo prosthesis surgery after priapism episodes, the presence of corporal fibrosis secondary to repeated episodes of priapism makes insertion of the prosthesis technically difficult, often requiring extended or double corporotomies or the use of cavernotomes to excavate the corporal bodies, as well as necessitating downsizing prosthesis cylinders to fit into the scarred corporal bodies [Monga *et al.* 1996; Tausch *et al.* 2007; Ralph *et al.* 2009]. Complication rates following prosthetic surgery for post-priapism fibrosis are higher than standard penile prosthesis implantation, often involving loss of length and lower satisfaction rates, as well as greater surgical difficulty and increased rate of complications, including urethral injury, device erosion, and infection [Rees *et al.* 2002; Tausch *et al.* 2007; Ralph *et al.* 2009]. The greater risk of erosion and infection for penile prosthesis surgery following acute episodes of priapism is likely secondary to the increased incidence of penile manipulations and repetitive introduction of bacteria into the penile shaft with recurrent aspirations/irrigations or prior shunt procedures. Further, if prostheses are delayed, multiple reconstructive approaches may be necessary in the course of prosthetic surgery to address complicated deformities or penile tissue loss from past recurrent episodes of ischemic priapism [Monga *et al.* 1996; Montague and Angermeier, 2006].

Proposed advantages of immediate penile prosthesis implantation in the context of

acute priapism include resolution of the priapic episode, treatment of the inevitable ED, avoiding possible complications and failures of shunting procedures, and prevention of penile shortening [Ralph *et al.* 2009; Monga *et al.* 1996; Rees *et al.* 2002; Tausch *et al.* 2007]. Some experts have also suggested using a vacuum erection device immediately following a major priapism episode in preparation for penile prosthesis surgery, with the hope of reducing the development of penile fibrosis over time prior to surgery, and possibly maintaining penile length [Burnett and Sharlip, 2013].

Treatment of nonischemic priapism

Initial management of nonischemic or high flow priapism differs significantly from other forms of priapism. For this type of priapism, first-line management should be clinical surveillance [Berger *et al.* 2001; Montague *et al.* 2003; Broderick *et al.* 2010]. This is in accordance with reports documenting spontaneous resolution in over two-thirds of all cases by surveillance alone [Montague *et al.* 2003; Broderick *et al.* 2010]. While aspiration has a diagnostic role, it is not recommended as a form of treatment.

Intervention for nonischemic priapism should only be considered as a last resort [Berger *et al.* 2001]. Several options are available, including cavernosal artery embolization in combination with penile arteriography, or arterial ligation using intraoperative CDU [Berger *et al.* 2001; Montague *et al.* 2003; Broderick *et al.* 2010] These should be thoroughly and cautiously discussed with patients prior to proceeding, secondary to the risk of complications. These may include ED, occurring in as many as 50% of procedures, as well as penile gangrene, gluteal ischemia, purulent cavernositis, and perineal abscess [Montague *et al.* 2003; Broderick *et al.* 2010]. This discussion should be followed by informing the patient of the relatively low risk of complications if no active treatment is performed. If intervention is opted for, selective arterial embolization is recommended as first-line intervention [Montague *et al.* 2003]. Both nonpermanent (i.e. autologous clot, absorbable gels) and permanent (i.e. coils, ethanol, polyvinyl alcohol particles, and acrylic glue) embolization materials are available for use. All of these intervention materials achieve a 75% resolution rate [Montague *et al.* 2003]. However, nonpermanent agents are preferred over permanent agents because they are associated with a lower incidence of subsequent ED [Berger *et al.* 2001].

While conservative management is the initial recommendation for nonischemic priapism, Mwamukonda and colleagues studied the possible role of androgen blockade as an alternative therapy [Mwamukonda *et al.* 2010]. In this study, seven men underwent monthly 7.5 mg intramuscular leuprolide injections, as well as adjunct treatments of bicalutamide and ketoconazole. Therapy duration ranged from 2 to 6 months and was discontinued after symptom resolution. Mean follow up was 2 years. While most patients experienced decreased libido and fatigue during treatment, six men reported complete resolution of priapism with return to baseline potency on treatment withdrawal.

Treatment of stuttering priapism

Treatment of stuttering priapism should follow the guidelines for episodes of ischemic priapism, thus proceeding in an aggressive stepwise pattern, until the acute episode is resolved. Following current guidelines, at our institution, men consulting for stuttering priapism are referred to a hematology specialist to rule out the presence of blood dyscrasias, and are taught self-injection therapy for home use. They are instructed how to draw up the medication (typically phenylephrine) and the technique for low-dose self injections (no more than 100 μg of phenylephrine) to treat acute episodes. If after two to three self injections the acute episode has not resolved, they are instructed to present to the emergency department for formal evaluation. While this provides a method for patients to treat their own priapism episodes at home, thus decreasing potential complications of prolonged priapism, as well as the inconvenience and associated healthcare costs of hospitalization, the drawback still remains that this method is only reactive and does not prevent the priapism episodes from occurring. Lastly, all patients with stuttering priapism have serum testosterone levels verified, and if low, will be counseled about testosterone supplementation. Studies have shown that hypogonadism is highly prevalent in men with SCD. In hypogonadal men, supplementation of testosterone to achieve normal levels was not associated with an increased risk of priapism episodes, but was found to actually decrease the frequency of priapism episodes in these men as well as improve sexual function [Burnett *et al.* 2013; Morrison *et al.* 2013].

While treatment of acute episodes of stuttering priapism remains similar to ischemic priapism, management of stuttering priapism should focus on prevention of future episodes. A multitude of therapies have been reported to produce successful outcomes in the management and prevention of stuttering priapism. The most widely used of these are hormonal therapies, which include gonadotropin-releasing agonists, androgen receptor antagonists, and 5α-reductase inhibitors, as well as other agents including digoxin, gabapentin, baclofen, terbutaline, and even phosphodiesterase 5 (PDE5) inhibitors [Montague *et al.* 2003; Bivalacqua and Burnett, 2006; Levey *et al.* 2012]. While promising, the limiting factor in widespread use of these therapies is the absence of outcomes data. Most of these reports come from small case studies or expert opinion, precluding strong recommendations for their use at this time. Following is a brief description of the currently available treatment options for recurrent priapism.

Hormonal agents

Antiandrogens, 5α-reductase inhibitors, and gonadotropin-releasing hormone agonists with or without intermittent self administration of sympathomimetic agents for acute episodes have been shown to be successful medical management options for some patients with stuttering priapism [Berger *et al.* 2001; Montague *et al.* 2003; Burnett and Bivalacqua, 2007; Levey *et al.* 2012]. As antiandrogenic agents, these therapies can negatively affect sexual function and physical composition. Therefore, they are not recommended in young patients who have not reached puberty or adult stature, and they should not be used in men desiring fertility. Additionally, extended treatment courses may be necessary to prevent recurrence [Montague *et al.* 2003]. Treatment can be stopped after a few months to evaluate whether priapism recurs, and if it does, treatment may be restarted. However, there is minimal information regarding the efficacy and safety of most of these agents and none have been investigated in controlled clinical studies. To date, only one randomized, placebo-controlled trial using a synthetic estrogen, diethylstilbestrol (DES), has been performed to treat patients with stuttering priapism. This study showed that DES caused termination of the stuttering episode in all patients, but recurrence occurred in more than 50% of the patients (five of nine) following termination of treatment [Chinegwundoh and Anie, 2004]. Antiandrogens are not recommended for treatment as they induce a hypogonadal state with the resultant side effects, including hot flashes, decreased bone mineral density, decreased energy, fatigue, decreased muscle mass, and decreased libido in otherwise young virile men. [Berger *et al.* 2001; Montague *et al.* 2003; Bivalacqua and Burnett, 2006; Burnett and Bivalacqua, 2007; Mwamukonda *et al.* 2010; Levey *et al.* 2012].

Digoxin

Digoxin, most commonly used in patients with congestive heart disease, is an inhibitor of the sodium–potassium pump. By inhibiting the smooth muscle membrane sodium–potassium adenosine triphosphatase, it reduces the sodium concentration gradient and thus increases the intracellular calcium levels [Gupta *et al.* 1995, 1998; Muneer *et al.* 2008b; Yuan *et al.* 2008]. This regulates smooth muscle tone, leading to detumescence. A small *in vivo* double-blind, placebo-controlled trial involving six patients showed that on maintenance doses of 0.25–0.5 mg of digoxin daily, patients experienced a decrease in sexual desire, excitability, and a concomitant decrease in penile rigidity while preserving patient plasma levels of testosterone, estrogen, and luteinizing hormone [Gupta *et al.* 1998]. Further, a multicenter study investigating the use of digoxin in idiopathic stuttering priapism found that on those same maintenance doses, patients reported fewer hospital visits and better quality of life with no adverse effects [Levey *et al.* 2012]. While these results are promising, routine use of digoxin as a first-line management option is not recommended, as digoxin requires continuous monitoring of serum levels and carries its own side-effect profile. Muneer and colleagues investigated the potential effects of digoxin for preventing irreversible smooth muscle dysfunction that follows recurrent ischemic insults by using an *in vitro* model of ischemic priapism [Muneer *et al.* 2008a]. In this study, smooth muscle tone recovery was evaluated after exposure to 4 h of hypoxia and acidosis. Their results showed that administration of digoxin, as well as other antioxidants, did not prevent the resultant smooth muscle dysfunction or fibrosis occurring after ischemic priapism. As such, the use of digoxin for the treatment of stuttering priapism may not mitigate the risk for the development of ED.

Gabapentin

The rationale behind the treatment of priapism with gabapentin arose from reported side effects of sexual dysfunction including anorgasmia and

decreased potency experienced by patients taking gabapentin [Perimenis *et al.* 2004]. While the exact mechanism of action remains unknown, animal studies have attempted to clarify gabapentin's therapeutic effect in the management of priapism [Yuan *et al.* 2008; Dong *et al.* 2011]. In these studies, inhibition of calcium efflux from smooth muscle cells in the corpora of rats, with consequent inhibition of smooth muscle relaxation, served to explain the therapeutic response seen in gabapentin users [Yuan *et al.* 2008]. Another potential mechanism may be gabapentin's ability to reduce testosterone and follicle-stimulating hormone levels, as seen in a study by Daoud and colleagues [Daoud *et al.* 2004]. In a small case series, three men with recurrent priapism were given gabapentin. All responded to treatment within 48 h of administration and remained free from recurrent episodes at 16 and 24 months respectively. The third man discontinued gabapentin after 6 months of being priapism free, and subsequently developed recurrent priapism. After restarting gabapentin, he remained priapism free at 9 months' follow up [Perimenis *et al.* 2004]. Gabapentin may be a safe alternative for the management of refractory idiopathic priapism, although further research is necessary to validate these findings.

Baclofen

Baclofen exerts well known inhibitory effects on sexual function both in animals and humans. There are only a few small studies on the use of baclofen for treatment and prevention of priapism, however it has shown to be most beneficial in patients with spinal spasticity and recurrent reflexogenic erections [D'Aleo *et al.* 2009]. Reflexogenic erections are often associated with muscle spasticity in men with spinal cord lesions and neurologic disease. It is presumed that baclofen, a γ-aminobutyric acid derivative, exerts its effects on the central nervous system as well as on the bulbo- and ischiocavernous muscles [Denys *et al.* 1998; Rourke *et al.* 2002; D'Aleo *et al.* 2009]. While the characteristics and pathophysiology of this form of priapism are still being studied, reports have described a beneficial response with the use of intrathecal baclofen over an oral form, suggesting a dose-dependent response [Denys *et al.* 1998; Rourke *et al.* 2002; D'Aleo *et al.* 2009] The literature does not categorize this type of priapism as ischemic or nonischemic, so further studies are needed to assess the relationship between recurrent reflexogenic erections and ischemic stuttering episode [Broderick *et al.* 2010].

Ketoconazole

While ketoconazole is a well known antifungal agent, one of its resultant side effects is a reduction in testosterone levels. It is this side effect that underlies its use in the treatment of metastatic prostate cancer, prevention of postoperative erections, and is the rationale for its use in treating recurrent priapism [Evans *et al.* 2004; DeCastro *et al.* 2008; Abern and Levine, 2009]. Prednisone is generally coadministered with ketoconazole due to the ability of ketoconazole to block production of adrenal steroids. In a small case series of eight patients with recurrent stuttering priapism, ketoconazole with prednisone was shown to prevent recurrent priapism while retaining sexual function in men for a follow-up period of 1.5 years [Abern and Levine, 2009]. This combination may be a potentially effective treatment for prepubertal men or those desiring fertility. While it was reportedly well tolerated in these patients and cost effective, results will need to be extrapolated into randomized, controlled trials before gaining widespread use [Abern and Levine, 2009].

Terbutaline

Few studies exist evaluating the use of oral terbutaline, a β-adrenergic agonist, in priapism. Further, most of these studies include patients who had pharmacologically induced priapism through intracavernosal injections. In one study involving three paraplegics with pharmacologically induced priapism, two injections of 5 mg terbutaline 15 min apart alleviated priapism in two of the patients. The third patient required a third dose to achieve detumescence [Soni *et al.* 1994]. Additionally, a larger placebo-controlled study comparing terbutaline with phenylephrine and placebo, in 75 patients with pharmacologically induced priapism, terbutaline was significantly better than placebo in achieving detumescence, occurring in 38% of patients [Lowe and Jarow, 1993]. Contrastingly, in a randomized, prospective, double-blind, placebo-controlled trial involving terbutaline in 24 patients with pharmacologically induced priapism, their results did not show any benefit with oral terbutaline over placebo in treating priapism [Govier *et al.* 1994]. As with previously mentioned therapeutics, there is limited evidence for terbutaline's use in treating or preventing recurrent priapism, however it may be more useful in prevention of priapism secondary to pharmacological injections.

PDE5 inhibitors

PDE5 inhibitors have shown promise in the prevention of recurrent/stuttering priapism of varying etiologies. Oral PDE5 inhibitors such as sildenafil or tadalafil are commonly used as medical treatment for ED. However, new scientific evidence has shown they have a paradoxical effect in alleviating recurrent/stuttering priapism [Burnett, 2003; Champion *et al.* 2005; Burnett *et al.* 2006a, 2006b; Bivalacqua *et al.* 2009]. This stems from research suggesting that priapism may be related to altered vascular homeostatic actions in the penis. The leading proposal in this regard is the notion of aberrant signaling of the endothelium-derived nitric oxide (NO) and PDE5 signal transduction pathway in the penis, suggesting that recurrent priapism may be caused by reduced NO availability [Shalev *et al.* 1999; Kato *et al.* 2009; Hannan *et al.* 2013]. In a small case series, daily PDE5 inhibitor therapy reduced ischemic priapism episodes in men with stuttering priapism. None of the patients reported any adverse events associated with PDE5 therapy and only one patient did not respond to treatment [Burnett *et al.* 2006]. This patient had SCD-associated priapism with a history of severe recurrent episodes. There are now long-term data regarding therapy with PDE5 inhibitors in men with recurrent idiopathic priapism. The results demonstrate that PDE5 inhibitors alleviated priapism in men with idiopathic priapism, as well as SCD-associated priapism, without affecting their normal erectile capacity [Burnett *et al.* 2006; Pierorazio *et al.* 2011; Segal *et al.* 2013]. In these studies, the initial dose of sildenafil citrate was 25 mg daily administered orally with escalation up to 50 mg daily, and doses of tadalafil at 5–10 mg three times a week, with fair success results. Even in cases of glucose-6-phosphate dehydrogenase deficiency and thalassemia-related priapism, PDE5 inhibitors have shown to resolve recurrence and prevent further priapic episodes while preserving erectile function [Burnett and Bivalacqua, 2008; Tzortzis *et al.* 2009].

PDE5 inhibitors should only be started in patients under conditions of complete penile flaccidity. Patients should be counseled to take PDE5 inhibitors midmorning, preferably while at work, during a time completely unrelated from any sexual stimulation or arousal. It is not recommended that they be started at nighttime as patients with SCD tend to have early morning erections associated with sickling and nighttime PDE5 inhibitor administration may exacerbate this.

Efficacy is usually seen within 2–4 weeks of dosing [Broderick *et al.* 2010]. PDE5 inhibitors are currently considered investigational at the present time for the treatment of stuttering ischemic priapism and are contraindicated in this setting in the packaging labels [Champion *et al.* 2005; Bivalacqua and Burnett, 2006; Bivalacqua *et al.* 2009; Tzotzis *et al.* 2009]. Additionally PDE5 inhibitors are costly and may not be covered by insurance companies, and are associated with their own side effect profile. Despite these limitations, PDE5 inhibitors are a promising new preventative therapy for priapism. Randomized, placebo-controlled clinical trials are currently underway in the hope of establishing their efficacy.

Future targets for treatment of priapism: molecular mechanisms

Scientific progress in priapism has progressed greatly, particularly in the areas of molecular science. Preclinical investigations have proposed potential roles of NO, opiorphins, and adenosine signaling pathways as primary intracorporeal mechanisms for priapism, driving novel therapeutic approaches [Sharifzadeh *et al.* 1995; Shalev *et al.* 1999; Filippi *et al.* 2000; Champion *et al.* 2005; Nolan *et al.* 2005; Yuan *et al.* 2008; Bivalacqua *et al.* 2009, 2012; Kanika *et al.* 2009; Wen *et al.* 2010].

Opiorphins

Opiorphins are peptides that act as potent endogenous neutral endopeptidase inhibitors [Hannan *et al.* 2013]. Studies have shown that in sickle cell mice, there is an increased expression of the mouse opiorphin homologue in corporal tissue compared with wild-type mice, suggesting their role as important mediators in erectile physiology [Kanika *et al.* 2009]. Kanika and colleagues injected plasmid-expressing genes that encoded for opiorphins intracorporally into retired breeder rats. Following intracavernous injections, the breeder rats expressed a priapic-like condition. Further analysis of those rats showed that enzymes in the polyamine synthesis pathway were notably upregulated in those rats compared with controls. Further, these episodes of priapism could be prevented by injecting inhibitors of the polyamine synthesis pathway into breeder rats prior to inoculation with these plasmids. These results suggest that upregulation of the polyamine synthetic pathway plays a role in

the development of priapism. This represents exciting possibilities for future targets of prevention.

Adenosine

Adenosine is a signaling nucleoside that shares many common features with NO. Both are potent vasodilators, induce cyclic nucleotide second messengers, and both affect penile erection [Sharifzadeh *et al.* 1995; Shalev *et al.* 1999; Filippi *et al.* 2000; Dai *et al.* 2009; Wen *et al.* 2010]. Studies in both animals and humans have shown that intracavernous injection of adenosine results in tumescence and penile erection, providing evidence that excess adenosine may contribute to priapism [Sharifzadeh *et al.* 1995; Filippi *et al.* 2000; Dai *et al.* 2009]. Supporting this, the use of an adenosine receptor antagonist, has been shown to inhibit these adenosine-induced erections [Dai *et al.* 2009; Wen *et al.* 2010]. Mi and colleagues also showed that, in SCD transgenic mice, an accepted model for priapism that elevated adenosine levels through increased adenosine receptor signaling induced prolonged penile erection [Mi *et al.* 2008]. Further, unexpected priapic activity was displayed in the mice lacking adenosine deaminase, an enzyme necessary for the breakdown of adenosine. These results suggest the possibility of new molecular pathways that represent potential targets for the future prevention of priapism.

Conclusion

Priapism still represents a great challenge in therapeutic management among erectile disorders. While all acute episodes of ischemic priapism should be managed emergently, the primary goal remains that of prevention. Treatment involves aspiration/irrigation with sympathomimetic injections, surgical shunts, and penile prosthesis insertion. Nonischemic priapism may be conservatively managed initially. The primary goal of therapy for stuttering priapism is prevention, but acute episodes should be managed in accordance with guidelines for ischemic priapism. Several new therapies driven by discoveries in the molecular pathways of priapism are on the horizon, which may supplement current treatment protocols. More research and support are necessary to target preventative efforts in treating this rare but clinically devastating condition.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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