Review Article

Priapism in Sickle-cell Disease: Emergency Room Intervention

Akinsegun Akinbami, Ebele Uche, Adedoyin Dosunmu

Department of Hematology and Blood Transfusion, College of Medicine, Lagos State University, Lagos, Nigeria

Abstract

Priapism is one of the diverse complications of sickle cell disease (SCD). SCD is one of the many causes of priapism. Ischaemic and stuttering priapisms are the types seen in SCD. Apart from pain and psychological trauma associated with ischaemic and stuttering priapism, erectile dysfunction and impotence are the most severe complications of priapism in SCD that may require the use of penile prosthesis in SCD patients. The outcome of priapism complications is time-dependent and dependent on the type of management administered. This review highlights, the anatomy of the penis, physiology of normal erection, focusing on pathophysiology and management of priapism in SCD so as to create better awareness of this condition amongst physicians involved in the management of SCD.

Keywords: Emergency, priapism, sickle-cell disease

Introduction

Sickle-cell disease (SCD) is a genetic abnormality in which glutamine on the 6th position of the β-hemoglobin chain is replaced with valine as a result of a single point mutation affecting the replacement adenine with thymine on its deoxyribonucleic acid structure. One of the consequences of the mutation is sickling of the red blood cells (RBCs). The sickled RBCs impede free flow of blood of affected vessels causing obstruction, congestion, hypoxia, and lactic acidosis, all contributing to the pathophysiology of priapism in SCD.

Priapism is the development of prolonged penile erections leading to tissue ischemia and development of functional erections in the absence of sexual arousal or desire.[1,2]

Three types of priapism exist, namely ischemic priapism also known as veno-occlusive or low flow, stuttering priapism or recurrent ischemic priapism (RIP), and nonischemic priapism (arterial high flow).

Ischemic and stuttering priapisms are associated with SCD with prevalence rates of 40%.[3] It is characterized by pain and is a medical emergency. Unlike ischemic priapism, nonischemic priapism is nonpainful and is usually secondary to unregulated cavernous arterial inflow, caused by arteriovenous fistula, iatrogenic needle injury, and pelvic trauma causing arteriosinusoidal fistula formation; it is not a medical emergency.[4] Knowledge of priapism among SCD patients in Nigeria is poor; 74.6% of the patients had no knowledge of priapism[5] despite a high prevalence of priapism of between 30%–40% among them. Nearly, 89% are estimated to experience priapism by the age of 20 years.[3,6]

Erectile dysfunction (ED) is one of the many complications of priapism. ED is secondary to tissue ischemia and subsequent cavernosal fibrosis which is a time-dependent complication.[7]

Overview of the Anatomy of the Penis

The penis is made up of three erectile columns, i.e. two corporal cavernosa and a corpus spongiosum which is situated in the central groove of the paired corporal cavernosa. The penis also has columns enclosing fascial layers, nerves, lymphatics, and blood vessels.

The paired corpora cavernosa and the corpus spongiosum are covered by a dense fibrous sheath of connective tissue called tunica albuginea. The space of the corpora cavernosa contains arteries, nerves, muscle fibers, and venous sinuses lined with flat endothelial cells; an areola tissue separates the corpora cavernosa from the tunica albuginea.

Address for correspondence: Dr. Akinsegun Akinbami, Department of Hematology and Blood Transfusion, College of Medicine, Lagos State University, PMB 21266, Ikeja, Lagos, Nigeria.
E-mail: ajoke_clinic@yahoo.co.uk

Access this article online

Quick Response Code:

Website: www.atpjournal.org

DOI: 10.4103/atp.atp_17_17

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Akinbami A, Uche E, Dosunmu A. Priapism in sickle-cell disease: Emergency room intervention. Ann Trop Pathol 2017;8:5-10.

The penile skin encloses the three corpora and folds on itself to form the foreskin overlying the glans and corona. There is an abundant smooth muscle of the penis and scrotum, called the dartos fascia fusing with the superficial perineal (Colle) fascia. The Dartos fascia is attached to the deep penile (Buck) fascia and loosely attached to the skin in the penis containing superficial arteries, veins, and nerves of the penis.

The skin of the penis is supplied by external pudendal arteries which arise from the femoral artery, and deep structures are supplied by internal pudendal artery. The superficial, intermediate, and deep veins drain the penis. The penis is supplied by pudendal and cavernous nerves.

Physiology of Normal Erection

Normal erection is largely driven by nitric oxide (NO/cyclic guanosine monophosphate [cGMP]) pathway. RIP has been described to be induced by dysregulation of NO/cGMP signaling pathway.[8]

Also involved mechanisms in normal erection are the cyclic adenosine monophosphate (cAMP) pathway and vascular/neurogenic pathway regulated by NO synthase (NOS) enzyme, the mediator of NO synthesis. NOS are of three types, nerve NOS (nNOS), endothelium NOS (eNOS), and iNOS (nonspecific – all cells). The three types of NOS and L-arginine in the presence of oxygen catalyze formation of NO.[9,10]

NO generated majorly from nNOS and partly from eNOS stimulates guanylate cyclase which catalyzes guanosine triphosphate to cGMP, the latter stimulates the production of protein kinase G, opening potassium channels, and closing calcium channels. The effects of cGMP relax smooth muscles of the penis causing tumescence (erection).

Phosphodiesterase-5 (PDE5) degrades the 3'5' bonds of cGMP to its inactive 5'GMP; this induces detumescence.[11] PDE5 is targeted by sildenafil, vardenafil, and tadalafil which have estrogenic properties. PDE 2, 3, and 4 (PDE2, PDE3, and PDE4) mediate the cAMP pathway which is targeted by papaverine.

Priapism in Sickle-Cell Disease

Stasis and low blood flow rates within the sinusoids of the corpora cavernosa predispose the penis to veno-occlusive crises, thus obstructing its venous drainage, resulting in viscous and hypoxic blood. Normal neuronal production and surges in cGMP causes nocturnal erections, insufficient basal level of PDE5 which degrades the 3'5' bonds of cGMP to its inactive 5'GMP is responsible for uninhibited cGMP, and this causes recurrent ischaemic priapism in sickle cell disease.

Pathophysiology of priapism in SCD is associated with a reduction in bioavailability of endothelium-derived NO.[12] A reduction in NO is consequent on hemoglobinemia associated with chronic hemolysis in SCD; hemoglobin is an avid scavenger of intravascular NO. Second, arginase, a byproduct of hemolysis, degrades L-arginine in the vasculature, thus causing a reduction in L-Citrulline. Third, the function and formation of endothelium-derived NO is impaired by excess reactive oxygen species (ROS) and their mediators produced from chronic hemolysis.[13,14]

Ischemic priapism induced-vascular endothelium damage causes loss of eNOS which also contributes to a significant reduction in NO bioavailability.[15]

Posttranslational modification of eNOS at Ser-1177 site has been reported to cause functional impairment and subsequent reduction in the level of NO.[16]

In SCD, chronic reduction in activation of eNOS causes decreased production and function of NO, thus downregulation of PDE5.[17]

Following stimulation either neurologically or erectogenically in sexual activity or sleep, cavernosal relaxation is induced by accumulation of cGMP; however, normal detumescence mechanism is impaired because of reduced basal levels of PDE5 due to reduced level of eNOS in SCD.

Pentapeptides such as opiorphins have also been implicated in the pathogenesis of priapism in SCD; they mediate cavernosal smooth muscle function causing excessive relaxation and engorgement of corpora cavernosa associated with priapism.[18] Opiorphin homolog genes are expressed significantly in the prostrate and penile smooth muscle.[19]

In animal models, there is an improved erectile function in aged rats at lower doses and priapic-like condition at higher doses following experimental gene transfer of opiorphin homologs.[20-22]

In SCD, there is a loss of maintenance of ROS such as superoxide, hydrogen peroxide, hydroxyl radicals, and reactive nitrosative species (RNS) such as peroxynitrite and s-nitrosothiols by antioxidant enzymes and scavengers of oxygen radicals such as superoxide dismutase and glutathione peroxidase that under normal physiologic conditions maintain them.[23]

The loss is due to increased sources of oxidative stress and activation of protein degradation pathways in the corporal tissues of animal models of priapism as confirmed by increased levels of NADPH oxidase subunits.[24,25] The implication of the loss of maintenance of both ROS and RNS in association with penile reperfusion injury occurring during the period of ischemia relief following priapism episodes contributes to cavernosal tissue damage associated with priapism.[26]

Superoxide decreases NO bioavailability by degrading NO to peroxynitrite, thus distorting NO/cGMP pathway and promoting priapism. Heme and globin are products of hemoglobin degradation. Heme oxygenase (HO) degrades heme to biliverdin, iron, and carbon monoxide.[27,28] HO exists as three isoforms HO1, HO2, and HO3; HO1 reacts to a variety of stress mediators such as heat and NO donors, it is

upregulated in cavernosal tissues of artificially-induced, animal priapic models.[27] It is thought to have antioxidant properties as it is upregulated in vascular smooth muscle, endothelial cells, and cardiac tissue in hypoxia.[29] The antioxidant protective mechanism during hypoxia is facilitated by interactions between HO and NO/cGMP pathways.[30] It is not clear whether the up-regulation of HO-1 in response to tissue hypoxia is an alternative induction mechanism of priapism.[30]

RHO/RHO Kinase

Rho A/Rho-kinase (ROCK) signal transduction pathway is responsible for maintaining the penis in a flaccid state.[31,32] There is a dysregulation of Rho signaling with reduced Rho A expression in human SCD penis.[33] Reduced Rho A/Rock signaling causes reduced vasoconstriction in the penis in SCD, thus enhancing altered vasodilatory effects of the penis contributing to priapism.[19]

Diagnosing Ischemic Priapism

Diagnosis is self-evident, history of time of onset is important to determine whether the duration of priapism is below 4 h or more, priapism shorter than 4 h may not be considered for medical therapy and priapism longer than 4 h should be attended to emergently. Previous history of priapism highlights recurrent priapism which is a recurrent form of ischemic priapism associated with painful erections occurring repeatedly with intervening period of detumescence. Drug history is important because some drugs induce priapism; they are antihypertensives, anticoagulants, alcohol, marijuana, cocaine, papaverine, phentolamine, and prostaglandin E.

Physical examination includes examination of the genitalia, perineum and abdomen for any evidence of trauma, although non-ischaemic priapism is usually secondary to trauma, it is important to examine these areas even when ischaemic priapism is being considered. The physical inspection should include the phallus to determine the extent of tumescence. In priapism generally, corpora cavernosa are affected, and the spongiosum and glans penis are spared. The penis is completely rigid in ischemic priapism unlike in nonischemic priapism.

Laboratory investigations include a full blood count and peripheral smear; these give an insight into the diagnosis of SCD; priapism secondary to myeloproliferative or lymphoproliferative disorders are elucidated if the total white blood cell count is markedly elevated. Reticulocyte count is elevated in SCD. Hemoglobin electrophoresis and quantification determine the type of hemoglobinopathy; penile blood gas measurement is required to confirm ischemic priapism in which blood sample aspirated from corpora cavernosa is usually hypoxic, hyperbaric, and acidotic; PO_2 <30 mmHg, normal arterial should be >90 mmHg and the normal mixed venous blood should be 40 mmHg; PCO_2 in ischemic priapism should be >60 mmHg, normal arterial should be <40 mmHg, and the normal mixed venous blood should be 50 mmHg; the pH will be <7.25, normal arterial should be 7.40, and the normal mixed venous blood should be 7.35 [Table 1].

Penile color duplex ultrasound is noninvasive and confirms little or no blood flow in the cavernosal arteries in ischemic priapism. Lithotomy or frog-leg positions are the recommended positions for performing color duplex ultrasound. Penile arteriography is a substitute for duplex ultrasound; it is, however, invasive, not recommended but may be performed as part of embolization procedure.

Urine toxicology is useful for screening psychoactive drugs intake which could induce priapism in SCD.

Treatment of Priapism In Sickle-Cell Disease

Treatment could be medical or surgical. The goal of treatment is to intervene as early as possible to prevent subsequent episode and reduce the significant risk of ED.

Medical Management

A stepwise treatment plan should start with intracavernosal injections of phenylephrine dosed 100–200 μg every 5 min until detumescence but not exceeding 1000 μg/h which vasoconstrict corporal cavernosal smooth muscle causing detumescence.[34]

Phenylephrine has minimal beta-adrenergic stimulatory effects unlike other sympathomimetics which have cardiac inotropic and chronotropic side effects.

An intracavernosal injection of phenylephrine is followed by aspiration and irrigation with saline, followed by irrigation with phenylephrine. A local penile shaft block which may be a circumferential penile block, a subcutaneous local penile shaft block, a dorsal nerve block, or oral conscious sedation for pediatric patients is recommended before intracavernosal injections of phenylephrine, aspiration, and irrigation which provides local pain control.[35] Other oral adrenergic agents used are terbutaline,[36] pseudoephedrine, and epheredin.[4] The priapism in sickle cell study could not establish advantage of oral adrenergic agents such as ephedrine and etilefrine over placebo in the prevention of priapism.[37]

PDE5 inhibitors use was found to reduce priapism and restore PDE5 gene activity.[38] The use of PDE5 inhibitors in acute cases of priapism has been reported;[39] however, improvement in symptoms may not be due to short-term changes in PDE5 levels and may potentially worsen priapic events.[40]

The use of PDE5 inhibitors is paradoxical to it eretogenic properties, the mechanism of action is to

Table 1: Laboratory findings of penile blood gas

	Ischemic priapism	Normal arterial	Normal mixed venous blood
PO_2	<30 mmHg	>90 mmHg	40 mmHg
PCO_2	>60 mmHg	<40 mmHg	50 mmHg
pH	<7.25	7.40	7.35

re-establish basal levels of cGMP in the penis, thus reseting PDE 5 levels expression and activity.[40] Burnett *et al*. conducted a controlled clinical trial to determine safety and efficacy of sildenafil for priapism prevention;[41] they concluded that the use of sildenafil by systemic dosing may offer strategy to prevent RIP in patients with SCD. They could not establish any significant adverse effects on the use.

Hydroxyurea use seems to be beneficial in RIP prevention.[42,43] Anele *et al*. reported on the advantage of hydroxyurea use in the prevention of RIP.[44] The mechanism of action may be due to the fact that hydroxyurea is an NO donor because it reacts with hemoglobin to form NO, thus correcting the reduced bioavailability of NO associated with RIP.[45,46]

Induction of fetal hemoglobin and reduction of hemolysis also correct NO bioavailability of severe hemolysis.[47] Hydroxyurea is also useful in reversing ED because it downregulates endothelin-1, a pro-fibrotic molecule, with a likely role in the corporal fibrosis associated with priapism.[48,49]

Nocturnal oxygen desaturation has been reported to contribute to the pathogenesis of priapism;[50] therefore, prophylactic nocturnal oxygen or use of continuous positive airway has been advocated.

Treatment with hormonal therapy such as stilbestrol and GnRH analogs were proposed by Chow and Payne[51] and Serjeant *et al*.[52] because they downregulate pituitary gland function. Similarly, antiandrogenic agent like ketoconazole was suggested[53] because it reduces serum testosterone. However, side effects of hormonal therapy such as infertility, gynecomatsia, delayed growth/development due to premature epiphyseal plate closure, and reduced libido pose significant disadvantages; they are therefore contraindicated in boys in reproductive age groups and men wishing to conceive.

The advantages of the use of red cell exchange or simple transfusions in preventing or treating acute priapism have not been well substantiated, rather neurologic complications such as convulsions, hemiparesis, and cerebral hemorrhages associated with the procedure have been reported.[54]

Newer agent like pentoxyfylline reduces fibrosis and TGF-β mediated deposition of collagen in the tunica albuginea[55] it facilitates recovery of erections in a rat model of erectile dysfunction post prostatectomy[56] it also reduces collagen density in an ischaemic induced priapism rat model.

Surgical Management

Surgical management is indicated if priapism duration is >72 h and in failed medical treatment. It should be considered a second-line management because of higher risk of ED. The objective of surgical management is to establish anastomosis between corpora cavernosa and glans, corpos spongiosum or vein for drainage in order to reduce congestion in the corpora carvernosa. This is done by opening up the tunica albuginea. There are four types of surgical shunts, i.e. the distal (corporaglanular shunt), proximal (corpora spongiosal shunt), Burnett's technique, and vein anastomosis/shunts (Grayhack's Procedure). The distal shunt consists of creating an open bilateral excision of circular cone segments of distal tunica albuginea through the glans penis, along with a subsequent glans closure by means of a running suture with absorbable material. This is the Al-Ghorab's prodecure[57] while the proximal shunt is done by creating a communication between corpora cavernosum and the corpus spongiosum through a trans-scrotal or perineal approach; this is the Quackle's technique.[58] Burnett's technique is a modification of Al-Ghorab shunt involving a retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glanular excision.[59] The vein anastomosis/shunts also known as Grayhack's procedure, in which there is mobilization of the saphenous vein below the junction of the femoral vein and anastomosing the vein end-to side onto the corpos cavernosum.[60]

Conclusion

If priapism is presented after >36 h of onset or if there is failure of both medical and surgical interventions, ED becomes inevitable and penile prosthesis implantation should be considered as early as possible because severe corporal fibrosis makes penile implantation difficult at a later date.[61]

Acknowledgment

The authors thank Miss Oluwatosin Soetan for editorial assistance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Berger R, Billups K, Brock G, Broderick GA, Dhabuwala CB, Goldstein I, *et al.* Report of the American Foundation for Urologic Disease (AFUD) Thought Leader Panel for evaluation and treatment of priapism. Int J Impot Res 2001;13 Suppl 5:S39-43.
2. Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, *et al.* American Urological Association guideline on the management of priapism. J Urol 2003;170:1318-24.
3. Adeyoju AB, Olujohungbe AB, Morris J, Yardumian A, Bareford D, Akenova A, *et al.* Priapism in sickle-cell disease; incidence, risk factors and complications – An international multicentre study. BJU Int 2002;90:898-902.
4. Olujohungbe A, Burnett AL. How I manage priapism due to sickle cell disease. Br J Haematol 2013;160:754-65.
5. Adediran A, Wright K, Akinbami A, Dosunmu A, Oshinaike O, Osikomaiya B, *et al.* Prevalence of priapism and its awareness amongst male homozygous sickle cell patients in Lagos, Nigeria. Adv Urol 2013;2013:890328.
6. Mantadakis E, Cavender JD, Rogers ZR, Ewalt DH, Buchanan GR. Prevalence of priapism in children and adolescents with sickle cell anemia. J Pediatr Hematol Oncol 1999;21:518-22.
7. Broderick GA. Priapism and sickle-cell anemia: Diagnosis and nonsurgical therapy. J Sex Med 2012;9:88-103.

8. Champion HC, Bivalacqua TJ, Takimoto E, Kass DA, Burnett AL. Phosphodiesterase-5A dysregulation in penile erectile tissue is a mechanism of priapism. Proc Natl Acad Sci U S A 2005;102:1661-6.
9. Burnett AL, Lowenstein CJ, Bredt DS, Chang TS, Snyder SH. Nitric oxide: A physiologic mediator of penile erection. Science 1992;257:401-3.
10. Rajfer J, Aronson WJ, Bush PA, Dorey FJ, Ignarro LJ. Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. N Engl J Med 1992;326:90-4.
11. Corbin JD, Francis SH. Cyclic GMP phosphodiesterase-5: Target of sildenafil. J Biol Chem 1999;274:13729-32.
12. Akinsheye I, Klings ES. Sickle cell anemia and vascular dysfunction: The nitric oxide connection. J Cell Physiol 2010;224:620-5.
13. Aslan M, Ryan TM, Adler B, Townes TM, Parks DA, Thompson JA, *et al.* Oxygen radical inhibition of nitric oxide-dependent vascular function in sickle cell disease. Proc Natl Acad Sci U S A 2001;98:15215-20.
14. Houston M, Estevez A, Chumley P, Aslan M, Marklund S, Parks DA, *et al*. Binding of xanthine oxidase to vascular endothelium. Kinetic characterization and oxidative impairment of nitric oxide-dependent signaling. J Biol Chem 1999;274:4985-94.
15. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: Biology, pathophysiology, genetics, translational medicine, and new research directions. Am J Hematol 2009;84:618-25.
16. Musicki B, Ross AE, Champion HC, Burnett AL, Bivalacqua TJ. Posttranslational modification of constitutive nitric oxide synthase in the penis. J Androl 2009;30:352-62.
17. Lin CS, Chow S, Lau A, Tu R, Lue TF. Human PDE5A gene encodes three PDE5 isoforms from two alternate promoters. Int J Impot Res 2002;14:15-24.
18. Fu S, Tar MT, Melman A, Davies KP. Opiorphin is a master regulator of the hypoxic response in corporal smooth muscle cells. FASEB J 2014;28:3633-44.
19. Bivalacqua TJ, Musicki B, Kutlu O, Burnett AL. New insights into the pathophysiology of sickle cell disease-associated priapism. J Sex Med 2012;9:79-87.
20. Tong Y, Tar M, Davelman F, Christ G, Melman A, Davies KP, *et al.* Variable coding sequence protein A1 as a marker for erectile dysfunction. BJU Int 2006;98:396-401.
21. Tong Y, Tar M, Monrose V, DiSanto M, Melman A, Davies KP, *et al.* HSMR3A as a marker for patients with erectile dysfunction. J Urol 2007;178:338-43.
22. Tong Y, Tar M, Melman A, Davies K. The opiorphin gene (ProL1) and its homologues function in erectile physiology. BJU Int 2008;102:736-40.
23. Wood KC, Granger DN. Sickle cell disease: Role of reactive oxygen and nitrogen metabolites. Clin Exp Pharmacol Physiol 2007;34:926-32.
24. Musicki B, Liu T, Sezen SF, Burnett AL. Targeting NADPH oxidase decreases oxidative stress in the transgenic sickle cell mouse penis. J Sex Med 2012;9:1980-7.
25. Kanika ND, Melman A, Davies KP. Experimental priapism is associated with increased oxidative stress and activation of protein degradation pathways in corporal tissue. Int J Impot Res 2010;22:363-73.
26. Munarriz R, Park K, Huang YH, Saenz de Tejada I, Moreland RB, Goldstein I, *et al.* Reperfusion of ischemic corporal tissue: Physiologic and biochemical changes in an animal model of ischemic priapism. Urology 2003;62:760-4.
27. Jin YC, Gam SC, Jung JH, Hyun JS, Chang KC, Hyun JS, *et al.* Expression and activity of heme oxygenase-1 in artificially induced low-flow priapism in rat penile tissues. J Sex Med 2008;5:1876-82.
28. Shamloul R. The potential role of the heme oxygenase/carbon monoxide system in male sexual dysfunctions. J Sex Med 2009;6:324-33.
29. Kato GJ, Gladwin MT. Evolution of novel small-molecule therapeutics targeting sickle cell vasculopathy. JAMA 2008;300:2638-46.
30. Morrison BF, Burnett AL. Stuttering priapism: Insights into pathogenesis and management. Curr Urol Rep 2012;13:268-76.
31. Chitaley K, Wingard CJ, Clinton Webb R, Branam H, Stopper VS, Lewis RW, *et al.* Antagonism of rho-kinase stimulates rat penile erection via a nitric oxide-independent pathway. Nat Med 2001;7:119-22.
32. Wang H, Eto M, Steers WD, Somlyo AP, Somlyo AV. RhoA-mediated ca2+ sensitization in erectile function. J Biol Chem 2002;277:30614-21.
33. Lagoda G, Sezen SF, Cabrini MR, Musicki B, Burnett AL. Molecular analysis of erection regulatory factors in sickle cell disease associated priapism in the human penis. J Urol 2013;189:762-8.
34. Song PH, Moon KH. Priapism: Current updates in clinical management. Korean J Urol 2013;54:816-23.
35. Anele UA, Le BV, Resar LM, Burnett AL. Blood 2015;125:3551-58.
36. Yuan J, Desouza R, Westney OL, Wang R. Insights of priapism mechanism and rationale treatment for recurrent priapism. Asian J Androl 2008;10:88-101.
37. Olujohungbe AB, Adeyoju A, Yardumian A, Akinyanju O, Morris J, Westerdale N, *et al.* A prospective diary study of stuttering priapism in adolescents and young men with sickle cell anemia: Report of an international randomized control trial – The priapism in sickle cell study. J Androl 2011;32:375-82.
38. Bivalacqua TJ, Musicki B, Hsu LL, Berkowitz DE, Champion HC, Burnett AL, *et al.* Sildenafil citrate-restored eNOS and PDE5 regulation in sickle cell mouse penis prevents priapism via control of oxidative/nitrosative stress. PLoS One 2013;8:e68028.
39. Bialecki ES, Bridges KR. Sildenafil relieves priapism in patients with sickle cell disease. Am J Med 2002;113:252.
40. Burnett AL, Bivalacqua TJ, Champion HC, Musicki B. Long-term oral phosphodiesterase 5 inhibitor therapy alleviates recurrent priapism. Urology 2006;67:1043-8.
41. Burnett AL, Anele UA, Trueheart IN, Strouse JJ, Casella JF. Randomized controlled trial of sildenafil for preventing recurrent ischemic priapism in sickle cell disease. Am J Med 2014;127:664-8.
42. Saad ST, Lajolo C, Gilli S, Marques Júnior JF, Lima CS, Costa FF, *et al.* Follow-up of sickle cell disease patients with priapism treated by hydroxyurea. Am J Hematol 2004;77:45-9.
43. Al Jam'a AH, Al Dabbous IA. Hydroxyurea in the treatment of sickle cell associated priapism. J Urol 1998;159:1642.
44. Anele UA, Mack AK, Resar LM, Burnett AL. Hydroxyurea therapy for priapism prevention and erectile function recovery in sickle cell disease: A case report and review of the literature. Int Urol Nephrol 2014;46:1733-6.
45. Cokic VP, Beleslin-Cokic BB, Tomic M, Stojilkovic SS, Noguchi CT, Schechter AN, *et al.* Hydroxyurea induces the eNOS-cGMP pathway in endothelial cells. Blood 2006;108:184-91.
46. Gladwin MT, Shelhamer JH, Ognibene FP, Pease-Fye ME, Nichols JS, Link B, *et al.* Nitric oxide donor properties of hydroxyurea in patients with sickle cell disease. Br J Haematol 2002;116:436-44.
47. Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood 2010;115:5300-11.
48. Lapouméroulie C, Benkerrou M, Odièvre MH, Ducrocq R, Brun M, Elion J, *et al.* Decreased plasma endothelin-1 levels in children with sickle cell disease treated with hydroxyurea. Haematologica 2005;90:401-3.
49. Shi-Wen X, Chen Y, Denton CP, Eastwood M, Renzoni EA, Bou-Gharios G, *et al.* Endothelin-1 promotes myofibroblast induction through the ETA receptor via a rac/phosphoinositide 3-kinase/Akt-dependent pathway and is essential for the enhanced contractile phenotype of fibrotic fibroblasts. Mol Biol Cell 2004;15:2707-19.
50. Setty BN, Stuart MJ, Dampier C, Brodecki D, Allen JL. Hypoxaemia in sickle cell disease: Biomarker modulation and relevance to pathophysiology. Lancet 2003;362:1450-5.
51. Chow K, Payne S. The pharmacological management of intermittent priapismic states. BJU Int 2008;102:1515-21.
52. Serjeant GR, de Ceulaer K, Maude GH. Stilboestrol and stuttering priapism in homozygous sickle-cell disease. Lancet 1985;2:1274-6.
53. Abern MR, Levine LA. Ketoconazole and prednisone to prevent recurrent ischemic priapism. J Urol 2009;182:1401-6.
54. Danielson CF. The role of red blood cell exchange transfusion in the treatment and prevention of complications of sickle cell disease. Ther Apher 2002;6:24-31.
55. Shindel AW, Lin G, Ning H, Banie L, Huang YC, Liu G, *et al.* Pentoxifylline attenuates transforming growth factor-β1-stimulated collagen deposition and elastogenesis in human tunica albuginea-derived fibroblasts part 1: Impact on extracellular matrix. J Sex Med 2010;7:2077-85.
56. Albersen M, Fandel TM, Zhang H, Banie L, Lin G, De Ridder D, *et al.* Pentoxifylline promotes recovery of erectile function in a rat model of

postprostatectomy erectile dysfunction. Eur Urol 2011;59:286-96.
57. Lue TF, Pescatori ES. Distal cavernosum-glans shunts for ischemic priapism. J Sex Med 2006;3:749-52.
58. Burnett AL. Surgical management of ischemic priapism. J Sex Med 2012;9:114-20.
59. Segal RL, Readal N, Pierorazio PM, Burnett AL, Bivalacqua TJ. Corporal Burnett "Snake" surgical maneuver for the treatment of ischemic priapism: Long-term followup. J Urol 2013;189:1025-9.
60. Kihl B, Bratt CG, Knutsson U, Seeman T. Priapsim: Evaluation of treatment with special reference to saphenocavernous shunting in 26 patients. Scand J Urol Nephrol 1980;14:1-5.
61. Salonia A, Eardley I, Guiliano F, Moncada I, Hatmouratidis K. Guidelines on Priapism. www.uroweb.org/guidelines/onlineguidelines. European Association of Urology 2015. p. 13.