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REVIEW

Penile transplantation: an emerging option for genitourinary reconstruction

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SUMMARY

Penile transplantation is an emerging option for patients with severe genital defects not amenable to traditional reconstructive options. In this article, we discuss the burgeoning problem of severe male genitourinary trauma in the military, the limitations of traditional reconstructive options in addressing these problems, and the potential for penile transplantation to provide improved outcomes. We also review the preclinical research and limited worldwide experience with penile transplantation to date, including lessons learned, and discuss the many important technical, logistical, and ethical considerations pertaining to penile transplantation that must be addressed to maximize the likelihood of successful implementation.

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Introduction

Patients with severe penile defects often suffer from debilitating physical and psychosocial sequelae, including inability to have sexual intercourse or urinate while standing, feelings of emasculation, disruption of interpersonal relationships, and profound loss of quality of life. While traditional phalloplastic reconstruction can produce satisfactory outcomes in many cases, it is limited by a high rate of complications involving prosthesis extrusion and urinary strictures and fistulae. Furthermore, there is a growing cohort of patients with traumatic penile loss and concomitant extremity injuries who are not candidates for autogenous reconstruction because they lack adequate donor sites. For patients who have either failed autogenous reconstruction or are not appropriate candidates, penile allotransplantation may offer a viable alternative. In this article, we will discuss the burgeoning problem of severe male genitourinary trauma in the military, the limitations of traditional reconstructive options in addressing these problems, and the potential for penile transplantation to provide improved outcomes. We will also review the limited worldwide experience with penile transplantation to date, including lessons learned, and discuss the many important technical, logistical, and ethical considerations pertaining to penile transplantation that must be addressed to maximize the likelihood of successful implementation.

Combat-related genitourinary trauma: a growing problem in the military

The recent conflicts in Iraq and Afghanistan have brought into focus the devastating consequences of severe male genitourinary (GU) trauma. Although these injuries are not new, the increased use of improvised

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explosive devices and ground deployment, as well as improvements in body armor, has led to more soldiers surviving blast injuries that would have previously been fatal and returning from the battlefield with total or near-total penile loss [1–4]. The rate of GU trauma among injured servicemen rose dramatically, from 7.2% in 2009 to 12.7% in 2010 and 14% in 2011, with the increased deployment of combat troops and foot patrols in Afghanistan [5]. Service members returning with these injuries often battle with debilitating physical and psychosocial sequelae well after their wounds have healed [2,6]. Unfortunately, the extent and complexity of their injuries can preclude adequate reconstruction with traditional techniques; those who present with perineal blast injuries and concomitant multiple extremity trauma and/or amputation often lack suitable donor sites for autogenous reconstruction. Of the 1367 male service members who sustained GU trauma during Operation Iraqi Freedom and Operation Enduring Freedom, 28.7% also had at least one extremity amputation, the large majority of which were at or above the knee [7]. For these patients, alternative approaches to GU reconstruction are desperately needed.

Limitations of traditional reconstructive options

There are a number of reconstructive options available for total penile reconstruction, all of which make use of the patients' own tissues to create a neophallus. However, none fully address all of the ideal goals of phalloplastic reconstruction, including acceptable appearance, a competent urethra, tactile and erogenous sensibility, and sufficient rigidity and durability to allow for sexual penetration [8,9].

The radial forearm free flap (RFFF) was first used for phalloplasty in 1984 [10] and is considered by many to be the contemporary gold standard [11]. The RFFF has the advantages of being relatively thin, supple, and hairless, thereby mimicking native penile shaft skin and allowing for excellent esthetic outcomes (Fig. 1). Because it receives robust sensory innervation from both the medial and lateral antebrachial cutaneous nerves, the RFFF can provide excellent erogenous and protective sensation, with patients often reporting the ability to orgasm [12–14].

Despite offering excellent esthetics and sensation, the RFFF has significant limitations. Because the RFFF, like most flaps used for phalloplasty, requires insertion of an implantable prosthesis to achieve erection, it is prone to high rates of implant-associated complications. In the largest series of RFFF for phalloplasty, Monstrey *et al.* [11] noted a 44% prosthesis explantation rate due to malpositioning, technical failure, or infection. Other series have also noted similar rates of prosthesis-associated complications [14–16], leading some to abandon use of prostheses altogether [17]. In addition to implant-associated complications, all of the described techniques for autogenous phalloplastic reconstruction suffer from unacceptably high rates of urethral complication. Many different approaches for neo-urethroplasty have been developed, none of which have satisfactorily addressed this problem. The most widely used approach is the "tube-within-a-tube" technique, with an outside-in tube of vascularized dermis within the flap serving as the neo-urethra [18]. Other techniques for neo-urethral construction make use of skin [19,20] or mucosal grafts [21], as well as pedicled mucosal [22,23] or skin [24,25] flaps. Unfortunately, all of the described techniques are plagued by high rates of urinary complications, with strictures and fistulae commonly occurring at the anastomosis of native and neo-urethra. The largest series to date of RFFF reported a 42% rate of urinary complications, including a 32% rate of neo-urethral stricture, and a 21% rate of urinary fistula formation [11]. These complication rates are favorable in comparison with others reported in the literature [12,17,26–30].

Penile transplantation as an emerging solution

Given the increased incidence of severe GU trauma among service members and the limitations of the currently available options for phalloplastic reconstruction, a better solution is sorely needed. Vascularized composite allotransplantation (VCA) of the face and upper extremity is being performed around the world and is gaining acceptance as an alternative to autogenous reconstruction and prostheses [31,32]. In select cases, the potential for markedly improved esthetic and functional outcomes can justify the additional risks associated with lifelong immunosuppression and rejection. Although more controversial, penile transplantation may provide improved outcomes following severe GU trauma, particularly for patients who are lacking flap donor sites or have already failed traditional reconstruction.

Penile transplantation has been performed three times to date with mixed results (Table 1). The first attempt was performed in Guangzhou, China, in 2006 for a 44-year-old man who suffered traumatic amputation of the penis [33,34]. The procedure involved anastomosing the dorsal arteries and superficial and deep dorsal veins, with 15.5 h of cold ischemia time.

Transplant International 2017; 30: 441–450

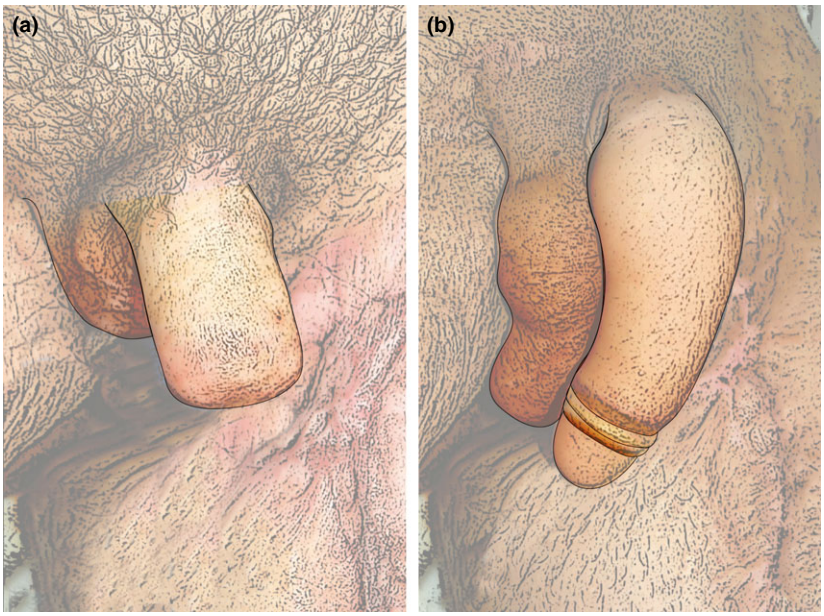


Figure 1 (a) Penile defects resulting from blast injury. (b) Reconstruction of defect with radial forearm free flap.

Postoperatively, the patient was treated with dextran for anticoagulation and mycophenolate mofetil, cyclosporine and prednisone for immunosuppression. The procedure was deemed a technical success by the surgical team, but the transplanted organ was removed at the request of the patient on postoperative day 14 due to apparent "psychological rejection." This case was met with criticism, focused in part on patient selection [35]. The surgical team later noted that the appearance of the shaft skin prior to explantation was consistent with insufficient vascular perfusion with epidermolysis and necrosis, possibly due to failure to reconstitute blood supply from the external pudendal vessels [36]. This acknowledgement came in light of a later published deceased donor study demonstrating the importance of utilizing the external pudendal vessels to perfuse the shaft skin in the setting of penile transplantation [37]. The first successful penile transplant was performed in South Africa 8 years later, in December 2014 [38]. The recipient was a 21-year-old male who suffered partial loss of his penis as a complication of ritual circumcision. The surgery lasted 9 h and involved anastomosing the dorsal arteries and veins. The postoperative course was complicated by an arterial thrombosis, requiring revision of the anastomosis 4 days after surgery. The patient was taken back to the operating room a second time to drain a hematoma and repair a urethral fistula [38]. The patient ultimately did well, achieved erectile function soon after transplantation, and is reported to have impregnated his girlfriend [38]. More recently, in May 2016, a third penile transplant was performed in Boston, Massachusetts, for a 64-year-old male who, 4 years prior, underwent penectomy to treat penile squamous cell carcinoma. The procedure lasted for 15 h and involved anastomosing the dorsal and cavernosal arteries. He was released from the hospital 3.5 weeks after the surgery in good condition, with adequate perfusion to the transplanted organ and no signs of rejection [39].

Enhancing the utility of penile transplantation: maximizing benefits and minimizing risks

Unlike solid organ transplantation, VCA is not meant to be *life-saving*, but rather *life-enhancing*. Therefore, the viability of penile transplantation as a reconstructive option will rely heavily upon its ability to provide meaningfully improved outcomes in comparison with current reconstructive options while also minimizing the risks associated with lifelong immunosuppression and potential rejection.

The potential benefits that may be offered by penile transplantation in comparison with current reconstructive options include a more normal appearing phallus, improved erectile function without the need for a prosthesis, greater durability, improved urethral patency with fewer complications related to fisutulae and strictures, and improved erogenous sensation. We will next discuss the theoretical advantages offered by penile transplantation pertaining to each of these important

Table 1. Summary of penile transplantation cases performed to date.

Location	Patient age	Cause of penile loss	Surgical time (h)	Vascularization approach	Immunosuppression	Complications	Outcomes
Guangzhou, China	44	Traumatic amputation	15.5	Dorsal artery, deep dorsal vein, superficial dorsal vein	Mycophenolate mofetil, prednisone, cyclosporine	Partial necrosis	Removal of transplanted penis due to psychological rejection on postoperative day 14
Cape Town, South Africa	21	Circumcision complicated by partial amputation	9	Dorsal arteries, deep dorsal veins, superficial dorsal veins	Mycophenolate mofetil, prednisone, tacrolimus	Arterial thrombosis, hematoma, partial skin necrosis	Restoration of urinary and sexual function
Boston, USA	64	Penectomy to treat squamous cell carcinoma	15	Dorsal arteries, cavernosal arteries, deep dorsal veins, superficial dorsal veins	Mycophenolate mofetil, prednisone, tacrolimus	Unknown	Viable organ without signs of rejection, psychological acceptance

reconstructive goals, as well as the technical considerations that must be addressed to realize those advantages. We will then describe the current status of immunosuppression used in VCA and the efforts being made to minimize the associated risks.

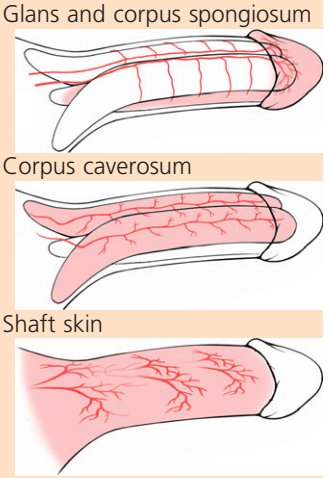
Vascularization approach

One of the most important technical considerations pertaining to penile transplantation is how best to vascularize a penile allograft. Our recent cadaveric studies have indicated the importance of utilizing multiple vascular pedicles to provide optimal graft perfusion [37] (Table 2). The dorsal arteries (DAs) provide the sole blood supply to the glans and should be perfused to prevent distal graft necrosis. The DAs also provide ample perfusion to the corpus spongiosum and urethra and will therefore likely be important in ensuring urethral perfusion and patency, especially because the small size and high variability of the urethral arteries preclude their use in transplantation. Because the cavernosal arteries (CAs) provide the principal blood supply to the corpora, we anticipate that perfusing the CAs will increase the likelihood of achieving optimal erectile function. It should be noted that for proximal transplantation, the CAs can be perfused by anastomosing the DAs proximal to the origin of the CAs, in which case direct CA anastomosis may not be necessary.

Importantly, the skin of the penile shaft, as well as the surrounding suprapubic, groin, and scrotal skin, is exclusively perfused by the external pudendal vessels arising from the superficial femoral artery and greater saphenous vein [37]. A recently published study describing a dog model for penile transplantation did not use the external pudendal vessels and demonstrated a high rate of skin necrosis [36]. The surgeons who performed the first penile transplant utilized the dorsal arterial system alone to perfuse the graft. Although they reported adequate perfusion, the published picture of the graft at postoperative day 14 demonstrates

Table 2. Principal perfusion territories supplied by vascular pedicles of penile allograft.

Artery	Principle perfusion territory
Dorsal	Glans and corpus spongiosum
Cavernosal	Corpus caverosum
External pudendal	Shaft skin



Transplant International 2017; 30: 441–450

significant discoloration and desquamation of the shaft skin [33,34]. The surgical team later noted the likelihood of inadequate shaft skin perfusion and the possibility that this was due to failure to reconstitute the external pudendal blood supply [36]. During penile replantation, the external pudendal blood supply cannot be reconstituted, likely explaining the very high incidence of shaft skin necrosis that has been noted following replantation [40]. These findings suggest that the external pudendal vessels should be used in the setting of proximal penile transplantation to prevent shaft skin necrosis. Using the external pudendal will also allow for surrounding groin, suprapubic, and scrotal skin to be included with the graft for resurfacing of surrounding defects, when present [37] (Fig. 2).

Erogenous sensation

An important functional goal of penile reconstruction is restoration of erogenous sensation. As with all types of VCA, sensory function following penile transplantation requires adequate peripheral nerve regeneration into the graft. In comparison with other types of VCA, the distance that axons must regenerate to reach their targets is relatively short, which should facilitate rapid and robust reinnervation of the shaft and glans skin. While reported outcomes pertaining to sensory function following autogenous reconstruction have been positive [15,19], there is reason to believe that penile transplantation may provide enhanced sensitivity and orgasm potential. Penile skin contains a distinct composition of sensory receptors not seen elsewhere in the body [41], including a specialized encapsulated receptor only found in the glans and nipples that is believed to play a critical role in triggering erogenous sensation [42], suggesting that a penile allograft would likely confer greater erogenous sensation than the various flaps used for phalloplasty.

Erectile function

Beyond sensory reinnervation to provide erogenous sensation, restoration of sexual function following penile transplantation will also depend on the ability to achieve erection. Traditional reconstructive options typically rely on an inflatable or malleable prosthesis to allow for erection and penetration with the neophallus. However, flap reconstruction with implanted prosthesis is prone to an unacceptably high rate of prosthesis infection and extrusion [11]. Although some reconstructive techniques, including the fibula osteocutaneous free flap, avoid use of an implant by incorporating a bony component, this option is far from ideal as the flap remains permanently erect and the osseous component of the flap is susceptible to warping and resorption. In contrast, a penile transplant includes all of the natural apparatus required for erection, including the corpora cavernosa, thereby allowing for erection without the use of an implant. Patients undergoing penile replantation following traumatic amputation tend to report satisfactory return of erection [43], as did the first patient to undergo successful penile transplantation [38]. However, the mechanisms by which this occurs are unclear. Erectile function is dependent on autonomic innervation provided by the cavernous nerves that carry autonomic fibers. Because they are very small in caliber and diffusely organized throughout the penis, direct epineurial coaptation of the cavernous nerves in the setting of transplantation is likely not feasible. It is possible, however, that autonomic fibers associated with the recipient's dorsal and cavernosal vessels can regenerate across the vascular anastomoses to reinnervate the allograft. It's also possible that the severed autonomic fibers in the tunica of the recipient's penile stump will directly neurotize the transplanted corpora following approximation. Another possible explanation for return of erectile function following penile replantation and transplantation involves diffusion of vasoactive substances from the recipient stump to the transplanted corpora, without requiring direct autonomic innervation. As the field of penile transplantation progresses, it will be important to delineate the mechanisms by which return of erectile function occurs so as to develop interventions to optimize outcomes.

It is unknown how the various immunosuppressive medications may affect erectile function following penile transplantation. However, there is some evidence to suggest that some immunosuppressants may be favorable to others in this regard. Two retrospective analyses of factors influencing erectile function following renal transplantation found a correlation between cyclosporine A treatment and erectile dysfunction [44,45]. These findings, if real, could be due to inhibition of nitric oxide-mediated smooth muscle relaxation [46] or vascular endothelial cell dysfunction [47]. Our preliminary data using an *ex vivo* model of transplantation with human corporal tissue and peripheral blood mononuclear cells demonstrate that cyclosporine A impairs smooth muscle relaxation. In contrast, tacrolimus did not impair smooth muscle relaxation. Beyond having less deleterious effects on erectile function, there is reason to believe that tacrolimus may improve recovery of

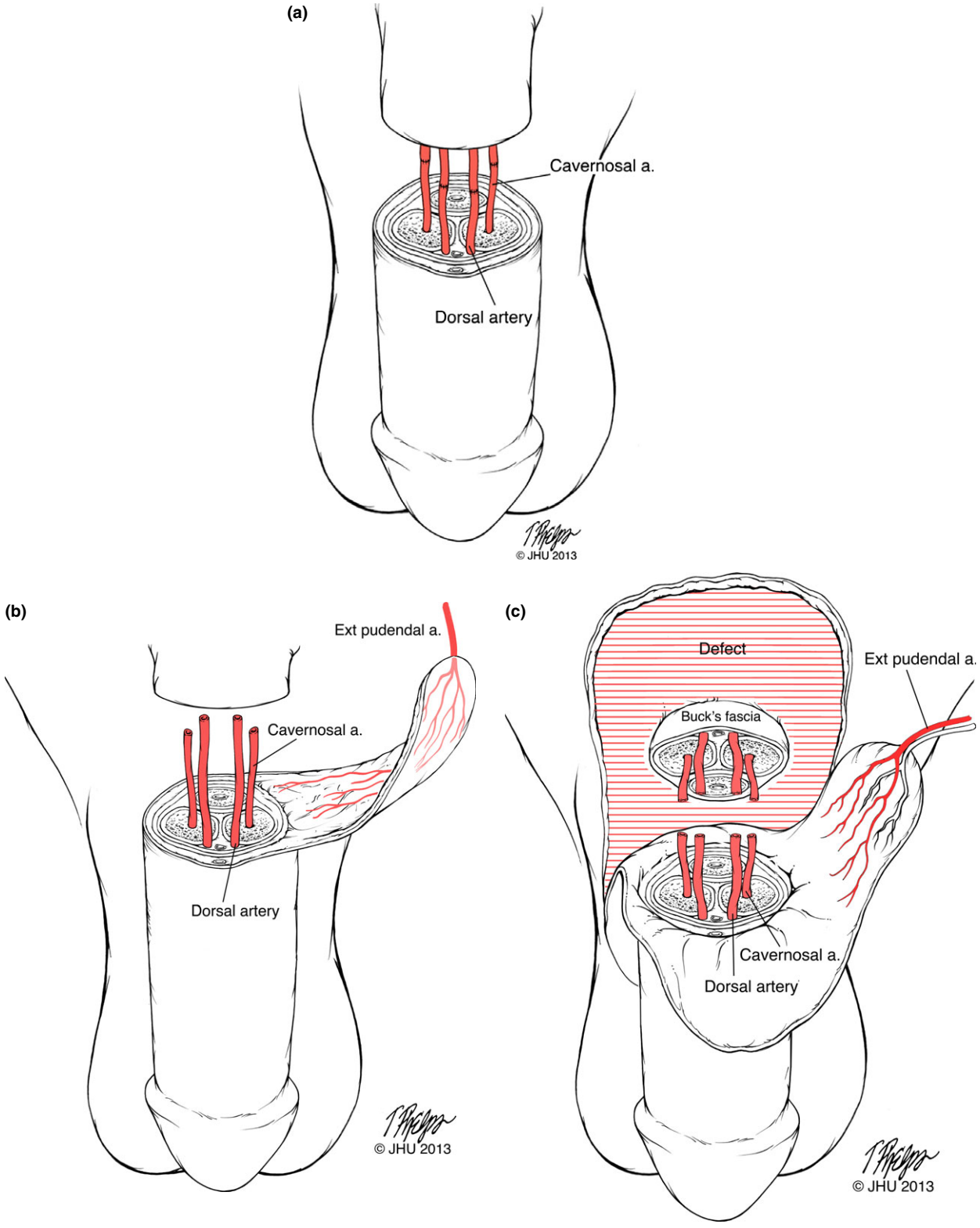


Figure 2 Recommended strategy for vascularizing penile allografts for reconstructive transplantation. (a) Mid or distal shaft transplant: dorsal and cavernosal arteries, only. (b) Proximal shaft: dorsal, cavernosal, and external pudendal arteries with skin bridge. (c) Proximal shaft with surrounding defect: dorsal, cavernosal, and external pudendal arteries with additional skin to resurface defect. (Republished from Tuffaha *et al.* [37]).

erectile function after penile transplantation by enhancing autonomic nerve regeneration into the graft. Tacrolimus has been shown in numerous studies to accelerate and augment axonal regeneration [48,49]. Work from our group and others has demonstrated the neuroprotective and neurotrophic effects of tacrolimus and other related immunophilin ligands in rodent cavernosal nerve injury models, with tacrolimus treatment resulting in greater axonal regeneration, neuroprotection, and enhanced erectile function [50–52]. Thus, in the setting of penile transplantation, tacrolimus may serve dual roles of preventing rejection while also enhancing nerve regeneration and erectile function. It should also be noted that phosphodiesterase type 5 inhibitor therapy for treatment of erectile function, should it be needed following penile transplantation, is efficacious following solid organ transplantation and does not detrimentally interact with tacrolimus or cyclosporine A.

Urethra

Another important goal of penile reconstruction is restoration of urinary function. To this end, there is reason to believe that penile transplantation will provide better outcomes than traditional reconstructive options. As described above, autogenous penile reconstruction is plagued by an unacceptably high rate of urinary complications, including urinary fistulae and strictures [11]. These complications tend occur at the junction of the native urethra and the neo-urethra, which is typically constructed with skin or buccal mucosa. In contrast, urethral repair in the setting of penile transplantation involves anastomosing the recipient's native urethra to a "true" urethra within the transplanted penis, which will likely provide greater long-term patency. Following traumatic penile amputation and subsequent replantation, the rate of urinary strictures and fistulae is relatively low as compared to autogenous phalloplastic reconstruction [43]. We anticipate that urethral outcomes will be better with transplantation than with replantation, given the more controlled environment in which it will occur [53,54]. It is important to note the possibility of urothelial rejection resulting in urethral stricture. As such, close monitoring and early treatment of acute rejection will be important.

Immunosuppression

Beyond maximizing the benefits afforded by penile transplantation, it is of utmost importance that every effort be made to also minimize the associated risks. Although clinical results with VCA have been encouraging, use of lifelong, high-dose, multidrug immunosuppression is associated with a profound side effect profile and hampers broader application of this relatively young, evolving field. Currently, VCA has no standard immunosuppressive regimen, but most patients have been treated with a "conventional" triple-drug immunosuppressive strategy extrapolated from solid organ transplantation [55]. However, novel protocols are being investigated with the aim of reducing the amount of immunosuppression needed for allograft maintenance. The ideal protocol would induce donor-specific tolerance and completely eliminate the need for long-term maintenance immunosuppression after VCA, and progress is being made to this end [56]. However, until tolerance protocols are successfully implemented in the clinical arena, other approaches are needed to reduce the burden of conventional triple-drug therapy. With this goal in mind, our group has implemented a novel immunomodulatory protocol that has demonstrated efficacy in reducing the amount of immunosuppression needed for allograft maintenance [57]. In brief, patients undergoing upper extremity transplantation receive short-course depletional induction with alemtuzumab and methylprednisolone prior to transplantation, followed by intravenous donor bone marrow cell infusion 14 days after transplantation. All patients received low-dose maintenance monotherapy with tacrolimus, weaned to 4–12 ng/ml/day. Thus far, we have had favorable functional and immunologic outcomes using this protocol [57], and believe it is readily translatable to penile transplantation. However, it should be noted that one of the proposed mechanisms by which donor-derived bone marrow transfusion may attenuate the allo-immune response in upper extremity transplantation involves bone marrow engraftment within the bony niche of the transplanted limb, thereby inducing a state of micro-chimerism. Because penile transplants do not contain bone, this process will not occur and may impact the efficacy of this approach. As such, it will be important to closely monitor outcomes and adjust the immunosuppression regimen, if necessary.

While the process of rejection in VCA has been extensively studied in many different models, there are a number of specialized tissue types specific to the penis that may have implications in this regard. The skin component in VCA is widely considered to be the most immunogenic component of the graft [58]. For this reason, monitoring protocols typically rely upon observing the skin for clinical signs of rejection and performing biopsies for histologic evaluations when needed. While

it is possible that the skin is also the most immunogenic component of a penile allograft, this may not necessarily be the case. Our preliminary preclinical data using both heterotopic penile transplantation in rats and *ex vivo* tissue mixed lymphocyte reactions suggest that the various penile tissues, including the urothelium, cavernous sinuses (in particular the vascular endothelium and smooth muscle), and neurovascular structures, all undergo different rates of rejection. Interestingly, the cavernosal endothelium and urethral mucosa undergo apoptosis early in the rejection process [59]. The unique tissue types and functions associated penile transplantation may allow for novel monitoring strategies not amenable to other types of VCA. For example, it may be possible to employ urinalysis techniques to detect early rejection of the urothelium. Additionally, because erectile function is dependent on vascular health [60], erectile dysfunction in the setting of penile transplantation may serve a harbinger of chronic allograft rejection. As the field of penile transplantation continues to progress, rigorous scientific studies using preclinical animal models and human tissues are needed to further our understanding of the molecular mechanisms of rejection specific to penile tissue, establish appropriate monitoring protocols, and develop immunosuppressive regimens that prevent rejection without hindering functional recovery.

Logistical, procedural, and ethical considerations

Given that penile transplantation is in its infancy, implementing a successful penile transplantation program will require development of de novo protocols that take into account a number of important logistical, procedural, and ethical consideration. We will next discuss the rationale for the salient components of the protocol we have developed at Johns Hopkins.

Inclusion criteria

At present time, we are only considering patients with severe traumatic penile defects who either do not have adequate donor sites to attempt traditional reconstruction or have already tried and failed traditional reconstruction. This will ensure that the patients we enroll are in significant need of penile restoration and lacking alternative options. However, as we learn more about the outcomes that can be expected with penile transplantation, the indications may potentially be expanded to include other causes of penile defects.

Given the considerable limitations of the currently available options, patients requiring penile reconstruction who suffer from conditions other than GU trauma may benefit from penile transplantation in the future. We have initially chosen to exclude patients with congenital penile defects or gender dysphoria because they typically have adequate donor sites for conventional reconstruction, making it more difficult to justify the potential risks associated with the procedure and lifelong immunosuppression. However, these patient populations may be deemed to be candidates in the future as the outcomes with penile transplantation become better delineated, particularly if protocols can be developed to minimize the risks associated with immunosuppression and rejection. Patients with defects resulting from treatment of penile cancer are not appropriate candidates for penile transplantation at this time, given the risks of disease progression that would be posed by immunosuppression. However, this may change in the future if tolerance protocols are developed that obviate the need for immunosuppression.

Patient selection and screening

Patients who meet the inclusion and exclusion criteria are given the option to proceed with an extensive screening process to determine whether they are suitable candidates for penile transplantation. Intensive psychosocial evaluation is perhaps the most critical part of the screening process. The psychosocial impact of traumatic penile loss is profound, affecting many aspects of a patient's life. Beyond the obvious impact on urinary and sexual functioning, a significant penile defect can damage a man's sense of identity and self-esteem, with severe and persistent detrimental effects on global well-being and interpersonal relationships. The process of undergoing penile transplantation may exacerbate baseline dysfunction and distress by introducing additional significant psychosocial stressors. As such, it is imperative that all patients receive long-term psychiatric support beginning at the time of enrollment and continuing after transplantation. This will also likely facilitate compliance with long-term immunosuppression.

Donor matching

There are a number of considerations specific to VCA that will limit the donor pool for a given patient. Beyond HLA matching and screening for pathogens, it is also important to ensure that the physical appearance

Transplant International 2017; 30: 441–450

of the donor organ is appropriate and acceptable to the recipient. Prior to being listed for transplantation, an in-depth discussion with the patient will occur to delineate his wishes in this regard.

Multidisciplinary team

Given the complexity of penile transplantation, successful implementation will require a multidisciplinary approach. The ideal surgical team will be comprised of multiple Urologists and Plastic Surgeons working together at all stages of the procedure. Input from Transplant Surgery and Medicine will also be important in managing immunosuppression and potential postoperative complications. Psychiatrists will play an important role in candidate selection and well as postoperative monitoring and psychosocial support. Ethicists should also be involved in developing protocols that are consistent with the pertinent ethical principles and compliant with institutional review board requirements, as well as in addressing unanticipated scenarios that arise during implementation in which their input would be of value.

Conclusions

Penile transplantation is an emerging option for reconstructing severe penile defects not amenable to traditional reconstructive option. The potential advantages of penile transplantation over autogenous reconstruction include a more normal appearing phallus, improved erectile function without the need for a prosthesis, improved erogenous sensation, greater durability, and improved urethral patency with fewer complications related to fisutulae and strictures. To maximize the utility and viability of penile transplantation as a reconstructive option, careful attention must be given to the many technical, logistical, and ethical considerations pertaining to penile transplantation. At Johns Hopkins, we will initially offer penile transplantation to patients with traumatic defects who have either failed traditional reconstructions or are not candidates for these procedures due to a lack of donor sites. However, these indications may expand as the outcomes associated with penile transplantation become better delineated, particularly if immunomodulatory protocols that reduce the need for immunosuppression can be successfully employed.

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Conflict of interest

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