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Review Article

# Lessons learned from the world's first successful penis allotransplantation

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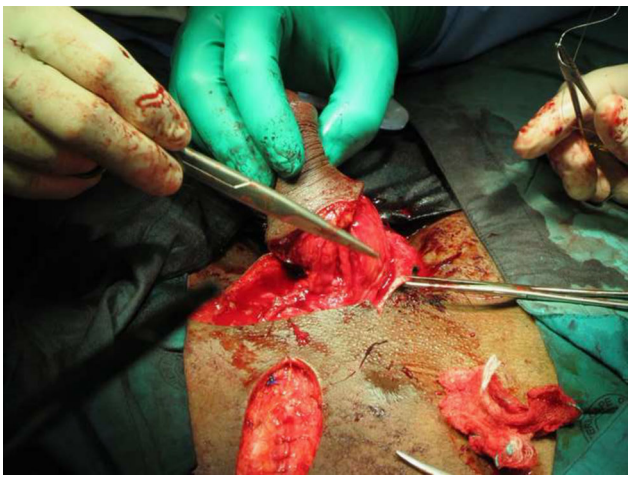
**Abstract** We performed a successful penis allotransplantation on 11 December 2014. Sharing the lessons learned might help more patients in need to be treated this way. We divided the project into manageable segments that was each overseen by an expert. The ethical review and conduct paved the way for a publically acceptable and successful project. Screening for a psychological stable recipient is important. The most difficult part of the project was finding a donor penis. This was successfully negotiated with the family of a brain dead donor by creating a neophallus for the donor, thereby maintaining the dignity of the donor. Working with transplant coordinators that are sympathetic to aphallic men is crucial. Surgeons versed in microvascular techniques is a critical part of the team. Transplant immunologists have to adapt to treat composite tissue transplantation patients.

**Graphical Abstract**



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## 1 Introduction

Vascularized composite tissue allotransplantation (VCA) is an established frontier in reconstructive surgery [1]. Our team performed a successful penis transplantation on 11 December 2014, after a period of planning and research. A similar procedure had previously been attempted at an institution in China, but failed due to the patient's partner insisting removal of the graft that had superficial skin necrosis early post-operatively [2].

This was a challenging project to complete successfully. We share the lessons that were learned so as to hopefully enable other centres to follow suit and ultimately contribute to helping a distressed and vulnerable patient population in need of penis transplantation.

### 1.1 Lesson 1. Correct indication

The only appropriate indications for penis transplantation are loss of the entire pendulous penis or absence of a penis in a patient that should have one, as is in major congenital malformations. Offering this procedure to males who perceive their genitalia as too small would be inappropriate; the risks associated with the procedure itself and also a lifetime of immune suppression treatment may lead to serious complications and eventually even leave the recipient aphallic. Furthermore, with the dire donor penis shortage organs should be used to assist those patients in real need. (Figs. 1 and 2)

### 1.2 Lesson 2. Divide the project up into segments and have an expert oversee each segment

From the start, we divided the project into separate segments, commencing right at the stage of Ethics Review Board submission. Expert consultants from the following disciplines were co-opted in order to maximise the chance of success:

- Forensic pathologist—To advise on the legal issues surrounding the transplantation of a penis from a deceased donor.
- Ethicist—with a mandate to make sure all proceedings adhere to good ethical practice.
- Transplant coordinator
- Psychologist—For ongoing input in both the pre- and post-operative periods
- Transplantation nephrologists—To Manage the immunosuppressive regimens. Our renal team adapted well to the novelty of caring for the participant.
- Plastic surgeons versed in microvascular surgery.
- Media liaison officer—Provided by our academic institution (University of Stellenbosch)
- Pathologist and dermatologist—Tasked with acquainting themselves with the unique aspects of VCA rejection.
- Team of nurses trained in the care of immunosuppressed transplant patients

### 1.3 Lesson 3. Ethical issues are a minefield

We benefitted much by having a dedicated applied ethicist on the team. Careful consideration during the planning

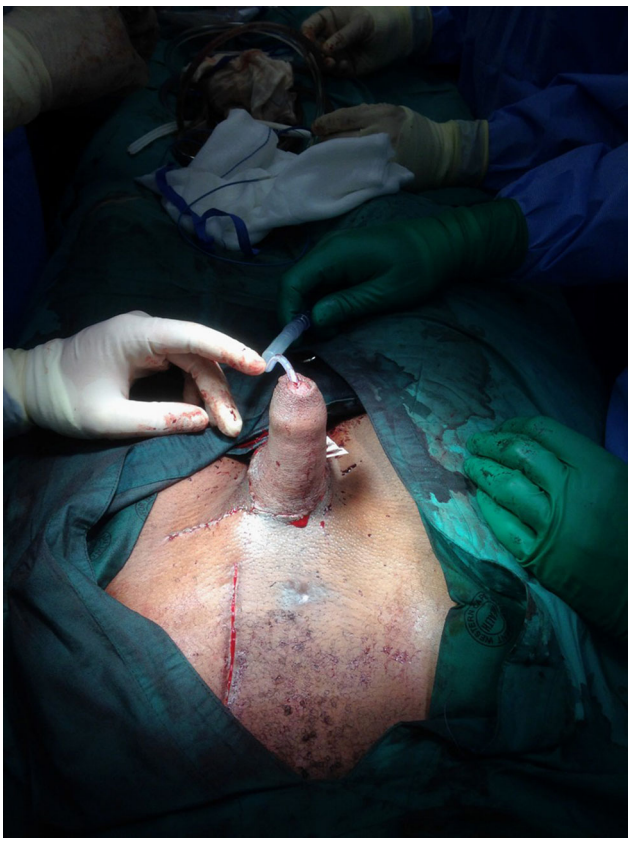

**Fig. 1** Penile allograft at the end of surgery. Note the urinary catheter that should have been placed suprapubically

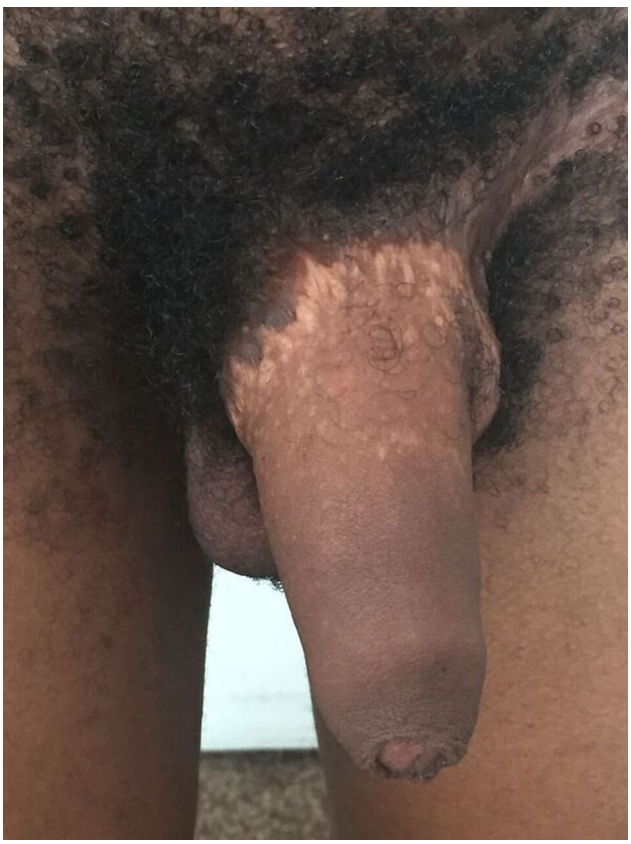

**Fig. 2** The penile allograft at 20 months post-operatively

phase of our study allowed us to anticipate potential pitfalls, two of which are worth mentioning here:

1) *Minimise therapeutic misconception:* Therapeutic misconception indicates a participant's failure to appreciate the difference between research and treatment. This can include an overestimation of clinical benefit from an experimental intervention, as well as underestimation of potential risk of harm [3, 4]. We implemented a rigorous informed consent process. Our participant was counselled over a 2-year period, prior to transplantation, and this allowed us the opportunity to promote and assess our participants' understanding of the risks involved and to promote truly informed and voluntary consent to the experimental procedure.
2) *Appropriately mitigate risk:* Our ethicist's inputs heightened awareness of, and spelled out risk mitigation steps for the emotional, social and psychological risks that our research participants might experience, in addition to the physical risks (including the myriad of potential side effects of long term immunosuppression). Based on these inputs our first transplant participant was selected to minimize risk. A number of participants were eligible for scientific reasons, but at substantially higher risk of physical and psychological harm. This particular patient was considered physically and psychologically suitable for VCA and was selected as the first research participant based on his favourable lower-risk profile.

### 1.4 Lesson 4. Psychological issues must be addressed in the recipient

The screening process used for our possible penis transplant recipients was similar to that used in our renal transplant program. However, we were very cognisant of the potential additional risk associated with receiving someone else's penis as far as conflicting the ego and disturbing of the self-image are concerned. A subsequent "ripple-effect" on the ego has previously been described and is associated with the very real risk of inducing psychosis. Although this may also occur as a consequence of renal (or any other organ) transplantation, the risk is higher in the case of a urogenital organ such as the penis [5–7]. In addition, the high-dose of steroids that was given as induction of immunosuppression, is known to be a separate risk factor for the development of acute psychosis [8].

### 1.5 Lesson 5. Practice on a cadaver

Despite the fact that we had been fully trained as urologists and are clinically active as part of a tertiary care urology service, we benefitted significantly from a focused dissection on a cadaver model. Harvesting of the dorsal neurovascular bundle below the symphysis pubis demonstrated the difference in vessel diameter between the proximal and the distal parts of the penis. We also realized that harvesting the penis so proximally allowed for approximately 3 cm of corpora cavernosa, as well as approximately 2 cm of urethra and corpus spongiosum to be removed, leaving an elongated vascular pedicle that would offer very valuable mobility during anastomoses.

### 1.6 Lesson 6. Reconstruct a phallus for the brain dead donor

The crucial turning point in our project we think was when we to offered the families of the potential penis donor the option of having a phallus created from the lower abdominal skin, following removal of their deceased relative's penis. It was clear that this gesture brought a definite change to the relatives' perception of penis donation: where families would previously reflexively refuse donation of their deceased relative's penis, they were now actually thinking before saying "no" with one family eventually agreeing. Our interpretation of this phenomena is that it is seen as restoring the dignity of the brain-dead donor in the eyes of the family. It appears that no family would agree to their relative entering the grave without his penis, or at least the semblance of a penis.

### 1.7 Lesson 7. Cool the harvested penis by direct intracorporeal injection of a standard transplant solution

The dissection of the dorsal neurovasculature and transection of the corpora induced spasm of the dorsal and cavernosal arteries, which resulted in our being unable to cannulate the vessels for the purpose of infusing the cooled organ preservation solution (Custodial$^{TM}$). We therefore proceeded to inject the Custodial$^{TM}$ solution directly into the copora cavernosa from the left side of the penis. Clear fluid could be seen flowing from the severed ends of the spongiosum, cavernosal bodies and dorsal veins of the penis. If clear fluid fails to extrude from the spongiosum then an additional injection of cooled Custodial$^{TM}$ could be performed directly into the glans penis—this should irrigate the entire corpus spongiosum and may even overcome possible vascular drainage differences in the donor penis [9, 10].

### 1.8 Lesson 8. Surgical principles that help

Consider using the deep inferior epigastric blood vessels to supply blood to the graft penis early on in the surgery, ignoring the native dorsal penile vessels. We wasted several

hours trying to dissect out the recipient's dorsal neurovascular complex, only to ultimately find the structures to have been obliterated as a complication of the previous infective process that was the original cause of penile loss. Utilising the deep inferior epigastric vessels supplied suitable diameter blood vessels with good flow and with a lot less effort.

The donor penis must be harvested underneath the pubic symphysis taking care to preserve the dorsal neurovasculature at its largest diameter. The donor penis, after having been cooled to 4 degrees Celsius, can then be prepared for transplantation on the bench by dissecting the dorsal neurovascular bundle free for a distance of about four centimetres. The proximal corpora and urethra are then trimmed but a slightly extended urethra is left to enable wide spatulation and tension-free anastomosis with the native urethra. We used interrupted sutures for the urethral anastomosis but in future will use a bi-layer of continuous mucosal sutures as well as a continuous suture to the outer corpus spongiosum as this will facilitate drainage via the corpus spongiosum itself.

It is absolutely imperative to have surgeons on the team who are experienced in performing microvascular anastomoses.

As was evident in our case, it is not essential to perform anastomosis of the cavernosal arteries, provided that good perfusion of the corpora cavernosa is attained by dorsal penile arterial supply. Intra-operatively we visualized copious amounts of bright red blood flowing freely from the severed spongiosal- and cavernosal ends after completion of the dorsal penile arterial anastomoses. This indicated adequate cavernosal blood flow despite having no anastomoses of the cavernosal arteries. The recipient's normal erectile function which started around 3 weeks post-operatively, further attests to this.

#### *1.8.1 Use state-of-the art equipment*

The dissection of the donor and recipient vessels and nerves require specialized microsurgical equipment that allow handling of structures with 1 mm diameter. This includes instruments, clamps, cannulas (to flush the lumen of the vessels), sutures and optical equipment (loupes, microscope). To improve speed and patency of the venous anastomosis we recommend the use of a GEM Microvascular Anastomotic COUPLER™ ring (Synovis Micro Companies Alliance Inc., Birmingham, Alabama). Besides clinical monitoring we propose the use of a Licox® monitor (Integra LifeSciences, Plainsboro, NJ), which measures the graft oxygen partial pressure and allows early detection of a vascular thrombus. Thrombectomy and reanastomosis can then be performed immediately to salvage the transplant as occurred in our participant.

#### *1.8.2 Be prepared for anatomical variants*

A superficial dorsal vein was not present in the donor penis and the recipient dorsal penis vessels were not patent. Plan alternative blood supply options before the operation and be flexible during the procedure to optimise arterial supply and venous outflow.

### 1.9 Lesson 9. Avoid using a trans-urethral catheter post-operatively—rather use a suprapubic catheter for bladder drainage

We encountered a problematic post-operative wound haematoma and infection, which was likely complicated by the presence of a urinary catheter in the urethra.

### 1.10 Lesson 10. Immunosuppression by the most experienced tranplant immunologists available

Composite tissue transplantation is still in its infancy compared to solid organ transplantation and much remains to be learned about the optimum use of immunosuppression in this form of transplantation [11–13]. Our immunosuppression regimen was premised on the skin being the most immunogenic component of the composite, although there is evidence that the risk of acute rejection of the skin is mitigated when it forms part of composite tissue transplant [14]. Nevertheless, we opted to maximise prophylactic immunosuppression, with induction therapy consisting of antithymocyte globulin and high dose steroids followed by maintenance with tacrolimus, mycophenolate mofetil and prednisone. These are some of the agents currently in use in composite tissue transplants [12]. The choice of polyclonal over monoclonal antibodies was purely an economic one, dictated by our unaffordability of the latter. The adequacy of our immunosuppression is attested to by the lack of any acute rejection. The graft was regularly monitored visually for any signs of rejection, especially initially. A future consideration is the implantation of a distal sentinel skin flap that can be biopsied without too much discomfort to the patient and that could be an early alert to acute rejection [15].

Having established that we had evidently avoided acute rejection, the question of whether we had over-immunosuppressed our recipient arose, when the patient developed an unusual fungal infection of his foot. This was a rare phaeohyphomycosis infection by the ubiquitous saprophyte Alternaria alternata and occurred 8 months after the transplant. The infection responded well, albeit slowly, to treatment. Controversy still prevails regarding the most appropriate treatment for this opportunistic infection, although a combination of topical treatment, surgery and systemic antifungal treatment may be required; in a recent

review systemic itraconazole was the most commonly used antifungal agent [16]. The disease is generally localised and seldom systemic. To date only a single possible mortality related to this infection has been reported [16, 17]. In view of this and the risks of using the various 'conazoles' (especially drug-drug interactions) and amphotericin B (especially its nephrotoxicity) we opted to treat the patient with surgery and a broad spectrum topical antifungal agent. The risks alternariosis are higher in solid organ transplants other than kidney transplants that are immunosuppressed more intensely [17]. To reduce the risk of infections, we would consider deescalating immunosuppression earlier in future rather than the delayed protocol we had followed in this patient.

Another important consequence of our immunosuppression was the transient decline in renal function blood levels. Tacrolimus dose was adjusted to maintain serum trough levels 10–15 ng/ml. After 10 months a marked elevation of the serum creatinine was noted and in the absence of any risk factors for declining renal function, the dose of tacrolimus was reduced and levels were maintained at 5–10 ng/ml. With this adjustment in tacrolimus dose, the renal function improved, but the long-term impact on kidney function of the tacrolimus is of concern in this young man [18, 19] as end stage kidney failure can occur in up to 28% of recipient of non-renal transplants [20]. The options we have are to reduce the risk of kidney injury is minimising calcineurin inhibitors—in our kidney transplant patients we reduce the dose of calcineurin inhibitors at 3 months, although this approach is refuted by the finding by Nankivell et al. [18] that the correlation calcineurin inhibitors dose and the renal pathological injury is poor. The alternative is to switch to calcineurin inhibitors sparing regimen that includes and mammalian target of rapamicin inhibitors, but these are associated with an increased of acute rejection [21].

### 1.11 Lesson 11. Obtain buy-in from hospital management

In the prevailing economic environment in South Africa it was very challenging to obtain adequate funding for all aspects of this project, and the majority of the cost would have to be regarded as forming part of a clinical incident. This represents a significant additional financial burden on our already constrained hospital budget, which could have caused hospital management to refuse to allow for this (essentially experimental procedure) to be performed in their hospital. We had frank and open discussion with the hospital management in 2011 that eventually led to their agreement to bear the cost of this project, when other sources of funding could not be obtained.

### 1.12 Lesson 12. Work with transplant coordinators who are sympathetic to aphallic men

We found that not all transplant coordinators were sympathetic towards the project or the potential recipients—for unknown and possibly deeply-rooted personal reasons. We speculate that this may be due to the coordinators' perception of the need for normal sexuality or the fear that asking for a donor penis may jeopardise the interview with a deceased's family when asking for the donation of other solid organs. Working with coordinators who do not approve of the project and have not fully bought into it, is sure to make finding penile donors extremely difficult. Fortunately, our team had a transplant coordinator who proved to be passionate about helping the recipients and she was the only person who engaged all of the potential donors' families to discuss possible donation.

### 1.13 Lesson 13. Handling the media

We were surprised and overwhelmed by the media attention that this operation created because we considered the hype to be out of proportion to the complexity of the surgery or the project. It does, however, underscore the public interest in transplantation—in particular when genitalia are involved. From attempts at facial transplantation in the United Kingdom we learned that the media could easily cause a public outcry in response to such a dramatic procedure, which may bring the project to a halt [22–24]. We avoided publicising details of the operation to assure ourselves of the success of the procedure and to deal calmly with the clinical issues The 3-month delay meant we could announce the success of the procedure with a fair amount of certainty. Having one media spokesperson for the team (team leader) and a media liaison officer are essential. All interviews should be monitored so that conflicting reports do not cause public confusion. It is important that the media officer screen all requests for interviews in order to avoid media houses taking a light-hearted or sexually perverse angle on the procedure.

## 2 Conclusion

Off all the factors listed above the most challenging for us was finding a donor penis. Potential donor families should be engaged respectfully by a motivated transplant coordinator. Protecting the dignity of the brain-dead donor by offering a skin phallus should be communicated and prioritized very early. Reconstructing a skin phallus for the donor that protected the donor's dignity was the crucial turning point in our project.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no competing interest.

## References

1 Bramstedt KA. Increasing donation opportunities for vascularized composite allografts: an analysis of worldwide donor registries and procurement organization web content (VOLAR Study). Prog Transplant 2016. (Epub ahead of print) doi:10.1177/1526924816664080
2 Hu W, Lu J, Zhang L, Wu W, Nie H, Zhu Y, et al. A preliminary report of penile transplantation. Eur Urol. 2006;50(4):851–3. Oct
3 Clark PA. Face transplantation: part II-an ethical perspective. Med Sci Monit. 2005;11(2):RA41–RA47.
4 Wendler D, Grady C. What should research participants understand to understand they are participants in research?. Bioethics. 2008;22(4):203–8.
5 Basch SH. Damaged self-esteem and depression in organ transplantation. Transplant Proc. 1973;5(2):1125–7.
6 Castelnuovo-Tedesco P. Organ transplant, body image, psychosis. Psychoanal Q. 1973;42(3):349–63.
7 Castelnuovo-Tedesco P. Ego vicissitudes in response to replacement or loss of body parts. Certain analogies to events during psychoanalytic treatment. Psychoanal Q. 1978;47(3):381–97.
8 Rome HP, Braceland FJ. The role of ACTH, cortisone and hydrocortisone in the provocation of certain psychologic responses. Res Publ Assoc Res Nerv Ment Dis. 1953;31:273–9.
9 Tuffaha SH, Sacks JM, Shores JT, Brandacher G, Lee WP, Cooney DS, et al. Using the dorsal, cavernosal, and external pudendal arteries for penile transplantation: technical considerations and perfusion territories. Plast Reconstr Surg. 2014;134(1):111e–9e.
10 Tuffaha SH, Budihardjo JD, Sarhane KA, Azoury SC, Redett RJ. Expect skin necrosis following penile replantation. Plast Reconstr Surg. 2014;134(6):1000e–4e.
11 Hui-Chou HG, Nam AJ, Rodriguez ED. Clinical facial composite tissue allotransplantation: a review of the first four global experiences and future implications. Plast Reconstr Surg. 2010;125(2):538–46.
12 Petruzzo P, Dubernard JM. The international registry on hand and composite tissue allotransplantation. Clin Transpl 2011;247–253.
13 Siemionow MZ, Kulahci Y, Bozkurt M. Composite tissue allotransplantation. Plast Reconstr Surg. 2009;124(6S):327–339.
14 Lee WPA, Yaremchuk MJ, Pan YC, Randolph MA, Tan CM, Weiland AJ. Relative antigenicity of components of a vascularized limb allograft. Plast Reconstr Surg. 1991;87(3):401–11.
15 Gander B, Brown CS, Vasilic D, Furr A, Banis JC, Cunningham M, et al. Composite tissue allotransplantation of the hand and face: a new frontier in transplant and reconstructive surgery. Transplant Int. 2006;19(11):868–80.
16 Hsu CC, Chang SS, Lee PC, Chao SC. Cutaneous alternariosis in a renal transplant recipient: a case report and literature review. Asian J Surg. 2015;38(1):47–57.
17 Gilaberte M, Bartralot R, Torres JM, Reus FS, Rodriguez V, Alomar A, et al. Cutaneous alternariosis in transplant recipients: clinicopathologic review of 9 cases. J Am Acad Dermatol. 2005;52(4):653–9.
18 Nankivell BJ, P'Ng CH, O'Connell PJ, Chapman JR. Calcineurin inhibitor nephrotoxicity through the lens of longitudinal histology: comparison of cyclosporine and tacrolimus eras. Transplantation. 2016;100(8):1723–31.
19 Naesens M, Lerut E. Calcineurin inhibitor nephrotoxicity in the era of antibody-mediated rejection. Transplantation. 2016;100(8):1599–600.
20 Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349(10):931–40.
21 Lim WH, Eris J, Kanellis J, Pussell B, Wiid Z, Witcombe D, et al. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. Am J Transplant. 2014;14(9):2106–19.
22 Morris PJ, Bradley JA, Doyal L, Earley M, Hagan P, Milling M, et al. Facial transplantation: a working party report from the Royal College of Surgeons of England. Transplantation. 2004;77(3):330–38.
23 Agich GJ, Siemionow M. Facing the ethical questions in facial transplantation. Am J Bioeth. 2004;4(3):25–7.
24 Siemionow M. Ethical considerations in face transplantation: ethical issues related to inclusion criteria for face transplant candidates. Arch Immunol Ther Exp (Warsz). 2011;59(3):157–9.