

Lessons Learned from Simultaneous Face and Bilateral Hand Allotransplantation

Matthew J. Carty, M.D.
Mikaël Hivelin, M.D.
Christian Dumontier, M.D.
Simon G. Talbot, M.D.
Marc David Benjoar, M.D.
Julian J. Pribaz, M.D.
Laurent Lantieri, M.D.
Bohdan Pomahac, M.D.

Jamaica Plain, Mass.; and Paris, France



The past 14 years have borne witness to the successful emergence of vascularized composite allotransplantation¹⁻⁷ and an increasing emphasis on defining its indications. Broadly speaking, candidates for this procedure must demonstrate a willingness to remain compliant with lifelong immunosuppression and an enthusiasm to participate in the rehabilitative regimens that follow allotransplantation.⁸ More pointedly, these patients must also suffer from injuries not amenable to standard reconstructive surgery or from conditions in which the currently available surgical techniques are inadequate.

One such population is patients with injuries involving both the face and the upper extremities, which have been increasingly prevalent among soldiers in war.⁹ The degree of functional impairment and social isolation suffered by these patients is often profound, leading some to argue that they may represent a population that has the most to gain from vascularized composite allotransplantation efforts.

From the Division of Plastic Surgery, Brigham and Women's Hospital/Faulkner Hospital; Department of Plastic and Reconstructive Surgery, University Hospital European Georges Pompidou; and Université René Descartes.

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The first two authors contributed equally to the generation of this article.

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Summary: The performance of simultaneous vascularized composite allotransplantation procedures on patients requiring both the face and bilateral hands remains controversial. The authors present their separate institutional experiences with this challenging procedure in the interests of dispelling misconceptions regarding this intervention and forwarding their understanding of the issues related to concomitant vascularized composite allotransplantation. (*Plast. Reconstr. Surg.* 132: 423, 2013.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, V.

With increasingly successful allotransplantation has come an interest in performing multiple simultaneous vascularized composite allotransplantation procedures. The safety of such concomitant procedures has been debated at some length; however, the controversy has rested primarily on hypothetical grounds, with limited reference to actual clinical experience.¹⁰

In the interests of clarifying the debate regarding the efficacy and safety of concomitant vascularized composite allotransplantation, we present our clinical experience regarding the only two cases of simultaneous face and bilateral hand allotransplantation reported to date.^{3,11} In providing the details of these interventions, we hope to forward our understanding of the opportunities and limitations offered by vascularized composite allotransplantation and contribute to our evolving notions of the boundaries of this developing field.

CASE REPORTS

Case 1

A 37-year-old man presented who had suffered extensive thermal injuries following attempted self-immolation, including destruction of facial soft tissues and bony architecture, and mid-carpal amputation of his hands bilaterally. Despite several acute reconstructive measures, he suffered extreme social difficulties

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Table 1. Case Detail Summary

	Case 1	Case 2
Location	Paris, France	Boston, Mass.
Date of injury	2008	2009
Comorbidities	Depression	Hypertension, former smoker
Age at transplant, yr	37	57
Date of transplant	April of 2009	May of 2011
HLA mismatch	4:6	4:6
Ischemia time	1 hr 55 min	<1 hr
Operative time	22 hr 38 min	20 hr 14 min
Hand allografts	Distal forearms bilaterally based on ulnar and radial arteries	Right: <i>Partial hand at mid carpus based on ulnar artery</i> Left: Mid forearm based on ulnar and radial arteries
Face allograft	Scalp, face excluding lower lip, based on external carotid arteries and internal jugular veins	Full face, based on facial arteries and internal jugular veins
Colloid requirements	66 units PRBCs, 62 units FFP, 9 packs platelets	23 units PRBCs, 16 units FFP, 0.3 pack platelets
Vascular issues	Primary vascular insufficiency in left hand and occipital allograft	Secondary vascular insufficiency in setting of prolonged sepsis-related hypotension
Infectious issues	Infection of necrotic allograft soft tissue caused by <i>Pseudomonas aeruginosa</i>	Pneumonia-related sepsis caused by <i>Pseudomonas aeruginosa</i> , <i>Proteus mirabilis</i> , and <i>Serratia marcescens</i>
Immunologic issues	None	None
Reoperations	Débridement of necrotic occipital scalp; revascularization of left hand allograft; removal of left hand allograft and upper third of facial allograft	Removal of bilateral hand allografts
Net outcome	Death	Success of facial allograft; failure of bilateral hand allografts

HLA, human leukocyte antigen; PRBCs, packed red blood cells; FFP, fresh frozen plasma.

because of his facial appearance and a lack of independence because of his extremity injuries. He presented to Assistance Publique-Hopitaux de Paris for evaluation for potential combined face and bilateral hand allotransplantation in May of 2008.

In April of 2009, a face and bilateral hand donor was identified within the same institution. The donor was a 59-year-old, brain-dead man with an extensive substance abuse history who suffered a hemorrhagic stroke. The donor and recipient demonstrated a four of six human leukocyte antigen mismatch (Table 1).

Both the face and bilateral hands were transplanted over the course of a single 23-hour anesthetic session, with excellent vascularity noted in all transplants at the end of the case. Details of the procedure were as follows:

- The transplant was performed by two surgical teams working simultaneously, each composed of two surgeons, two fellows, and two nurses.
- The facial allograft was procured over 10 hours based on the bilateral external carotid arteries and internal jugular veins and included the face and entire scalp, and the nasal bones.
- The hands were procured over 90 minutes under a single tourniquet run approximately 4 cm proximal to the wrists, based on both the radial and ulnar arteries. The tourniquets were then released and the limbs allowed to perfuse for approximately 30 minutes before vascular ligation. Blood loss during the period of tourniquet release was minimal.
- Total cold ischemia was less than 1 hour for the face, and 1 hour 55 minutes for the hands. Ischemia time was minimized because of the donor and recipient being located in the same institution.
- Preparation of the recipient began concomitantly with endotracheal tube placement by means of tracheostomy and vascular access through a left femoral arterial line and central venous catheter. The patient was positioned

supine in approximately 15 to 20 degrees of reverse Trendelenburg position.

- Transplantation of the hands was performed first and lasted approximately 6 hours. Osteosyntheses were performed, followed by microsurgical revascularization. On closure, a significant skin shortage was noted bilaterally, requiring split-thickness skin grafts obtained from the donor.
- Facial transplantation followed, and included microvascular anastomoses and neurotrophies of the infra-orbital, mental, and facial nerves at the levels of their respective foramina.
- The patient required a total of 66 units of packed red blood cells; 63 units of virus-inactivated plasma; nine units of platelet-rich plasma; two preparations of clotting factors II, VII, IX, and X; and six vials of fibrinogen. Nearly all of these products were required during the facial transplant portion of the procedure, which was characterized by massive bleeding and intermittent vasopressor support.
- Induction therapy included antithymocyte globulin, 1.25 mg/kg intravenously every day; prednisone taper; tacrolimus, 2 mg orally every 12 hours; and mycophenolate mofetil, 2 g intravenously every day. Initial antibiotic therapy consisted of cefotaxime, gentamicin, valganciclovir, and trimethoprim/sulfamethoxazole (Figs. 1 and 2).

The patient's postoperative course was initially uneventful. Monitoring of the allografts was performed by means of clinical examination and Doppler probe and was not concerning until postoperative day 3, when mild venous congestion in the left hand allograft was noticed and subsequently progressed despite leech therapy. Simultaneously, the patient demonstrated increased sputum production subsequently positive for *Pseudomonas aeruginosa*. Concomitantly, the facial allograft exhibited progressive swelling and necrosis in the right posterior scalp (Fig. 3). Biopsies performed at this time on both the hands and the face revealed Banff grade I (minimal) rejection.¹²

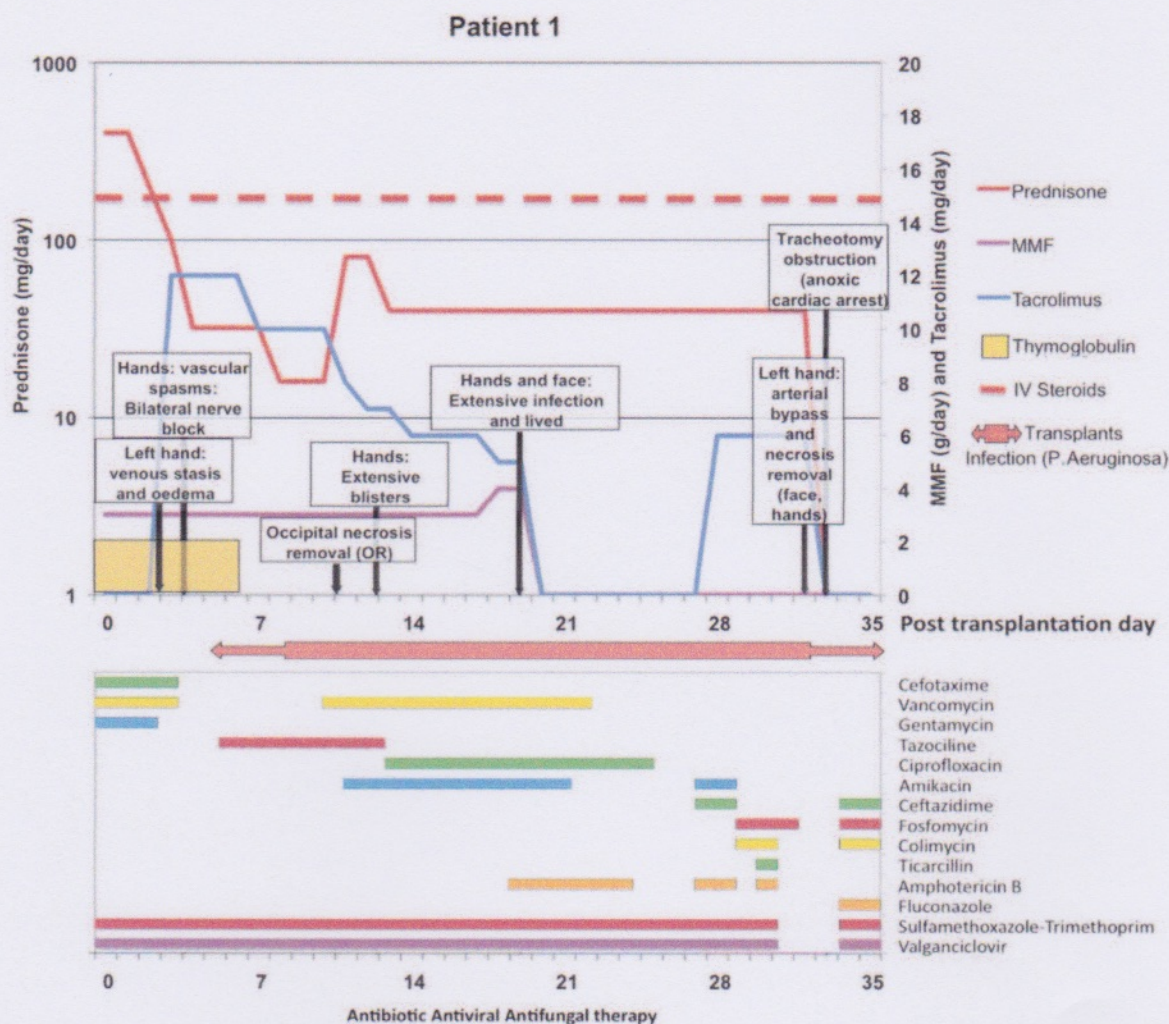


Fig. 1. Immunosuppressive and antibiotic therapy timeline for the patient in case 1 illustrating the management of early infections and severe adverse events. Continuous lines report steroids, tacrolimus, and mycophenolate mofetil doses. Dashed red line signifies the limit for steroid dose requiring intravenous administration. MMF, mycophenolate mofetil; IV, intravenous. (Reprinted with permission from Lantieri L, Hivelin M, Audard M, et al. Feasibility, reproducibility, risks and benefits of face transplantation: A prospective study of outcomes. *Am J Transplant.* 2011;11:367–378.)

Progressive compromise of both the left hand and occipital areas was noted through postoperative day 11, when bilateral subclavicular nerve blocks were applied in conjunction with aspirin/heparin therapy and the occipital region was surgically debrided. Despite the addition of both vancomycin and ciprofloxacin, the patient demonstrated frank infection of all allografts with multidrug-resistant *Pseudomonas*. Tacrolimus and mycophenolate mofetil therapy were both suspended on postoperative day 19.

By postoperative day 31, ongoing necrosis of the left hand allograft led to frank arterial insufficiency, necessitating radial artery reconstruction with a vein graft. Spontaneous rupture of the vascular repair postoperatively led to emergent return to the operating room, during which the patient suffered acute obstruction of his tracheostomy and transient hypoxic cardiac arrest for approximately 3 minutes. Following stabilization, the

patient underwent removal of the left hand allograft and the upper third of the facial allograft on postoperative day 32. All immunosuppressive therapy was suspended, and progressive improvement of all remaining allografts was noted. The patient demonstrated evidence of hypoxic brain injury attributable to his arrest episode; discussions with his family ultimately led to withdrawal of care followed by death on postoperative day 65. Autopsy revealed patent vascular anastomoses with no evidence of rejection in either of the remaining allografts (grade 0).¹³

Case 2

A 57-year-old woman presented who had been attacked by a chimpanzee in 2009, resulting in severe injuries to the soft tissues and bony architecture of her face, including complete bilateral blindness, and amputation of her right hand at the level of the mid



Fig. 2. Clinical photographs depicting the patient in case 1. Preoperative views illustrate the destruction of both orbicularis oculi and soft tissues of the upper two-thirds of the face and both hands. Postoperative views demonstrate significant facial allograft swelling, and extensive *Pseudomonas aeruginosa* infection on both hands. (Reprinted with permission from Meningaud JP, Benjoar MD, Hivelin M, et al. Procurement of total human face graft for allotransplantation: A preclinical study and the first clinical case. *Plast Reconstr Surg.* 2010;126:1181–1190.)

carpus and left hand at the level of the mid forearm. She underwent multiple acute procedures but continued to demonstrate significant difficulties with phonation/alimentation and lack of independence because of her injuries. She presented to Brigham and Women's Hospital for potential combined face and bilateral hand allotransplantation in May of 2010 and, over the course of the subsequent year, underwent extensive evaluation by a multidisciplinary team.

In May of 2011, a combined face and bilateral hand donor was identified in a nearby hospital, with a four of six human leukocyte antigen mismatch noted (Table 1). The donor was a brain-dead woman of approximately equivalent age who had suffered a hemorrhagic stroke; her medical history was notable for Raynaud phenomenon.

Both the face and bilateral hands were transplanted over the course of a single 22-hour anesthesia session, with excellent vascularity noted in all transplants at the end of the case. Details of the procedure were as follows:

- The transplant was performed by six separate two-surgeon operative teams—one at each anatomical site on both the donor and the recipient.

- The facial allograft was procured over 4 hours based on the bilateral facial arteries and internal jugular veins and included the anterior scalp, zygoma, maxilla, and skin envelope extending to the lower anterior neck.
- The right hand was composed of the ulnar four fingers and palm to the level of the mid carpus, based on the ulnar artery, and the left hand was procured at the level of the elbow based on the brachial artery; dissection was performed simultaneously in 2 hours under tourniquet control, after which the tourniquets were released and the limbs allowed to perfuse for approximately 90 minutes before vascular ligation. Blood loss during the period of tourniquet release was minimal.
- Cold ischemia time for all three allografts was less than 1 hour. Ischemia time was minimized because of the donor and recipient institutions being located adjacent to one another.
- Preparation of the recipient began concomitantly in a fashion similar to that of the French team. The patient's prior gastrostomy tube was placed, with gravity drainage.

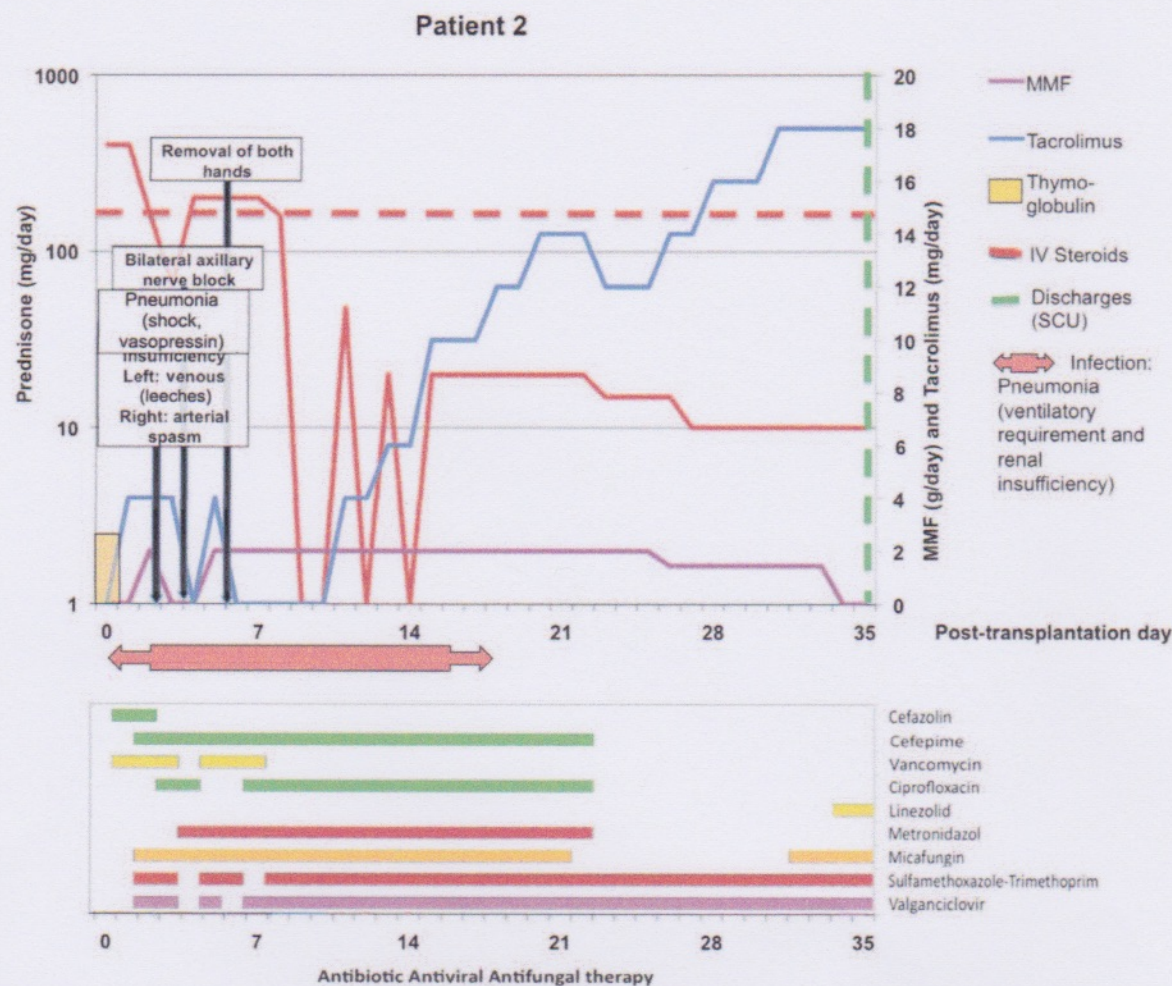


Fig. 3. Immunosuppressive and antibiotic therapy timeline for the patient in case 2 illustrating the management of early infections and severe adverse events. Continuous lines report steroids, tacrolimus, and mycophenolate mofetil doses. Dashed red line signifies the limit for steroid dose requiring intravenous administration. MMF, mycophenolate mofetil; IV, intravenous; SCU, surgical care unit. (Reprinted with permission from Lantieri L, Hivelin M, Audard M, et al. Feasibility, reproducibility, risks and benefits of face transplantation: A prospective study of outcomes. *Am J Transplant*. 2011;11:367–378.)

- Simultaneous microsurgical revascularization of the upper extremity allografts was performed first after initial osteosyntheses, followed by revascularization of the face. Coaptation of all additional structures (i.e., nerves and tendons) was performed following revascularization of the three allografts. Extensive thromboses within the donor limb venous systems were noted, requiring multiple revisions of the venous anastomoses.
- Subsequent inset of the bilateral limbs and face was performed simultaneously by three separate operative teams.
- The patient received a total of 23 units of packed red blood cells, 16 units of fresh frozen plasma, and 0.3 pack platelets. She remained hemodynamically stable throughout the procedure and did not require pressor support.
- Initial induction therapy included antithymocyte globulin, 1.5 mg/kg intravenously every day; Solu-Medrol

taper; tacrolimus, 2 mg orally every 12 hours; and mycophenolate mofetil, 1 g intravenously every 12 hours. Initial antibiotic therapy consisted of cefazolin, valganciclovir, micafungin, and trimethoprim/sulfamethoxazole (Figs. 1 and 2).

On postoperative day 1, she was noted to demonstrate mild venous congestion in the left hand allograft that proved responsive to manual compression and intravenous heparin therapy. She also demonstrated fever (102°F) and increased sputum production with associated right lower lobe opacification, leading to the addition of vancomycin and cefepime. On postoperative day 2, she progressed to septic shock requiring vasopressin and norepinephrine therapy, during which time she demonstrated acute vascular insufficiency to the bilateral hand allografts. Because of concerns about immunosuppression-related leukopenia in the setting of sepsis, her tacrolimus was discontinued.

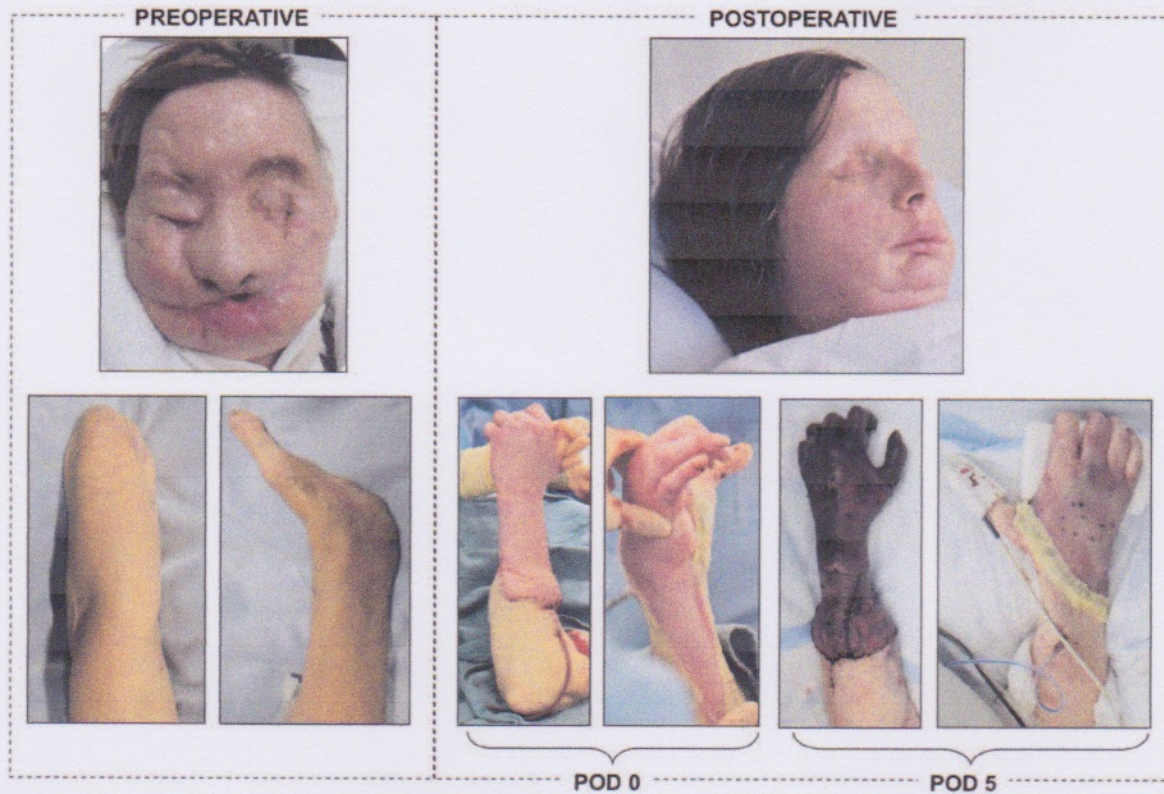


Fig. 4. Clinical photographs depicting the patient in case 2. Preoperative views illustrate extensive destruction of facial features and amputation of the entire left hand and partial right hand. Postoperative views demonstrate the viable facial allograft but progressive compromise of the hands, which were subsequently removed.

She remained hypotensive for the next several days with concomitant renal insufficiency, during which time sputum cultures demonstrated *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Serratia marcescens*. Over this interval, she exhibited a stable appearance in the facial allograft but progressively worsening vascular insufficiency in the bilateral hands. On the right, this manifested primarily as arterial insufficiency that proved transiently responsive to topical nitropaste therapy. On the left, this manifested primarily as venous insufficiency amenable to leech therapy; however, because of ongoing transfusion requirements, this intervention was discontinued. In addition, bilateral axillary nerve blocks and a low-dose dobutamine infusion were instituted, both of which promoted transient allograft improvements. However, both hand allografts were removed on postoperative day 5 (Fig. 4).

The patient subsequently demonstrated a prolonged recovery characterized by transient atrial flutter, limited renal insufficiency, and an extended ventilatory wean through postoperative day 17. No evidence of rejection was noted in either the surviving facial allograft or the removed hand allografts. She was ultimately discharged to a skilled nursing facility on postoperative day 38.

DISCUSSION

We present our experience with simultaneous face and bilateral hand allotransplantation in the interests of increasing our understanding of the

issues related to concomitant vascularized composite allotransplantation and providing insights as to how such procedures may be approached more successfully in the future. To begin, the principal issues in both cases were ischemic necrosis and infection: in the patient in case 1, necrosis set the stage for infection, whereas in the patient in case 2, infection led to subsequent necrosis. The cause of tissue compromise noted in both cases was likely multifactorial, including difficult vascular anastomoses, particularly on the donor venous side; soft-tissue edema resulting in venous compression and inadequacy of skin coverage; and catecholamine requirements in the setting of hypovolemic or septic shock. These concerns represent surmountable technical and physiologic challenges that, we feel, should not preclude further efforts at simultaneous vascularized composite allotransplantation.

More broadly, we feel that our experience addresses the notion that concomitant vascularized composite allotransplantation procedures somehow represent “too much” for patients to handle.

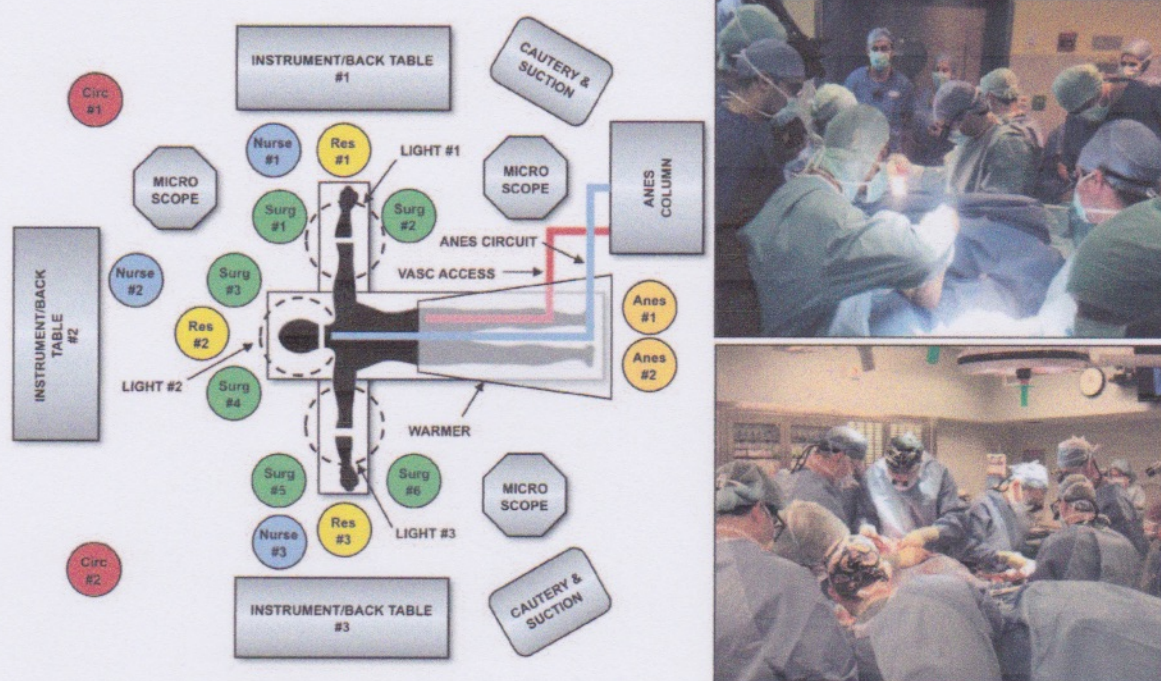


Fig. 5. Complex intraoperative arrangement of the surgical team during combined facial and bilateral hand allotransplantation. The schematic illustration understates the challenge of successfully orchestrating the mechanics of multiple simultaneous operative teams, which is more fully represented in intraoperative photographs from both reporting institutions (left). (Above, right) French team; (below, right) Boston team. Surg, surgeon; Res, resident; Anes, anesthesiologist; Circ, circulator.

Although this argument has not been formally defined to date, we suggest that it is based on three concerns: (1) antigenic burden; (2) extended anesthesia time; and (3) large-volume resuscitation.

In reference to the first issue, critics have previously declared the antigenic load of multiple composite allografts to be an immunologic concern.¹⁴ Neither experimental nor clinical experience to date validates this supposition. Early studies by Zhong et al., for example, demonstrated that the immunologic response mounted by rats to visceral transplants appears to diminish with increasing antigenic load.¹⁵ Furthermore, it has been demonstrated both clinically¹⁶ and experimentally^{17,18} that the amount of transplanted tissue may have a positive influence on transplant antigenic outcomes through the induction and maintenance of chimerism. More recently, Gordon et al. quantified the amount of skin surface area for various combinations of face and hand allotransplants¹⁹; using this study as a reference, we estimate the total skin surface area of our patients as approximately 2300 cm² (case 1) and 1600 cm² (case 2). These antigenic burdens are similar to those of isolated bilateral limb allotransplantation

procedures performed to date, none of which has met with significant immunologic challenges.²⁰⁻²² Therefore, there is little evidence to suggest that the antigenic burden of concomitant vascularized composite allotransplantation procedures per se represents a safety prohibition.

With regard to extended anesthesia time, we fully acknowledge the well-documented risks of prolonged exposure to anesthetic agents²³; however, we also note that our institutional experiences with single allograft vascularized composite allotransplantation procedures have included several cases that were of approximately equivalent length that have been performed without catastrophe.^{11,24}

Finally, the challenge of maintaining relative normovolemia in the setting of a prolonged operation has been well-described in the vascularized composite allotransplantation population.²⁵ Reports of massive transfusion requirements, in particular, have been documented in multiple vascularized composite allotransplantation cases over the past several years.^{11,26} The metabolic, hemodynamic, and coagulopathic effects of large-volume replacement are uncontested.²⁷ What

remains open to debate, however, is our capacity to diminish such requirements with increasing experience. Based on communications between our programs in advance of the second described procedure, for example, we were able to incorporate strategies to limit blood loss such that the latter case required less than half of the colloid products of the former.

Although we argue that no single one of the above-mentioned concerns should necessarily serve as an impetus to prohibit the undertaking of concomitant vascularized composite allotransplantation procedures, we do acknowledge that the combination of all three poses a significant challenge. Toward this end, we posit that future performance of concomitant vascularized composite allotransplantation procedures must be approached in the same light as intensive visceral allotransplants, with a particular emphasis on meticulous attention to surgical and medical management.²⁸ Among those factors requiring attention are the following:

- Pulmonary protection: Pulmonary compromise must be avoided through aggressive head-of-bed elevation, regular clearance of endotracheal tube secretions, and active continuous gastric evacuation.
- Limited blood loss: Excessive blood loss has historically occurred at the site of the recipient beds and allograft raw surfaces. Measures used to limit such losses include the use of tumescent solution, pneumatic tourniquets, induced hypotension, intraoperative cell salvage devices, and advanced coagulation monitoring methods such as thromboelastography.^{29,30}
- Limited operative time: Concomitant vascularized composite allotransplantation procedures require exquisite coordination among members of the operative team to perform steps in parallel rather than in series. This endeavor necessitates a highly organized surgical team of appropriate manpower (Fig. 5). In addition, discrete shifts should be defined before limit fatigue, to maximize operative efficiency and permit individuals to play to their technical strengths. Successful execution of these surgical roles can be maximized through rehearsals of these procedures with the entire operative team well in advance of the actual operation, including anesthesiologists and operating room support staff.
- Limited tissue ischemia: We do not currently understand how tissue reperfusion injury affects the recipient's recovery following vascularized composite allotransplantation. In the absence of definitive data, we advocate procurement of the donor allografts as late as possible with as much dissection of individual structures as feasible before ischemia. In addition, we favor minimal transport time and rapid revascularization of allografts, ideally to achieve less than 1 hour of ischemia time. Finally, we advocate that supranormovolemic status be established just before allograft revascularization to compensate for the increased circulating blood volume requirement that is realized on completion of anastomoses.
- Aggressive infection prophylaxis: Both of the cases highlighted in this report suffered complications caused by infection, not rejection; such opportunistic infections are well-documented in the general vascularized composite allotransplantation literature.^{2,31} Whether this suggests that immunosuppression in concomitant vascularized composite allotransplantation recipients should be less aggressive than the regimens used is unclear. What is certain, however, is that broad-spectrum antibiotic prophylaxis is critical, guided by transplant infectious disease specialists throughout the course of care. In the face of clinically apparent infection in concomitant vascularized composite allotransplantation recipients in the posttransplant setting, we suggest an immediate reduction in immunosuppression to permit the patient to mount an appropriate immunologic response. Our experience to date suggests that such withdrawal does not provoke acute rejection, perhaps in part because of the well-known immunosuppressive impact of sepsis.
- Timely allograft débridement/removal: The infectious burden of necrotic tissue is of paramount concern in concomitant vascularized composite allotransplantation recipients who appear to demonstrate a susceptibility to severe postoperative infections. Our experience argues for the timely and definitive débridement of nonviable tissues when required, including the removal of full allografts; this potential catastrophe

requires that reconstructive backup options always be preserved. Although débridement may be distressing to both the patient and the operative team, the consequences of maintaining devitalized biomass may be dire. Stated simply, adherence must be made at all times to the principle of life over limb and/or face.

Beyond these factors, our experience requires us to further consider patient selection and operative timing. Although the recipients described in this report demonstrated a significant age discrepancy, both arguably had compromised cardiopulmonary and metabolic reserve because of their prolonged posttraumatic medical histories. Although neither patient was enlisted for allotransplantation callously, even more intensive screening of candidates than is currently performed may be warranted. In addition, our experience supports the position argued by some that such transplantation procedures should perhaps be undertaken in a sequential fashion, with separate procedures and—by extension—donors for the face and hands. The immunologic impact of such an endeavor is presently unknown and is surely a topic worthy of further investigation.

CONCLUSIONS

In closing, we offer the perspectives described in this article to further the ongoing discovery process that currently characterizes vascularized composite allotransplantation. Although it is tempting make statements regarding what endeavors should be undertaken with regard to simultaneous vascularized composite allotransplantation procedures, we have specifically avoided being overly prescriptive in our discussion of lessons learned. The practice of concomitant vascularized composite allotransplantation is at far too fledgling a stage to make statements any more declarative than what we have stated above. In this vein, we offer our collective experience in the interest of advancing—rather than deciding—the debate concerning simultaneous vascularized composite allotransplantation.

Matthew J. Carty, M.D.
Division of Plastic Surgery
Brigham and Women's Hospital/Faulkner Hospital
1153 Centre Street
Jamaica Plain, Mass. 02130
mcarty@partners.org

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PATIENT CONSENT

Patient and guardian provided written consent for use of patients' images.

REFERENCES

1. Schneeberger S, Morelon E, Landin L, ESOT CTA Committee. Vascularized composite allotransplantation: A member of the transplant family? *Transplantation* 2012;93:1088–1091.
2. Petruzzo P, Lanzetta M, Dubernard JM, et al. The International Registry on Hand and Composite Tissue Transplantation. *Transplantation* 2010;90:1590–1594.
3. Pomahac B, Pribaz J, Eriksson E, et al. Three patients with full facial transplantation. *N Engl J Med*. 2012;366:715–722.
4. Knott PD, Hicks D, Braun W, Strome M. A 12-year perspective on the world's first total laryngeal transplant. *Transplantation* 2011;91:804–805.
5. Delaere P, Vranckx J, Verleden G, De Leyn P, Van Raemdonck D; Leuven Tracheal Transplant Group. Tracheal allotransplantation after withdrawal of immunosuppressive therapy. *N Engl J Med*. 2010;362:138–145.
6. Levi DM, Tzakis AG, Kato T, et al. Transplantation of the abdominal wall. *Lancet* 2003;361:2173–2176.
7. Carollo K. First double leg transplant patient may soon walk. Available at: <http://abcnews.go.com/Health/double-leg-transplant-patient-walk/story?id=14054438>. Accessed February 13, 2012.
8. Amirlak B, Gonzalez R, Gorantla V, Breidenbach WC III, Tobin GR. Creating a hand transplant program. *Clin Plast Surg*. 2007;34:279–289, x.
9. Owens BD, Kragh JF Jr, Wenke JC, Macaitis J, Wade CE, Holcomb JB. Combat wounds in operation Iraqi Freedom and operation Enduring Freedom. *J Trauma* 2008;64:295–299.
10. Siemionow M, Zor F, Gordon CR. Face, upper extremity, and concomitant transplantation: Potential concerns and challenges ahead. *Plast Reconstr Surg*. 2010;126:308–315.
11. Lantieri L, Hivelin M, Audard V, et al. Feasibility, reproducibility, risks and benefits of face transplantation: A prospective study of outcomes. *Am J Transplant*. 2011;11:367–378.
12. Cendales LC, Kirk AD, Moresi JM, Ruiz P, Kleiner DE. Composite tissue allotransplantation: Classification of clinical acute skin rejection. *Transplantation* 2006;81:418–422.
13. Rüegg EM, Hivelin M, Hemery F, et al. Face transplantation program in France: A cost analysis of five patients. *Transplantation* 2012;93:1166–1172.
14. Siemionow M, Zor F, Gordon CR. Face, upper extremity, and concomitant transplantation: Potential concerns and challenges ahead. *Plast Reconstr Surg*. 2010;126:308–315.
15. Zhong R, He G, Sakai Y, et al. Combined small bowel and liver transplantation in the rat: Possible role of the liver in preventing intestinal allograft rejection. *Transplantation* 1991;52:550–552.
16. Starzl TE, Demetris AJ, Murase N, Ildstad S, Ricordi C, Trucco M. Cell migration, chimerism, and graft acceptance. *Lancet* 1992;339:1579–1582.
17. Nasir S, Bozkurt M, Klimczak A, et al. Large antigenic skin load in total abdominal wall transplants permits chimerism induction. *Ann Plast Surg*. 2008;61:572–579.

18. Nasir S, Bozkurt M, Krokowicz L, Klimczak A, Siemionow M. Correlation of chimerism with graft size and revascularization in vascularized and nonvascularized skin allografts. *Ann Plast Surg.* 2009;62:430–438.
19. Gordon CR, Zor F, Siemionow M. Skin area quantification in preparation for concomitant upper extremity and face transplantation: A cadaver study and literature review. *Transplantation* 2011;91:1050–1056.
20. Cavadas PC, Ibáñez J, Thione A, Alfaro L. Bilateral transhumeral arm transplantation: Result at 2 years. *Am J Transplant.* 2011;11:1085–1090.
21. Tufts A. Munich surgeons perform world's first transplantation of whole arms. *BMJ* 2008;337:a1162.
22. Cavadas P. Personal communication, February 1, 2012.
23. Macdonald DJ. Anaesthesia for microvascular surgery: A physiological approach. *Br J Anaesth.* 1985;57:904–912.
24. Institutional analysis of facial allotransplantation operative times, BWH Vascularized Composite Allograft Program, February 22, 2012. Unpublished data.
25. Siemionow M, Zor F, Gordon CR. Face, upper extremity, and concomitant transplantation: Potential concerns and challenges ahead. *Plast Reconstr Surg.* 2010;126:308–315.
26. Gordon CR, Siemionow M, Papay F, et al. The world's experience with facial transplantation: What have we learned thus far? *Ann Plast Surg.* 2009;63:572–578.
27. Hynynen M, Eklund P, Rosenberg PH. Anaesthesia for patients undergoing prolonged reconstructive and microvascular plastic surgery. *Scand J Plast Reconstr Surg.* 1982;16:201–206.
28. Losee J. Update on the UPMC Hand Transplantation Program. Paper presented at: Harvard Combined Plastic Surgery Program Grand Rounds; April 2012; Boston, Mass.
29. Waters JH, Yazer M, Chen YF, Kloeke J. Blood salvage and cancer surgery: A meta-analysis of available studies. *Transfusion* 2012;52:2167–2173.
30. Liumbruno GM. Thromboelastography and thromboelastometry and the management of intra-operative transfusion therapy in massively bleeding patients. *Blood Transfus.* 2012;10:400–401.
31. Schneeberger S, Lucchina S, Lanzetta M, et al. Cytomegalovirus-related complications in human hand transplantation. *Transplantation.* 2005;80:441–447.

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Discussion: Lessons Learned from Simultaneous Face and Bilateral Hand Allotransplantation

Jaimie T. Shores, M.D.
W. P. Andrew Lee, M.D.
Gerald Brandacher, M.D.
Baltimore, Md.

We read with great interest the recent article by Carty et al. entitled "Lessons Learned from Simultaneous Face and Bilateral Hand Allotransplantation."¹ The authors, who have combined their separate institutional experiences with the most challenging procedure of a combined vascularized composite allotransplantation, provide a detailed description of two cases of concomitant vascularized composite allotransplantation in the form of a simultaneous face and bilateral hand transplantation. Although these two cases represent the only ones in the medical literature to date, the authors are not alone in attempting such "polyanatomical" transplantation. Recent media reports and surgical center reports at the Third Biennial Meeting of the American Society for Reconstructive Transplantation held in November of 2012 in Chicago, Illinois, have confirmed that a concomitant bilateral hand and leg transplantation was attempted in Turkey, resulting in not only the loss of the transplanted grafts but also the death of the patient.² At another center in Turkey, a triple limb transplant was attempted and resulted in the early loss of a unilateral leg transplant and patient death within 4 months.³

Although it is difficult to ascertain all the factors contributing to graft loss and patient death in these cases of concomitant vascularized composite allotransplantation, what is evident from the peer-reviewed literature, the lay press, and podium presentations at national/international meetings, is the distressing reality that the mortality rate of such concomitant or polyanatomical vascularized composite allotransplantation is 75 percent (three of four patients). The remaining 25 percent (one of four patients) survived life-threatening complications to lose two of the three

transplanted grafts, ultimately acquiring the result that a more "conventional" isolated face transplant could have provided.

Vascularized composite allotransplantation represents one of the newest surgical innovations and horizons in which advancements of surgical technique coupled with progress in transplant immunology offer new reconstructive possibilities not previously conceivable. Although the field is still in its infancy, it is imperative that we be critical. Careful analysis of indications, successes, and failures must be performed to ensure that a few high-profile "failures" do not result in unnecessary restraint in application to appropriate candidates who may benefit from a balanced application of this technology with our best intentions and conservative expectations.

As we stand on the precipice of possibility, we again must ask ourselves what *can* we do and what *should* we do. To argue that these operations should never be attempted would be naive and short-sighted. Nevertheless, the mortality rate is 75 percent and the rate of graft (limb) loss in the surviving patient is 100 percent. How do we ensure the safety of patients who are desperate to consent to operations they, in many cases, cannot possibly fully understand in all their complexity? Mandating that strict ethical oversight is being provided goes without saying. Requiring that the teams involved have previous experience in the type of transplant performed (e.g., face, upper limb, or lower limb) individually before being combined with other transplants seems prudent given the outcomes discussed.

Utmost consideration should be given to patient selection, meticulous preoperative planning, and team experience. By itself, hand or face transplantation is a rare operation performed at

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relatively few centers throughout the world. The experience at most centers is small, with only a handful of institutions and surgical teams accumulating experience of more than three to five cases. Thus, how much experience is necessary to successfully complete not one type of vascularized composite allotransplantation in a single episode, but three (bilateral hands and face) or four (bilateral hands and legs)? Obvious questions must be asked: How many surgeons with experience in vascularized composite allotransplantation and the individual components of the operation to be performed are necessary? Should a lack of experience in the type of transplant being performed (hand or face transplantation) exclude a surgical team from being allowed to pursue such a combined attempt?

Although we have no doubt that the future of vascularized composite allotransplantation is bright and that the encountered obstacles will eventually be overcome, we must approach it conservatively and with great respect for the science involved and, above all, patient safety. More basic and translational research on the quantity of tissue undergoing ischemia-reperfusion injury or tissue antigenicity that can be tolerated is necessary. Currently, there is no scientific foundation or data from animal models available with regard to concomitant vascularized composite allotransplantation. Concerns with issues such as antigenic burden, extended anesthesia time, large-volume resuscitation, and ischemia-reperfusion injury are extrapolated from solid organ and multivisceral transplantation or limb replantation and lack scientific evidence in vascularized composite allotransplantation. In addition, work on prolonging the lifespan of skeletal muscle-rich vascularized composite allotransplants so that transplants may be performed in stages instead of in one combined setting may be

beneficial and ultimately enhance the chances of successful and safe completion of such monumental operations.

An open and transparent discussion of these issues as provided by Carty et al. in the preceding article will help to increase our understanding of the risks, challenges, and potential limitations of concomitant vascularized composite allotransplantation and provide much needed insight regarding how such transplants may be considered more safely and successfully in the future. As more new centers are embarking on vascularized composite allotransplantation, we need to be very considerate as we expand indications to avoid “getting ahead of ourselves” and facing setbacks and catastrophic outcomes that could jeopardize the future of the entire field and patient safety. Instead, we should consider how to avoid these pitfalls while still encouraging advancement and tilting the risk-to-benefit ratio in our patients’ favor.

Gerald Brandacher, M.D.

Reconstructive Transplantation Program
Department of Plastic and Reconstructive Surgery
The Johns Hopkins University School of Medicine
Ross Research Building 749D
720 Rutland Avenue
Baltimore, Md. 21205
brandacher@jhmi.edu

REFERENCES

1. Carty MJ, Hivelin, M, Dumontier C, et al. Lessons learned from simultaneous face and bilateral hand allotransplantation. *Plast Reconstr Surg*. 2013;132:423–432.
2. Today's Zaman. Turkish hospital performs triple limb and face transplant. January 22, 2012. Available at: <http://www.today-szaman.com/news-269227-turkish-hospital-performs-triple-limb-and-face-transplant.html>. Accessed March 20, 2013.
3. Sheets CA. Atilla Kavdir dead months after receiving triple-limb transplant in Turkey. May 2, 2012. Available at: <http://www.ibtimes.com/atilla-kavdir-dead-months-after-receiving-triple-limb-transplant-turkey-694734>. Accessed March 20, 2013.