

# Hand transplantation: current challenges and future prospects

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**Abstract:** Over the last two decades, 113 vascularized composite allotransplantation (VCA) of the hand have been performed in 76 patients globally. The procedure that was once regarded as experimental has certainly emerged as a clinical reality with multiple centers worldwide now performing it. The psychological and physical impact of losing an upper extremity is profound. Amputees face significant challenges contributing to disability and dependence even with activities of daily living. Hand transplantation offers functions with restoring sensation, voluntary motor control, and proprioception, as well as a sense of feeling “whole” again. Along with these benefits, however, transplantation carries a significant risk profile attributed to the complications of life-long immunosuppression and possible rejection. Moreover, the procedure carries a significant financial burden to the health care system. As hand VCA is becoming more widely accepted and performed worldwide, there are still many challenges that will face its rapid growth. This review highlights some of the challenges facing hand VCA including patient selection, effect on quality of life, financial burden, functional outcomes, and complications of immunosuppression.

**Keywords:** hand transplantation, vascularized composite allotransplantation

## Introduction

The first attempted hand transplantation was performed in Ecuador in 1964. The transplant survived 2 weeks but was lost to acute rejection.<sup>1</sup> Over the next three decades, surgical advancements in replantation microsurgery as well as medical advancements in transplant immunology and immunosuppressive therapy allowed for the success of such a procedure.<sup>2</sup> In 1998, the second hand transplant was performed in Lyon, France. The patient ultimately lost the transplant after 2 years because of rejection secondary to medication noncompliance.<sup>3,4</sup> Following this, the first successful hand transplant with long-term survivability was performed in Louisville, Kentucky, in 1999.<sup>5</sup> The patient remains the longest surviving hand transplant recipient, 17 years since transplantation.

Subsequent to this success, hand transplantation has evolved from what used to be regarded as experimental and potentially unethical to a procedure that is accepted and recognized, with 113 transplants performed on 76 patients worldwide.<sup>6-17</sup> Though it offers sensation, function, cosmetic, and psychological benefits, there are significant risks associated with the lifelong immunosuppressive medication required with transplantation.<sup>4,5,7,12,18-34</sup> This article aims to outline the challenges of hand transplantation by discussing patient selection, effect on quality of life, financial burden, functional outcomes, and risks of immunosuppression.

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## Incidence, etiology, and alternative treatment

Upper extremity amputation in young patients is typically the result of trauma, infection, or is secondary to congenital anomalies. For older patients, amputation is more likely a result of medications or peripheral vascular diseases. The incidence of upper extremity loss is variable in the literature, though it is estimated to be 11.6 in 100,000 adults.<sup>35</sup>

The psychological and physical impact of losing an upper extremity is profound. Such a loss results in significant disability, with severe impact on quality of life. The mainstay of treatment for hand amputation has been prosthesis. Various forms of prostheses are available and range from a nonfunctional cosmetic prosthetic, to a hook, to a more advanced myoelectric prosthetic. Though a prosthetic may provide an assisting hand, it is limited by the burden of weight, discomfort, limited usefulness, and lack of functional feedback. Additionally, bilateral amputees face unique challenges with basic grooming, self-care, and activities of daily living contributing to significant disability and dependence.<sup>36</sup>

As a form of vascularized composite allotransplantation (VCA), hand transplantation can functionally offer a far superior option than prostheses. It provides superior dexterity with restoring sensibility, intrinsic muscle function, and proprioception. Moreover, it can potentially provide a match in color, size, and overall appearance. However, these benefits could be outweighed by the complications secondary to the life-long immunosuppression required.<sup>6-7</sup>

## Patient selection

Eligibility and indication for hand transplantation remain to be a challenge and topic of debate. Generally speaking, indications for transplant are based on both the expected preoperative success of transplant and the impact on function for the patient. Indications may include amputation of the dominant hand, bilateral amputations, distal amputations (less nerve regeneration required), and abrupt amputations with clean end points of distal stump.<sup>37,38</sup> Table 1 outlines the inclusion and exclusion criteria used by several USA hand transplant centers.<sup>39</sup>

An assessment of the whole person is required to determine eligibility. This involves a multidisciplinary team to properly evaluate the possible medical, psychological, and social impacts of one's amputation as well as to determine their potential for success and improved outcomes with transplant. Centers that contemplate performing hand VCA must have the capacity for a multidisciplinary team such as the one listed in Table 2.

**Table 1** Inclusion and exclusion criteria for hand transplant recipients used by several USA hand transplant centers

Inclusion criteria	Exclusion criteria
Age 18–69 years	Age <18 or >69 years
No medical condition with negative immunologic, surgical, or functional implications	Chronic infection
No psychosocial issues	Malignancy
No cancer in past 10 years	Immune condition
No HIV	Coagulopathies
Willingness to consent to cell collections/storage/bone marrow infusion	Hematologic disease
Greater than 6 months since extremity injury with attempt at rehabilitation	Connective tissue or vascular disease
	Lipopolysaccharidosis
	Amyloidosis
	Metabolic/genetic bone disease
	Red flags during screening

**Note:** Reproduced from MacKay BJ, Nacke E, Posner M. Hand transplantation: a review. *Bull Hosp Jt Dis.* 2014;72(1):76–88. With permission.<sup>39</sup>

**Table 2** Sample multidisciplinary team required for a hand transplant center

Physicians	Health care aid
Replantation surgery	Ethics
Plastic surgery	Psychology
Orthopedic surgery	Rehabilitation services
Transplant surgery	Occupational therapy
Psychiatry	Physiotherapy
Infectious diseases	Social work
Immunology	
Internal medicine	
Physiatry	
Anesthesia	
Hematology	
Neurology	

Predictors of non-adherence to immunosuppressive medication regimens include inadequate social support, higher education, and less conscientiousness.<sup>40</sup> Patient selection and education are crucial as intensive daily hand therapy and significant morbidity are associated with immunosuppression.<sup>27,41</sup> Once selection is determined, it is paramount to explore patients' expectations as well as educate them on the nature of the intense recovery.

## Effectiveness of hand VCA

Performing high-quality studies such as a randomized controlled trial to investigate the difference in outcomes between hand VCA and, for example, prosthesis application is not possible because of feasibility issues, ethical issues, costs, and patient recruitment. This poses a significant challenge when attempting to widely implement a new intervention

since little outcome data are available. However, when clinical trials cannot be performed, well-done observational studies and decision analyses are regarded as an acceptable method to help decide among different treatment options.<sup>42,43</sup>

Four decision analysis studies have been published,<sup>44–47</sup> evaluating the effectiveness of hand transplantation. The studies used differing methodology, populations, and assumptions in their decision analyses. Overall, bilateral hand transplantation showed improvement in health utility or at least showed an increased risk acceptance profile, whereas unilateral hand transplantation was not justified. These studies highlighted the significant impact that immunosuppressive side effects play on the overall utility of the procedure.

## Financial burden

Another challenge with implementing such a resource-heavy treatment option is the financial burden on the health care system. The direct and indirect costs associated with hand transplantation include surgical costs, days in hospital, immunosuppression treatment and complications, rehabilitation, and the opportunity cost of days off work.

Chung et al<sup>46</sup> performed an economic cost-utility analysis of hand transplantation in the United States using 100 medical students and showed that the mean surgical costs were \$13,796 for single and \$14,608 for bilateral hand transplants. This included preoperative assessments, hospitalization, and physician fees. Estimates for immunosuppressive therapy were \$433,282 for 40 years of treatment. Overall, a lifetime cost for hand VCA was \$528,000–\$530,000 (single or bilateral) versus single and bilateral prosthesis at \$20,000 and \$41,000, respectively. The cost of productivity loss for hand transplantation was \$42,265 and prosthetic adaptation was \$9,753.

Moreover, the estimated rehabilitation cost for a single hand transplant in one study was calculated to be \$53,336 for 226 hours of therapy and \$63,360 for 260 hours of therapy for a bilateral transplant.<sup>39</sup> Based on the limited evidence available, hand transplantation has shown to be significantly more costly than prosthesis and exceeds the predetermined threshold in cost-effectiveness analysis and therefore it is not cost-effective for a single hand transplant.<sup>39,46</sup> So far, the cost for most hand transplants has been covered by insurance companies, government grants, the ministry of defense, or individual hospitals. If this procedure was to become the standard of care for the treatment of a hand amputation, the economic impact would be very significant.

## Outcomes

Shores et al<sup>48</sup> published on the outcomes of hand and upper extremity transplantation in the worldwide experience in 2016.

This report included 72 patients with 107 total unilateral or bilateral upper limb transplants. With regard to mortality, 4 patients have died; 2 patients had combined hand and leg transplants; and 1 had combined hand and face transplants. The patient survival rate for unilateral or bilateral hand transplantation in isolation is 98.5%. A total of 24 limbs have been lost because of patient death (4 patients, 8 limbs), acute loss (3 patients, 5 limbs), and chronic limb loss (11 patients, 11 limbs). Transplants performed in China, however, have had issues with noncompliance or lack of access to immunosuppression resulting in 58% graft loss in their experience. When disregarding the Chinese group and the multisite heterogeneous transplants group, hand transplantation in Western Europe/Australia/US experience have had successful results with a mortality rate of 0% in 50 patients and a graft survival rate of 90.5% (7 of 74 limbs lost). Table 3 provides a summary of known hand and upper extremity transplants before 2016 as published by Shores et al.<sup>48</sup> Since then, six transplants have been performed, two at the University of Pennsylvania, one at the University of Louisville, two in India, and one in Canada. Certainly, this list may not be fully complete as there may be other unknown or unpublished hand transplantation data.

The patient population in hand transplantation is extremely heterogeneous with respect to anatomy, function, rehabilitation, and goals. For these reasons, evaluating and predicting outcomes for patients have proven to be a difficult task. In an attempt to address this issue, the International Registry on Hand and Composite Tissue Transplantation (IRHCTT) was developed as a means of collecting and synthesizing data on outcomes in a centralized and accessible manner. The registry has collected prospective data on transplant patients since 2002.<sup>7</sup> The last report,<sup>6</sup> published in 2011, includes 39 patients who underwent 57 hand transplants. With regard to immunosuppressive complications, a majority (90%) of patients had metabolic complications (hyperglycemia, end-stage renal disease, Cushing syndrome, hyperparathyroidism), and 77% of patients suffered from opportunistic infections at some point during follow-up. Other less common complications included hypertension, serum sickness, avascular necrosis of the hip, and skin cancer.

Evaluation of functional outcomes demonstrated that all patients developed protective sensation. Tactile sensibility was present in 90% of patients, and discriminative sensibility was present in 82%. Patients recovered sufficient motor function to perform most activities of daily living, including eating, driving, grooming, and writing. DASH scores averaged 38 at 1 year and 16 at 10 years post transplant (0 being the best possible score). Greater than 75% of patients had improved quality of life and the majority had returned to some manner of occupation.<sup>7,48,49</sup>

**Table 3** Summary of the known hand and upper extremity transplantations worldwide<sup>48</sup>

Country	Center	Unilateral (no. of patients)	Bilateral (no. of patients)	Total no. of limbs	No. of limbs lost	Mortalities
Australia	Melbourne	1		1		
Austria	Innsbruck	1	4	9		
Belgium	Brussels	1		1		
China	Six centers	9	3	15	7	
France	Lyon	1	5	11	1	
	Paris		1	2	2*	1*
Germany	Munich		1	2		
Iran	Tehran	1		1		
Italy	Milan	3		3		
	Monza		1	2		
Malaysia	Selayang	1		1		
Mexico	Mexico City		2	4	2	1
Poland	Wroclaw	5	1	7	1	
Spain	Madrid		1	2		
	Valencia		3	6		
Turkey	Ankara		1	2	2*	1*
Turkey	Antalya		3	6	2*	1*
United Kingdom	Leeds	1		1		
United States	Brigham and Women's Hospital, Mass.		2	4	2*	
	Emory, Ga.	1	1	3	2	
	Johns Hopkins University/University of Pittsburgh	2	4	10	1	
	Massachusetts General Hospital, Mass.	1		1		
	University of Louisville, Ky.	7	1	9	1	
	UCLA	1		1	1	
	University of Pennsylvania		1	2		
	Wilford Hall, Medical Center, Texas	1		1		
Totals		37	35	107	24	4

**Note:** \*Simultaneous hand and other body region transplantation (face or leg). Reproduced from Shores JT, Brandacher G, Lee WP. Hand and upper extremity transplantation: an update of outcomes in the worldwide experience. *Plast Reconstr Surg.* 2015;135(2):351e–360e. <http://journals.lww.com/plasreconsurg/pages/articleviewer.aspx?year=2015&issue=02000&article=00035&type=abstract>.<sup>48</sup>

## Immunosuppression

Perhaps the biggest challenge and impediment to hand transplantation growth is justifying the negative effects of life-long immunosuppression for a non-life-threatening condition. The compilation of foreign skin, muscle, nerve, tendon, and bone in VCA makes it exceedingly more challenging to avoid rejection than in solid organ transplantation. Specifically, skin has the tendency to be extremely antigenic requiring more aggressive immunosuppression.<sup>50</sup> Chronic immunosuppression has profound short- and long-term side effects predisposing patients to opportunistic infections, cancer, endocrinopathies such as diabetes and dyslipidemia, as well as end-organ damage, including nephrotoxicity and neurotoxicity.<sup>51</sup> These profound effects along with the expensive price of medications contribute significantly to the poor compliance of patients to their medication regimens.

Typically, a patient preparing for transplant will undergo several cycles of induction therapy to diminish the initial acute immune response, followed by a triple-drug therapy

protocol once transplantation has taken place for long-term immunosuppression.<sup>52–56</sup>

Induction agents work to deplete the T- and B-cell stores or interfere with the adaptive immune response at the time of alloantigen presentation with transplantation. Induction consists of a polyclonal or monoclonal antibody against thymocytes such as thymoglobulin and alemtuzumab.<sup>52–56</sup> This approach has reduced the need for long-term steroid use and the associated cardiovascular risk factors.<sup>57</sup>

Once transplantation has taken place, maintenance therapy begins with triple-drug therapy. Triple-drug regimens include a calcineurin inhibitor to prevent early activation of T cells (e.g., tacrolimus), an antimetabolite agent to prevent synthesis of nucleotides required in lymphocyte proliferation (e.g., mycophenolate mofetil), and a steroid (e.g., prednisone). Triple-drug therapy is guided by protocols developed for solid organ transplantation.<sup>57,58</sup> Doses and treatment regimens in VCA most resemble those used in renal transplant.<sup>58</sup> A balance is achieved by preventing graft rejection

while avoiding some immunity to prevent sepsis, end-organ damage, and neoplasia.

Newer regimens to decrease the risks of immunosuppression are currently being researched heavily. Specifically, protocols are now attempting to avoid the use of steroids and replacing tacrolimus with sirolimus. Steroids have significant cardiovascular side effects, resulting in nearly half transplant loss related to cardiovascular and infectious complications. Long-term use of tacrolimus results in nephrotoxicity, diabetes, hypertension, infection, and neoplasia.<sup>58</sup> However, it also has been shown to facilitate nerve regeneration and therefore has some benefit in VCA of the hand. This effect is applied to nerve transection with primary repair as well as grafts.<sup>59–61</sup> In an attempt to decrease systemic immunosuppression and focus on the antigenic nature of skin, topical steroids and tacrolimus have also been trialed.<sup>7</sup>

Moreover, novel approaches have been applied to adapt the immune system to tolerate the coexistence of donor and recipient immune cells through chimerism.<sup>62,63</sup> Donor bone marrow cells are infused into the recipient during induction therapy to develop tolerance of donor antigens.<sup>64–68</sup> Tolerance may be sufficiently achieved by only a few (1%) circulating donor lymphocytes. This area of research has been developed at the University of Pittsburgh, and early results suggest decreased immunosuppressive requirements with successful graft take.<sup>69</sup>

Data from the IRHCTT show that 85% of hand transplant recipients experience one or more episodes of acute rejection.<sup>6</sup> The clinical presentation includes erythematous maculopapular rash, hair loss, and desquamation. Close monitoring of skin changes is important to ensure there are no early signs of rejection. Similar to solid organ transplantation, acute rejection that is biopsied may show lymphocytic infiltrate. Chronic rejection is not well visualized histologically, but it is thought to cause intimal hyperplasia.<sup>7</sup>

## Ideal hand VCA unit

Successful hand VCA relies on the collaboration, financial support, and commitment by health care workers and the patient. The ideal hand VCA center would be established in an academic center where a solid organ transplant unit already exists. This is important since many of the ethical implications hopefully would have been addressed with the assistance of an ethicist and the details in transplant planning are already established. Supportive administration facilitates the coordination and open communication of all services involved. The necessary lifelong immunosuppressive drugs are extraordinarily expensive for patients. Therefore,

a commitment to drug coverage by the institution needs to be established to minimize this barrier and the catastrophic complication of rejection. Moreover, multiple disciplines are required for the success of such a procedure, and collaboration between all teams is crucial. The surgical team for the transplant should include both orthopedic and plastic surgeons. Other perioperative disciplines involved include immunology, psychiatry, infectious diseases, internal medicine, psychiatry, dermatology, neurology, hematology, and anesthesia. Successful VCA hand transplant is dependent on the postoperative rehabilitation. Therefore, an on-site occupational therapist and physiotherapist are important to streamline this essential therapy. Lastly, the center should have adequate psychological and social support for patients as this surgery carries great psychosocial impact.

## Summary

Hand transplantation is an emerging field in plastic, orthopedic, and transplant surgery that has become increasingly more popular and common in the last decade. The improvement in function and quality of life it offers is heavily recognized. The once considered “experimental” procedure is no longer the case. However, a newer debate of whether this procedure should be the standard of care for hand amputees is becoming popularized. This review highlights some of the challenges that hand transplantation faces including patient selection, effect on quality of life, financial burden, functional outcomes, and immunosuppressive complications. Before hand VCA becomes as widely accepted as solid organ transplantation has, these factors all need to be carefully studied and analyzed heavily. Hand transplantation in the appropriate candidate and settings may be a very suitable treatment option. Nevertheless, the sparse long-term data available, especially with respect to the immunosuppressive complications, still pose a significant barrier.

## Disclosure

The authors report no conflicts of interest in this work.

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