Hand Transplantation
A Review

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Abstract
Hand transplantation is a treatment option for complex injuries that leave patients with structural, functional, and aesthetic deficits that cannot be addressed by other means. It is a form of vascularized composite tissue allotransplantation (CTA). CTA is the highest rung the reconstructive ladder due to its complex technical and immunologic challenges. Despite completion of the first successful hand transplant in 1999, our understanding of hand transplantation is still evolving. Ongoing research is needed to improve functional outcomes and decrease the morbidity associated with long-term immunosuppression. This review will discuss the current protocols for upper extremity donation, transplant receipt, surgical technique, postoperative rehabilitation and immunosuppression, nerve regeneration, functional outcomes, ethical issues, and financial considerations.

Hand transplantation is a form of composite tissue allotransplantation (CTA). CTA is defined as the transfer of vascularized or non-vascularized heterogeneous tissues (skin, fat, muscle, nerve, bone, etc.) with different antigenicities from one person to another. It is a treatment option for complex injuries that leave patients with structural, functional, and aesthetic deficits that cannot be addressed by other means. CTA represents the highest rung of the reconstructive ladder because of the complex technical and immunologic aspects associated with it.

CTA was born out of necessity during World War II when patients with severe burn injuries did not have enough healthy skin available to graft burn defects and allograft skin was used. Scientific study of this practice by British biologist Dr. Peter Medawar and his colleagues elucidated the immunologic mechanism of allograft skin rejection in a series of Nobel Prize winning experiments, thereby birthing the field of transplant immunology and paving the way for all types of surgical transplantation. Dr. Earle Peacock, former Chair of Plastic Surgery at University of North Carolina at Chapel Hill, built on Medawar’s work and conducted important basic science research on allotransplantation. He is credited with coining the term composite tissue allotransplantation and performing the first non-vascularized CTA of a finger flexor tendon apparatus in 1957, 3 years after the first solid organ transplant. CTA has continued to develop with advances in immunology and surgical technique. To date, over 100 procedures have been performed worldwide.

Hand transplantation is the most common CTA with 70 reported cases since 1998.

History of Hand Transplantation
In 1964, the first hand transplant was performed by Dr. Gilbert in Ecuador. The patient was a bilateral upper extremity amputee that received a single hand transplant. Postoperatively, he was given azathioprine (a purine synthesis inhibitor) and prednisone for immunosuppression. The patient experienced acute rejection and underwent amputation 3 weeks post-transplant. This clinical failure in conjunction with experimental failures of skin bearing allografts lead to the belief that skin is prohibitively immunogenic and not amenable to allotransplantation. Scientific focus shifted towards the development of effective immunosuppressive regimens and improvement of solid organ transplant.

Several decades later (1996), Benhaim and colleagues published on successful immunosuppression after CTA in a rat model using cyclosporine (a fungal derived compound that decreases T cell activity) and mycophenolate mofetil.
(reversible purine synthesis inhibitor). These findings were subsequently confirmed in other studies. In 1998, the first modern hand transplant was performed by Dr. Jean-Michel Dubernard and colleagues in Lyon, France. The patient was a 48-year-old male who had sustained a traumatic circular saw amputation at the mid-forearm level in 1984 with immediate replantation and subsequent amputation of the nonfunctional limb in 1989. The donor was a 41-year-old brain dead beating heart donor. The surgery was a technical success, but the patient was non-compliant with his postoperative immunosuppression and rehabilitation regimen and elected to have his transplanted hand amputated in 2001. This initial procedure was followed a second hand transplant in 1999 by Dr. Warren Breidenbach and his team at the University of Louisville. The patient was a 37-year-old male who lost part of his dominant forearm and whole hand in a fireworks accident. He currently has the longest surviving transplant, now 13 years postop, with a functional result (hot and cold sensation, ability to distinguish textures, writing, tying shoes, phone use, opening doors, and throwing and catching a ball) and no major immunosuppressive complications.

Through 2011, 80 hand transplants have been completed in 13 countries (Table 1). Currently, there are 19 hand transplant centers registered with the International Registry of the Hand and Composite Tissue Transplantation Society. Epidemiology of Limb Loss

Published data on limb loss is relatively scarce, and most papers focus on the lower extremity. The quality of the publications is variable with incidence of limb loss differing significantly by geographic region. Yet, these publications are consistent in regards to cause of amputation. Amputations in young patient are usually secondary to congenital anomaly, trauma, or infection, while amputations in older patients are more likely to be secondary to medication toxicity or peripheral vascular disease.

Several papers have specifically addressed the upper extremity. Ziegler-Graham and coworkers estimated that 1.6 million Americans were living with limb loss in 2005; 540,000 of these were people with upper limb loss, 34,000 of which were classified as major loss (amputation around the level of the elbow). Østlie and associates estimated the prevalence of upper extremity loss at or proximal to the radiocarpal joint to be 11.6 per 100,000 in Norwegian adults. Roche reviewed 93 amputations in British children over the past 80 years and found 19% involved the upper extremity.

**Table 1** Hand Transplant Totals by Country Through 2011

<table>
<thead>
<tr>
<th>Year</th>
<th>China</th>
<th>France</th>
<th>Austria</th>
<th>Italy</th>
<th>Poland</th>
<th>USA</th>
<th>Belgium</th>
<th>Spain</th>
<th>Germany</th>
<th>Turkey</th>
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</tr>
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<td>5</td>
<td>8</td>
<td>24</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>80</td>
</tr>
</tbody>
</table>

Patient Eligibility for Receipt of Hand Transplant

Given that hand transplantation is an elective procedure, proper patient selection and preoperative education has been emphasized to maximize clinical success and secondarily to provide the scientific community with the best chance of gaining information necessary to further the field. There are no definitive indications for receipt of a hand transplant. Some broadly accepted reasons for transplant are bilateral or dominant hand amputations, amputations distal to mid-forearm, and sharp amputations.
amputations are preferred as there is less distance needed for nerve regeneration to target muscles.22,23

Holistic evaluation (medical, psychological, and social) similar to the process used for screening solid organ recipients is used to evaluate potential hand transplant candidates.24 Inclusion and exclusion criteria used by several USA hand transplant centers are outlined in Table 2.21,25-27

Several studies have shown that psychological and social variables are important predictors of who is likely to follow postoperative medication regimens in solid organ transplant.28-30 Preoperative medication non-adherence, lack of social support, higher education, and lower conscientiousness were all predictors of immunosuppressant non-adherence at one year.30 An unstable domestic relationship was a predictor of graft loss 6 to 12 months post-transplant.30

Proper patient selection is even more critical in hand transplantation than solid organ transplantation because receipts have to maintain a rigorous hand rehabilitation regimen (minimum: 3 to 6 hours per day, 5 days per week, for 3 to 6 months) in addition to immunosuppressive therapy.21,26

If a patient meets inclusion criteria, additional information (gender, handedness, type and level of injury, date of injury, complete medical and surgical history, photos of limb, and rehabilitation and prosthesis history) is requested prior to a face-to-face visit with the transplant team.21,25-27 During the initial visit, there is a discussion of previous operations, pertinent history, risks and benefits of transplantation, and patient expectations.21,25-27 Once this visit is completed and all parties express interest in pursuing a possible transplant, an IRB approved evaluation begins (Table 3).21,25-27 After the evaluation is complete, the transplant committee makes a final decision regarding patient eligibility for the transplant list.21,25-27

### Donor Allograft

Upper extremity composite grafts are considered vascularized tissues and not solid organs; therefore, government oversight is different than that of solid organs.31-33 The FDA, Human Resources and Services Administration, United Network of Organ Sharing (UNOS), Organ Procurement Transplant Network (OPTN), and 58 Organ Procurement Organizations (OPOs) oversee solid organ donation.34 The FDA oversees tissue safety.34 UNOS ensures fair, medically effective use of donated organs, and OPOs provide regional procurement and distribution services to donor hospitals and transplant centers, including consent for donation, donor infection screening, coordination of procurement teams in

### Table 2 Inclusion and Exclusion Criteria for Potential Hand Transplant Recipients Used by Several USA Hand Transplant Centers

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 18-69</td>
<td>Age &lt; 18 or &gt; 69</td>
</tr>
<tr>
<td>No medical condition with negative immunologic, surgical, or functional implications</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>No psychosocial issues</td>
<td>Malignancy</td>
</tr>
<tr>
<td>No cancer in past 10 years</td>
<td>Immune condition</td>
</tr>
<tr>
<td>No HIV</td>
<td>Coagulopathies</td>
</tr>
<tr>
<td>Willingness to consent to cell collection/storage/bone marrow infusion</td>
<td>Hematologic disease</td>
</tr>
<tr>
<td>Greater than 6 months since extremity injury with attempt at rehabilitation</td>
<td>Connective tissue or vascular disease</td>
</tr>
</tbody>
</table>

### Table 3 Hand Transplant Recipient Preoperative Evaluation

<table>
<thead>
<tr>
<th>Physical exam</th>
<th>Photographs of both limbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologic evaluation</td>
<td></td>
</tr>
<tr>
<td>X-rays of both extremities, diagnostic angiography, US venous mapping, MRI of residual limb, chest x-ray, and sinus x-rays</td>
<td></td>
</tr>
<tr>
<td>Laboratory evaluation</td>
<td></td>
</tr>
<tr>
<td>EKG, echo, PFTs for age/patient-appropriate cardiac/pulmonary evaluation</td>
<td></td>
</tr>
<tr>
<td>Age-appropriate cancer screening</td>
<td></td>
</tr>
<tr>
<td>Consultations as needed</td>
<td></td>
</tr>
<tr>
<td>Formal psychological evaluation</td>
<td></td>
</tr>
<tr>
<td>Functional evaluation</td>
<td></td>
</tr>
<tr>
<td>EMG/Nev, visit with a hand therapist, baseline DASH and SF-36, and brain MRI to determine baseline motor/sensory activity in cortical region responsible for affected extremity</td>
<td></td>
</tr>
<tr>
<td>Social evaluation with transplant social worker</td>
<td></td>
</tr>
</tbody>
</table>
OR, management of donor after death, and packaging and labeling of organs. \(^{34}\) Upper extremity donation is only federally regulated for tissue safety.\(^{31}\) Hand transplant centers have to create their own procurement policies, unofficially establish relationships with and educational in-services for local and regional OPOs and donor hospitals, and establish effective communication system with OPOs.\(^{34}\) It is widely accepted that solid organ donation takes priority, and a separate consent is needed for upper extremity donation.\(^{34}\) OPO members need to be educated on discussing loss of a visible part of the donor and explain that confidentiality of the donor may not be maintained despite best efforts to do so given the presence of fingerprints or other identifying features.\(^{34}\)

There is debate about the tissue designation of upper extremity composite grafts because they share significant similarities to solid organ donation, including procurement from beating heart donors to limit cold ischemia and time constraints to assess donor suitability, communicate with a potential recipient, and coordinate with procurement teams.\(^{34-36}\) There are concerns that lack of unified oversight may lead to graft loss, misallocation, inability to effectively track outcomes, and liability issues for all those involved.\(^{34,37}\)

There are no universally accepted inclusion or exclusion criteria for upper extremity donation. Table 4 lists the criteria used by the University of California at Los Angeles hand transplant program.\(^{23,34}\) In addition, numerous hand measurements (length of hand from wrist to crease to tip of middle finger; circumference of thumb, index finger, middle finger, and wrist; length of index finger; length from first web space to middle finger; length of thumb from the first web space; hand circumference at Kaplan’s cardinal line; length of Kaplan’s cardinal line; and ulnar length from the olecranon process to the ulnar styloid) are employed to compare potential donors and recipients.\(^{34}\) Many other programs follow a similar protocol.

Table 4  UCLA Hand Transplant Program Inclusion and Exclusion Criteria for Upper Extremity Donation

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor sex same as recipient</td>
<td>Absolute</td>
</tr>
<tr>
<td>Donor age similar to recipient</td>
<td>Risk of infection transmission as defined by CDC</td>
</tr>
<tr>
<td>Donor blood type compatible with recipient</td>
<td>HIV</td>
</tr>
<tr>
<td>Donor skin color and hair pattern similar to recipient</td>
<td>Hepatitis B/C</td>
</tr>
<tr>
<td>No identifying marks on donor limb</td>
<td>Current malignancy</td>
</tr>
<tr>
<td>Same EBV and CMV status of both donor and recipient</td>
<td>Limb paralysis</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
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<tr>
<td></td>
<td>RA or significant osteoarthritis</td>
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<tr>
<td></td>
<td>Connective tissue disease</td>
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<tr>
<td>Relative</td>
<td></td>
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<tr>
<td>Viral encephalitis</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled HTN</td>
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<tr>
<td>Vasculopathy</td>
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</tbody>
</table>

Once a donor has been confirmed, it is important to maintain perfusion of the limb and avoid placement of arterial or venous catheters.\(^{34}\) Harvest of life saving organs should take priority, but if possible, the limb should be harvested prior to compromising peripheral perfusion.\(^{38}\) Protocol for harvest sequence should be established with the OPO and discussed with other procurement teams prior to initiation of surgery.\(^{34}\) Harvest of the upper extremity should be completed under tourniquet with target time of 30 to 40 minutes.\(^{23,27,34}\) Fish mouth skin incisions are made approximately 3 cm above the elbow, and the vessels are identified and ligated.\(^{23,27,34}\) A brachial artery cannula should be placed, and the composite graft should be immediately perfused with University of Wisconsin perfusion solution.\(^{23,27,34}\) The remainder of the limb is then transected and removed from the donor, wrapped in moist gauze, placed in a triple organ transplant transport bag, and then bathed in an ice water solution.\(^{23,27,34}\) The graft should be continuously perfused through the brachial artery cannula during transport.\(^{23,27,34}\) The donor site should be sutured, and a prosthetic limb should be applied if requested by donor family.\(^{23,27,34}\)

Transplant Surgical Technique

Transplant surgical technique is adapted from the replantation technique introduced by Dr. Malt in his 1962 publication “Replantation of Severed Arms.”\(^{39,40}\) The operation is completed under tourniquet using general anesthesia with regional block for vasodilatation and pain control.\(^{14,15,41}\) Optimally, two teams are used for a single transplant and four teams are used for a double transplant.\(^{42,43}\) Ideally, the recipient and donor teams are in the same room for coordination.\(^{42,43}\)

Patient stump preparation can begin once the donor limb is procured and the logistics of travel are settled.\(^{23}\) Yet, if there is any concern about the quality of the allograft, recipient preparation should be delayed until the donor limb arrives
at the transplant site. The recipient undergoes preoperative vein mapping in the OR holding area.\textsuperscript{23} In the operating room, mid-lateral incisions are made and subcutaneous dissection is performed with care to preserve superficial veins.\textsuperscript{21} Each structure is tagged using a piece of Esmarch labeled with indelible ink using 2-0 silk.

Dorsal/volar mid-axial incisions with long skin flaps are utilized to expose the graft.\textsuperscript{23} The volar incision is extended to allow for release of the carpal tunnel. Subcutaneous dissection from proximal to distal is completed on iced sponges to minimize warm ischemia time. All structures are left longer than the anticipated need. Each structure is individually tagged with a piece of Esmarch bandage labeled with indelible ink using 2-0 silk. The donor is provisionally plated.

The typical surgical sequence for a mid-forearm transplant will be described. This is modified with more proximal amputations, as muscle bulk does not tolerate prolonged ischemia well.\textsuperscript{23} Hand transplant sequence differs from that of hand replantation to allow for restoration of bone length and relative tendon tension as well as completion of dorsal vein and nerve anastomosis with group fascicular repair in a bloodless field.\textsuperscript{23} For osteosynthesis, the goals are length, alignment, and rotation. Perpendicular osteotomies are used to allow for maximal compression. Tendon repairs can be completed by the surgeon’s method of choice. A Pulvertaft weave is used by many because it provides a strong repair amenable to early motion.\textsuperscript{44} Wrist extensors are repaired first and then thumb and digit extensors. The digits should extend with 20\textdegree{} to 30\textdegree{} of wrist flexion (tenodesis effect). For both extensors and flexors, proximal muscle repairs are usually limited to epimysium and perimysium. Tendon transfers are completed as needed. Vein repair is end to end. Two to four dorsal veins should be anastomosed. During vessel repair, it is important to avoid iatrogenic damage. Single artery repair can be done first if it is difficult to identify veins. An implantable Doppler is used around one vein. Nerve repair includes median (with palmar cutaneous if possible), ulnar (with dorsal sensory if possible), and radial (or PIN and radial sensory) using microscope. Distal repairs allow for more precise, group fascicular repair. Proximal repairs can be completed with epineural sutures. Radial and ulnar arteries are anastomosed using end-to-end repair distal to mid-forearm and end-to-side repair proximal to mid-forearm to prevent disrupting branches to muscle bellies. One artery is repaired to complete initial revascularization, and then the graft is warmed with sterile saline to decrease vasospasm. Radial artery injury is common, and angiogram, embolectomy, TPA, or bypass may be necessary. Initial revascularization is followed by anastomosis of a second artery and additional veins with repair of the flexor tendons to restore a normal resting finger cascade. Skin flaps are then trimmed, drains are placed, and flaps are inset. Full thickness skin grafts from the donor are used if necessary. The four flap interposing incision allows versatility and maximal exposure without a circumferential scar contracture.\textsuperscript{23} A non-constrictive dressing and splint are placed. The composite graft is monitored with an implantable Doppler and pulse oximeters on a finger from each hand for comparison.

**Transplant Immunology**

Once the technical aspects of the surgery are completed, the biology of transplantation must be addressed.

The immune system has two pathways of responding to foreign antigen.\textsuperscript{45} The innate immune response includes physical barriers (skin, mucous membranes) and cells (macrophages, neutrophils, natural killer cells) present from birth that immediately kill cells presenting foreign antigen. They present antigen bound to major histocompatibility (MHC) molecules to initiate an acquired response. The innate response is consistent and not dependent on previous antigen exposure (priming). It can also be initiated by complement. The acquired or adaptive immune response is a learned, specific elimination of foreign antigen that is remembered and amplified with repeated exposure to specific antigen presented with self-MHC. It is mediated by B and T cells. CD4+ T cells help B cells produce antibody. CD8+ T cells kill cells with foreign antigen.

After transplant, there are two existing cell populations: those of donor and those of the recipient. Portions of each of these cell populations are immunologically active.\textsuperscript{45,46} These immunologically active cells recognize the presence of foreign antigen (either that of the donor or the recipient), thereby activating innate and adaptive immune responses.\textsuperscript{45,46} This can lead to destructive processes, such as graft versus host and host versus graft reactions.\textsuperscript{45,46}

Immunosuppression is required to address this potentially catastrophic situation.

**Immunosuppression**

Immunosuppressant medications modulate various aspects of the immune response. They are generally grouped as induction agents (medications that deplete T and B cells or modulate cellular/antibody responses at the time of initial antigen presentation after transplantation), calcineurin inhibitors (CNI), co-stimulatory molecule blockers, antimetabolites, and mammalian target of rapamycin (mTOR) inhibitors.\textsuperscript{45}

There is no standard immunosuppression protocol for hand transplantation.\textsuperscript{45} Triple-drug therapy, similar to that used after a solid organ transplant (CNI, anti-proliferative agent, and prednisone), is common.\textsuperscript{45} Tacrolimus (CNI) is widely used.\textsuperscript{45} It enhances nerve regeneration but causes nephrotoxicity, diabetes, HTN, and post-transplant lymphoproliferative disorder.\textsuperscript{47} Sirolimus (mTOR inhibitor) can be used instead of tacrolimus to limit renal toxicity, improve glycemic control, and lessen neurotoxicity.\textsuperscript{26} Mycophenolate mofetil (MMF, antimetabolite that prevents synthesis of nucleotides needed for lymphocyte proliferation) is increasing in use.\textsuperscript{48} It causes bone marrow suppression and GI side
effects. Steroid use varies.\textsuperscript{45} Induction (lymphodepleting) agents are replacing steroids because of the cardiovascular morbidity (diabetes, HTN) and infection risk associated with long-term steroid use.\textsuperscript{8,26,44}

Long-term maintenance varies.\textsuperscript{45} It is typically a minimum of two agents. Petruzzo and colleagues reported the following breakdown of current regimens in use: 21.7% using steroids and tacrolimus; 8.7% switched to sirolimus; 8.7% on low-dose Tacrolimus, steroids, and everolimus; 4.3% on sirolimus and MMF; and 13% using no steroids.\textsuperscript{49} There is concern with weaning maintenance therapy postoperatively as this may lead to rejection.\textsuperscript{26,45} The first two Louisville patients received basiliximab induction and triple drug maintenance (tacrolimus/sirolimus, MMF, steroids) and have long-term graft function with no rejection (9 to 11 years).\textsuperscript{17} Steroid use was weaned in one patient 8 years postoperatively.\textsuperscript{17} The third Louisville patient received alemtuzumab induction and tacrolimus/MMF maintenance without issue until it was stopped when a mantle cell lymphoma was diagnosed.\textsuperscript{17} Subsequently, the patient experienced acute rejection.\textsuperscript{17} The fourth Louisville patient received the same therapy as third patient, but MMF was decreased 50% by 9 months; the patient experienced chronic rejection, and the graft was subsequently amputated due to vascular insufficiency.\textsuperscript{17}

**Chimerism**

The post-transplant goal is to create a chimeric immune system (coexistence of donor and recipient immune cells), thereby inducing tolerance and limiting rejection.\textsuperscript{50,51} There needs to be existence of approximately 1% of donor immune precursor cells in the recipient to induce tolerance.\textsuperscript{50} Chimerism may be promoted in hand transplant patients by giving the recipient donor bone marrow or via the production of immune precursor cells in vascularized donor bone marrow.\textsuperscript{6,52} The University of Pittsburgh uses alemtuzumab induction and tacrolimus maintenance after donor bone marrow infusion.\textsuperscript{53} The presence of chimerism decreases the need for postoperative immunosuppression.\textsuperscript{51} This has been done successfully in Pittsburgh without any graft loss.\textsuperscript{53}

**Transplant Rejection**

Despite immunosuppressive efforts, rejection can still occur. Transplant rejection occurs when a recipient’s immune system attacks and attempts to destroy transplanted tissue. It can be classified into acute and chronic rejection. The difficulty with preventing rejection in composite tissue allotransplantation, especially in a complex graft such as the upper extremity, is the presence of multiple tissues with different antigenicities.\textsuperscript{8,16,54,55} The relative antigenicity of tissues is skin > muscle > bone > cartilage > nerve.\textsuperscript{54,56-58}

**Acute Rejection**

Acute rejection is usually a cell-mediated response (predominantly lymphocytic) but may be accompanied by antibody-mediated rejection (AMR).\textsuperscript{59} It is reversible with an increase in immunosuppression or antibody treatment.\textsuperscript{59} Cellular rejection of hand transplants is focused in the skin.\textsuperscript{60-62} It is the site of initial rejection and has the most cellular infiltrate of all the tissues in established rejection.\textsuperscript{16,63} The skin is the most antigenic due to an increased concentration of local immune cells and tissue specific antigens.\textsuperscript{50-62} Experimentally, tolerance to all CTA tissues except skin has been induced.\textsuperscript{64} This is referred to as split tolerance.\textsuperscript{59} Acute rejection usually presents early in the post-transplant period but can also occur in a delayed fashion.\textsuperscript{59} The typical presentation is a local or diffuse erythematous or maculopapular rash on the graft.\textsuperscript{59} There can be associated edema, vesciculation, desquamation, ulceration, and necrosis.\textsuperscript{59} Atypical presentation is localized to the palms and nails.\textsuperscript{55}

The incidence of one episode of acute rejection is 85%, and 56% of recipients experience multiple episodes of rejection.\textsuperscript{8} This is significantly higher than solid organ transplant (10% in kidney in first year) and is thought to be secondary to ease of surveillance.\textsuperscript{66}

Biopsy is the gold standard for diagnosis of acute rejection.\textsuperscript{59} The Banff Working Classification has been developed for scoring, grading, and reporting acute rejection in CTA.\textsuperscript{57} Cell mediated rejection is characterized by a lymphohistiocytic (T cell predominant) and eosinophilic infiltrate that starts in the dermal vasculature, proceeds to dermal or epidermal junction, causes dermal or epidermal separation, and finally results in irreversible epidermal necrosis.\textsuperscript{59} Antibody mediated rejection is characterized by endothelial cell activation, leukocyte margination, microvascular injury, and subsequent tissue destruction and fibrosis.\textsuperscript{59} This is identified via immunohistochemical staining for C4d (degradation product of activated complement factor C4, a classic complement factor activated by binding of antibodies to target molecules, thereby an indirect marker of antibody response, evidence of graft injury, and presence of donor specific antibody [may be anti-HLA specific]).\textsuperscript{59,68-70}

Currently, the relationship between clinical and histopathologic acute rejection is not understood (i.e., there is not a direct correlation between the two), and each patient should be evaluated for acute rejection if there are concerns signs or symptoms.\textsuperscript{59}

**Chronic Rejection**

Chronic rejection is long-term loss of graft function due to damage from persistent immunologic response to graft.\textsuperscript{59} The factors contributing to chronic rejection are thought to be similar to solid organ transplant.\textsuperscript{71} Immunologic factors include timing of acute rejection, severe or repetitive humoral acute rejection, greater HLA mismatch, higher panel reactive antibodies of recipient, CMV positive donor to CMV negative recipient, steroid resistant acute rejection, and C4d and anti-donor antibodies.\textsuperscript{71} Non-immunologic factors include older donor, unstable donor, donor atherosclerosis, cadaver donor, prolonged cold ischemia, recipient comorbidities
of immunosuppressive treatments. The transplant literature has shown an increased risk of malignancy, up to 3 to 5 times that of the general population in renal transplant recipients, only one basal cell carcinoma has been reported in hand transplantation recipients.

**Graft Loss**

In the hand transplantation experience, six hands have been amputated in the USA and Europe postoperatively. One was the result of an acute postoperative thrombosis, one from a bacterial infection within the first 2 months postoperatively, and the others secondary to rejection. Seven hands have required postoperative amputation in China; all believed to be due to the lack of immunosuppressive treatment or medication non-adherence.

**Postoperative Rehabilitation**

The goal of postoperative rehabilitation is to improve function, quality of life, and self-esteem of transplant patient. There is no standard rehabilitation protocol; each is individualized to the particular patient. Rehabilitation cycles are employed (assessment, assignment, intervention, evaluation). Important principals include a consistent, well-trained team of therapists (including physical therapists, occupational therapists, and hand therapists), starting therapy as early as possible (early protective motion to decrease finger swelling, prevent ligament and capsular contractures, and maintain flexor and extensor balance), sensory reeducation to help recreate and organize the sensorimotor cortex projection of the hand, desensitization of hypersensitive areas, muscle strength, dexterity, consistent use of standardized measures of objective [including imaging, clinical tests (goniometer, dynamometer, pinch gauge, etc.), test batteries to evaluate strength, sensibility, dexterity, and motion] and subjective (symptoms, disability, handicap) hand and upper extremity function (DASH, Carroll test, Action Research)

<table>
<thead>
<tr>
<th>Time Post Hand Transplant</th>
<th>Rehabilitation Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 Weeks</td>
<td>Static splinting, positioning to control edema, active assisted motion of shoulder and elbow, and passive mobilization of wrist and hand from 2 weeks on.</td>
</tr>
<tr>
<td>3-6 Weeks</td>
<td>Continued static splinting with modification, scar management and compressive dressings, progressive passive flexion/extension of wrist starting at 4 weeks, active assisted flexion/extension of fingers starting at 5 weeks.</td>
</tr>
<tr>
<td>6-8 Weeks</td>
<td>Continued active movement of wrist and fingers, gripping exercises, use of resting splint at night and for periods during the day, possible introduction of a static wrist splint with fingers free.</td>
</tr>
<tr>
<td>8-12 Weeks</td>
<td>Tendon gliding exercise, focus on flexor-extensor balance, electrotherapy during eighth week to strengthen extrinsic muscles of forearm.</td>
</tr>
<tr>
<td>3-6 Months</td>
<td>Wrist stability and function, integration of transplanted hand into daily activities using aids as necessary.</td>
</tr>
<tr>
<td>6-12 Months</td>
<td>Focus on functional deficits and patient specific needs.</td>
</tr>
<tr>
<td>2 Years</td>
<td>Therapy intensity is decreased. Focus on upper extremity positioning, intrinsic training, and maintaining and reestablishing therapy goals for the patient to work on independently.</td>
</tr>
<tr>
<td>3 Years</td>
<td>Strengthening.</td>
</tr>
</tbody>
</table>
Nerve Regeneration and Cortical Reintegration

Nerve Regeneration

Successful peripheral nerve regeneration is essential to regaining function in hand allografts. The timing of its progress helps dictate functional improvement.

Peripheral nerve recovery after injury is well understood. Wallerian degeneration occurs in the area of injury clearing the way for nerve regeneration. Injured axons and macrophages release cytokines that direct Schwann cells to change from a myelinating function to a proliferative function. These Schwann cells (SCs) line up along the basement membranes of endoneurial tubes forming bands of Bünger. These bands support axonal regeneration. Injured axons form growth cones that turn into axons. With help from the axon cell body, these axons grow at 1 mm per day in humans to reach target neuromuscular junctions. In segmental nerve loss, nerve autograft can be interposed to allow this process to occur.

Nerve regeneration in hand transplantation is similar to interposition allograft with two major differences. The first is that SC migration only occurs in an antegrade fashion. This slows the process of regeneration and raises concerns about the capability of donor SCs to fully populate the nerve graft. Host SCs eventually switch from their post-injury proliferative state to their resting myelinating state or may even die, thereby hindering the regeneration process. This process is not well understood. Motor recovery seems to slow significantly at 1 year. This may be related to atrophic and fibrotic changes that occur in chronically denervated muscle. Sensory recovery appears to persist for longer.

Secondly, much higher doses of immunosuppressant are needed to prevent acute rejection given the composite nature of the hand allograft, thereby inhibiting subacute rejection episodes needed to kill donor SCs and stimulate migration of host SCs into the graft. This may lead to the persistence of a large population of donor SCs that may be a target of late rejection, leading to destruction of the nerves in the graft, eventually leaving the hand nonfunctional.

Surgically, several things can be done to enhance nerve regeneration. Proximally, the ulnar nerve is sensory-motor-sensory from radial to ulnar. Approximately 10 cm proximal to the wrist crease, the dorsal sensory branch separates, leaving a sensory component radially and the motor component ulnarly. The deep motor branch can be found distally and traced proximally to find the confluence of the dorsal sensory branch. At this level, there is a plane between the motor and sensory fibers delineated by a vessel. The sensory component is approximately 60% of the nerve at this level. The median nerve at the wrist is 95% sensory at the wrist. The recurrent branch can be identified and traced proximally to help identify the motor component. The anterior interosseous nerve at the level of the pronator quadratus can be cut and anastomosed directly or via nerve graft to the recurrent motor branch to help improve motor recovery.

As mentioned previously, tacrolimus, an immunosuppressant commonly used in hand transplantation, has been shown in several studies to enhance nerve recovery after injury in both animal and human models. Doolabh and coworkers and Feng and associates have also shown that it enhances nerve regeneration when interposition allografts are used. The mechanism by which tacrolimus supports nerve regeneration is not understood, but it is known to increase the number of regenerative nerve fibers, stimulate motor neuron recovery, and stop neuronal death. It should be given to the recipient as soon as transplant is imminent and should be included in chronic immunosuppressive regimens to maximize nerve regeneration. There is still research to be done to understand how to utilize this drug effectively, especially in combination with other immunosuppressants.

Given the long time needed for distal nerve regeneration, some basic science research has focused on ways to enhance the regenerative environment months after transplant. SCs incubated with TGF-B have been shown to increase distal nerve regeneration capacity in nerve injury models. There is still research to do to understand how to utilize this drug effectively, especially in combination with other immunosuppressants.

Cortical Reintegration

In addition to peripheral nerve regeneration, cortical reintegration is imperative to achieving a functional result.

Penfield and Rasmussen originally described the homunculus concept in 1950 to explain motor and sensory cortical organization of the central sulcus of the brain. Specific areas of the brain were identified as being responsible for anatomically and functionally independent body regions. While this concept is still generally accepted, more recent functional MRI studies in animals and humans have shown that while distinct motor and sensory areas exist for large body parts, there is overlap of the cortical regions responsible for smaller body parts. Furthermore, neurons responsible for movement of a particular body part can be scattered in the cortex, allowing for coordination of movement with other body parts.

Numerous studies have shown that cortical reorganization occurs after amputation with decreased cortical representation of the missing part and growth in the cortical representations of adjacent body parts. Dubernard and colleagues published the results of functional MRI studies on a bilateral hand transplant recipient pre-
postoperatively. They showed that post-transplant cortical activation associated with movement of the transplanted hands migrated during the postoperative course towards the region that would be anticipated to be responsible for hand function. Furthermore, the size of the cortical area activated by hand motion grew with time. Additionally, they also found that the cortical representation of the elbow reorganized in parallel with the development of the hand cortical region, demonstrating the brain’s plasticity and the ability to remodel even after amputation and intervening absence of a body part. Brenneis and coworkers and Frey and associates confirmed these findings.

**Functional Outcomes**

The International Registry on Hand and Composite Tissue Transplantation (IRHTCTT) has prospectively collected information on every case since 2002 (31 patients with 1 year follow-up) and has its own functional scoring system (Hand Transplantation Score System, HTSS). The HTSS is a 100-point scale that evaluates six functional areas: appearance (15), sensibility (20), movement (20), psychological and social acceptance (15), daily activities and work status (15), patient satisfaction and general well-being (15). A total score of 81 to 100 points is graded as an excellent outcome, 61 to 80 as good, 31 to 60 as fair, and 0 to 30 as poor. It has been shown to have good test-retest reliability and responsiveness and correlation with the DASH. Utilization of this scoring system has shown excellent outcomes approximately 6 years post-transplant. DASH has also been shown to significantly improve with time post-transplant. All patients with surviving single or double hand transplants have developed protective sensibility (90% have tactile sensibility and 84% have discriminative sensation). Extrinsic and intrinsic function recovers over variable time frames depending on level of amputation (usually 9 to 15 months postoperatively, confirmed by EMG if possible). Seventy-five percent of hand-transplant recipients report improvements in quality of life. Most patients can perform daily activities (eating, writing, dressing, and driving) 1 year post-transplant and many return to work.

Interestingly, Jablonski and coworkers compared five replantation patients with a patient who received a midforearm hand transplant and found similar range of motion in both, better strength in replants, and better sensibility in the transplant patient.

**Ethical Considerations**

Because of the need for lifelong immunosuppression and the risk of graft loss, there has been significant discussion regarding the ethics of hand transplantation.

As mentioned previously, hand transplantation is a quality of life procedure, not a lifesaving procedure. Therefore, the risk of the procedure has to be measured against the quality of life benefit. Benefits include restoration of functional status and normal body image and elimination of phantom limb phenomenon. These benefits are similar to hand replantation, and both derive function better than that of a prosthesis. Risks include those secondary to surgery and immunosuppression (infection, malignancy, post-transplant lymphoproliferative disease, hypertension, diabetes, nephrotoxicity, Cushing syndrome, potential shortening of lifespan). Supporters of hand transplantation cite the fact that not all solid organ transplants are lifesaving (e.g., kidney and pancreas), but note that these transplants are widely accepted with management and minimization of the risks of immunosuppression. Additionally, there is potential benefit to the patient and society from the social reintegration that occurs because of skill accumulation post hand transplant.

Opponents of hand transplantation cite the principle of non-maleficence (also known as Primum non nocere or first do no harm) as a reason for prosthesis use to avoid potentially harming a patient with surgery and immunosuppression.

Proponents of hand transplantation cite the principle of double effect as justification for the procedure. Double effect states that if the intent of procedure is for good and the benefit outweighs the risk, then the procedure is justified and can be undertaken. The issue of contention is whether risk versus benefit is clearly defined in hand transplantation. This is becoming clearer as outcome data improves.

It is unclear who can determine what is best for the patient. Numerous questions loom: Can the physician decide who receives or does not receive a hand transplant? Is there enough information for a trained medical professional to make an objective decision about hand transplantation or educate potential recipients? Are potential recipients the only ones qualified to determine need for transplantation or are they biased by emotion or are lacking in the medical knowledge to be able to make an informed decision, especially regarding a procedure that some consider experimental? Interestingly, data shows that nonmedical individuals with and without experience with immunosuppression and with and without actual or potential need for a transplant (including hand transplant) perceive risk of transplantation similarly.

Finally, the transplanted limb is constantly in view and may be viewed as foreign, potentially leading to psychological rejection of transplant, as evidenced by experience with first transplant of modern era. Also, fingerprints are linked with identity and do not change significantly after transplantation, potentially causing issues for both the donor and his or her family and the recipient.

**Financial Considerations**

Given the relative infancy of hand transplantation, there is little data on the financial impact of this procedure. If it becomes more common, cost evaluation will be an important
consideration when comparing hand transplantation to other forms of treatment for upper extremity loss.

Chung and colleagues surveyed 100 medical students on their preferences of using a prosthesis, undergoing a single hand transplant, or undergoing a double hand transplant as compared to their baseline normal function (including risks of immunosuppression). This data as well as the value of direct and indirect operational costs (cost of operation, hospital stay, immunosuppression, treatment of immunosuppressive complications, and time off from work) were used to determine quality adjusted life years (QALYs). Increment cost-usefulness ratio (ICUR—measurement of additional cost per QALY) by using one treatment instead of another) was calculated and compared to a threshold of $50,000/ QALY (determined from kidney transplant data). They found: lifetime cost for a single or double hand transplant ranged from $528,000 to $530,000, lifetime cost for a single prosthesis is $20,000, lifetime cost of a double prosthesis is $41,000, and the ICUR for a double hand transplant is $318,961/QALY. They noted that their results may be limited by the fact that not all costs were taken into account (for example, postoperative rehabilitation) and that data generated from medical students for QALY determination may not be accurate. McGill and associates estimated the rehabilitation cost for a single hand transplant to be $53,336 (226 hours of therapy) and $63,360 (260 hours of therapy) for a double hand transplant.

Both of these studies showed hand transplantation to be more expensive than current treatment with upper extremity prostheses.

Conclusion

Despite the completion of the first successful hand transplant 14 years ago, our understanding of hand transplantation continues to evolve. Ongoing research is needed to improve functional outcomes and decrease the morbidity associated with long-term immunosuppression.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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