The 2020 Facial Transplantation Update: A 15-Year Compendium

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Summary: Over the past 15 years, landmark achievements have established facial transplantation (FT) as a feasible reconstructive option for otherwise irreparable craniofacial defects. However, as the field matures and long-term outcomes begin to emerge, FT teams around the world are now facing new challenges. Data for this review were identified by searches of the PubMed/MEDLINE database from inception through August 2020. All English-language articles pertaining to FT were included. Significant advances in candidate selection, technology, operative technique, posttransplant care, and immunosuppressive management have contributed to the tremendous expansion of the field, culminating in the execution in the past 3 years of 2 facial re-transplantations, and most recently the world’s first successful combined face and double hand transplant in August 2020. Despite these achievements, the allograft donor pool remains limited, with long wait times, requiring surgical experimentation with cross-sex FT. Immunosuppressive management has improved, but significant adverse events continue to be reported. Most recently, the COVID-19 pandemic has placed an unprecedented strain on the healthcare system, with various implications for the practice of reconstructive transplantation. In this article, we provide the most comprehensive and up-to-date FT review, highlighting fundamental lessons learned and recent advancements, while looking toward the challenges ahead. Over the past 15 years, extensive multidisciplinary efforts have been instrumental to the establishment of FT as a feasible reconstructive option. As novel challenges are beginning to emerge, continued collaborative and multispecialty research efforts are needed to further this field. (Plast Reconstr Surg Glob Open 2021;9:e3586; doi: 10.1097/GOX.0000000000003586; Published online 21 May 2021.)

INTRODUCTION

The field of facial transplantation (FT) has significantly evolved since the first patient was operated on in 2005.1 Important advancements include improvements in preoperative evaluation, surgical preparation, operative techniques, and postoperative management, allowing for refinement of outcomes. With 48 FTs described to date, the field has expanded tremendously. However, as new milestones are reached, new obstacles are emerging that FT teams must now overcome. Additionally, the COVID-19 pandemic is reshaping the healthcare system as a whole, requiring adaptations for the delivery of care to FT candidates and recipients. We herein aim to provide the most comprehensive and up-to-date FT review as of August 2020, reflecting on the key lessons learned through 15 years of worldwide experience, discussing the field’s most recent advances, and examining future directions and challenges.

METHODS

Data for this review were identified by searches of the PubMed/MEDLINE database from inception through August 2020. The search included the keywords and subject headings listed in Table 1. Title and abstract screening was performed independently by 2 reviewers, followed by full-text review. All articles pertaining to FT were included. Additionally, because the most recent FT cases performed over the past 3 years have not yet been described in the peer-reviewed literature, a separate search via Google was conducted using the same search terms, as indicated in Table 1. Studies in languages other than English, conference abstracts, and animal studies were excluded.

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Table 1. PubMed/MEDLINE Comprehensive Search Strategy for Articles on Facial Transplantation²

| PubMed/MEDLINE Terms                  |
|--------------------------------------|
| Search                               |
| "facial transplantation" [MeSH:no exp]|
| "facial transplant" [tw]              |
| "facial transplantation" [tw]        |
| "face transplantation" [tw]          |
| "facial transplantation" [tw]        |
| "face allotransplantation" [tw]       |
| "face vascularized composite allotransplantation" [tw] |
| "facial vascularized composite allograft" [tw] |
| "face alloplasty" [tw]                |
| "face allograft" [tw]                 |
| "face composite tissue alloplastation" [tw] |
| "facial composite tissue allograft" [tw] |
| "face allotransplantation" [tw]       |
| "facial allotransplantation" [tw]     |
| "facial vascularized composite allograft" [tw] |
| "face vascularized composite allograft" [tw] |
| "face alloplasty" [tw]                |
| "face allograft" [tw]                 |
| "facial allograft" [tw]               |
| "face composite tissue alloplastation" [tw] |
| "facial composite tissue allograft" [tw] |
| "face allotransplantation" [tw]       |
| "facial allotransplantation" [tw]     |

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PRE-TRANSPLANTATION CONSIDERATIONS

Candidate Selection and Work-up
Compatibility between donor and recipient is para-
mount for success in FT. Traditional considerations in
solid organ transplantation (SOT) involve immunologic
cross reactivity and viral serology. With FT, additional fac-
tors include matching of skin tone, hair color, and facial
structure. Histocompatibility is generally more difficult
to attain, as most FT candidates are typically profoundly
immunosensitized secondary to initial resuscitation with
blood products and skin grafting.³ Although crossmatch-
ing is traditionally performed with peripheral blood using
flow cytometry, a disproportionate rate of false negatives
may be observed in highly sensitized patients. As a result,
many vascularized composite allotransplantation (VCA)
centers have now adopted the use of donor lymph nodes
for tissue typing.⁴ Viral serology mismatch poses addi-
tional challenges, as seen with 1 patient who developed
monoclonal B-cell lymphoma following FT with Epstein-
Barr virus mismatch.⁵

Context of the initial injury and baseline functional
status must also be considered. To date, 3 patients with
acquired bilateral blindness have undergone successful
FT.⁶-⁹ Criticism against FT for blind individuals has focused on
the recipients’ inability to appreciate the extent of their
pre-transplantation injury and aesthetic improvements fol-
lowing FT, as well as inability to fully assess others’ percep-
tions of their pre- and post- FT appearance. Furthermore,
blindness can compromise adequate self-monitoring for
rejection. Still, as seen with aesthetic surgery, blind
patients may benefit from FT, as it allows for significant
improvement in motor and sensory function, improved
self-image and successful social reintegration.¹⁰-¹¹ Thus,
blindness on its own should not warrant exclusion from
consideration for FT, and an extensive caretaker consent
process should be implemented to assess FT candidates’
support system.⁹

Of the 48 documented FTs, 21 have been performed for
high-energy ballistic facial trauma, with several index
injuries explicitly described as self-inflicted.¹²-¹⁵ To date,
only 1 of these patients has died by suicide, in the context
of longstanding suicidal behavior, lack of social support,
and significant financial encumbrance.¹⁶ Nonetheless,
numerous reports have demonstrated a decrease in
depressive symptoms, improvement in quality of life, sense
of self, and social reintegration following FT. Ethical anal-
yses have suggested that self-inflicted injury alone should
not be an absolute contraindication for FT.¹⁷,¹⁸ Regardless
of documented psychiatric history, comprehensive and
longitudinal psychiatric evaluation is an imperative com-
ponent of FT candidate work-up and ongoing care. Mental
health should be reassessed at all visits to support patient
compliance, and ultimately reduce the risk of allograft
failure.

Donor Pool Expansion
The VCA donor pool is limited. Despite 40% of brain-
dead donors meeting initial screening criteria for VCA
donation, wait times for FT may exceed 2 years, reflect-
ing the potential to expand the VCA donor pool.¹⁹
Furthermore, authorization for VCA donation is often
difficult to navigate with families, although educational
intervention has been proved to significantly increase will-
ingness to donate.²⁰

Currently available patient-oriented educational mate-
rial on VCA is well above both the National Institutes
of Health and American Medical Association’s recom-
mended reading level.²¹ Recent efforts to expand the
donor pool include optimization of the readability of and
access to VCA educational materials, conceptualization of
a multimodal VCA donation campaign strategy, research
investigating donor-recipient sex-mismatched FT, and
nationwide partnership to expand the donor search
radius.²²-²⁴ Additional investigations have also shown that,
although organ procurement coordinators play a criti-
cal role in discussions surrounding VCA, there are sig-
nificant disparities in distribution practices of educational
materials. Future collaboration with organ procurement
organizations (OPO) will be paramount to mitigate these
disparities.²⁵

SURGICAL CONSIDERATIONS

The Current State of Facial Transplantation
Since the first partial myocutaneous FT in 2005, efforts
to push the boundaries of facial reconstruction have been
documented worldwide, including the execution of full
FT, immediate FT bypassing autologous reconstruction,
re-transplantation for allograft failure and combined face,
and double hand transplant (FT-DHT). To date, 48 FTs
have been performed on 46 recipients (Table 2).²⁶,²⁷,³⁰,³¹
The most common indications for FT are craniofacial
defects from ballistic trauma (43.7%), followed by ther-
mal, chemical, or electrical burn injuries (25.0%). In 1
instance, FT was successfully executed following the acute
phase of injury, before any autologous reconstructive pro-
cedures, with encouraging outcomes.²⁷ The first described
case in an African American recipient was executed as a
full rather than the initially planned partial FT, because

2
| Patient | Surgical Team          | Location, Date of Transplant | Recipient (Age, Gender) | Indication                        | Extent of Defect       | Allograft Type | Allograft Vascular Pedicle | Status (COD, TFT) | Acute Rejection | Chronic Rejection |
|---------|------------------------|------------------------------|-------------------------|----------------------------------|------------------------|----------------|--------------------------|-------------------|----------------|------------------|
| 1       | Devauchelle, Dubernard | Amiens, France, 11/2005      | 38, woman Animal attack | Cheek, nose, lips, chin          | Partial                | Facial artery  |                         | Deceased (malignancy, 11 years) | Yes             | Yes              |
| 2       | Guo                    | Xi’an, China, 04/2006        | 30, woman Animal attack | Cheek, nose, upper lip, maxilla, orbital wall, zygoma | Partial                | Maxillary artery |                         | Deceased (non-compliance, 27 months) | Yes             | No               |
| 3       | Lantieri               | Paris, France, 01/2007       | 29, woman NF            | Forehead, brows, eyelids, nose, lips, cheeks | Partial                | ECA            |                         | Alive             | Yes             | No               |
| 4       | Siemionow              | Cleveland, Ohio, 12/2008     | 45, woman Ballistic trauma | Lower eyelids, nose, upper lip, orbital floor, zygoma, maxilla | Partial                | Facial artery  |                         | Deceased (infection, 11 y and 7 mo) | Yes             | No               |
| 5       | Lantieri               | Paris, France, 05/2009       | 27, man Ballistic trauma | Nose, lips, maxilla, mandible    | Partial                | ECA            |                         | Alive             | Yes             | No               |
| 6       | Lantieri               | Paris, France, 04/2009       | 37, man Third degree burn | Forehead, nose, eyelids, ears, cheek, maxilla | Partial                | ECA            |                         | Deceased (sepsis, 2 mo) | Yes             | No               |
| 7       | Pomahac                | Boston, Mass, 04/2009        | 59, man Electrical burn | Lower eyelid, cheek, nose, lips, maxilla, zygoma | Partial                | ECA + facial artery | ECA                        | Alive             | Yes             | No               |
| 8       | Lantieri               | Paris, France, 08/2009       | 33, man Ballistic trauma | Cheek, nose, lips, maxilla, mandible | Partial                | ECA            |                         | Alive             | Yes             | No               |
| 9       | Cavadas                | Valencia, Spain, 08/2009     | 42, man ORN after malignancy | Lower lip, tongue, floor of mouth, mandible | Partial                | CCA            |                         | Deceased (malignancy) | Yes             | No               |
| 10      | Devauchelle, Dubernard | Amiens, France, 11/2009      | 27, man Ballistic trauma | Mandible, upper and lower lips, chin, perioral area | Partial                | —              |                         | Alive             | Yes             | Yes              |
| 11      | Gomez-Ga               | Seville, Spain, 01/2010      | 35, man NF              | Ear, nose, lips, maxilla, mandible | Partial                | CCA            |                         | Alive             | Yes             | No               |
| 12      | Barret                 | Barcelona, Spain, 03/2010    | 30, man Ballistic trauma | Eyelids, nose, lips, lacrimal apparatus, zygoma, maxilla, mandible | Full                  | ECA            |                         | Alive             | Yes             | No               |
| 13      | Lantieri               | Paris, France, 06/2010       | 35, man NF              | Eyelids, nose, lips, oral mucosa | Full                  | ECA            |                         | Alive             | Yes             | Yes              |
| 14      | Pomahac                | Boston, Mass., 05/2011       | 25, man Electrical burn | Forehead, eyelids, left eye, nasal bone, check, lips | Full                  | Linguofacial trunk |                         | Alive             | Yes             | Yes              |
| 15      | Lantieri               | Paris, France, 04/2011       | 45, man Ballistic trauma | Nose, mandible, maxilla          | Partial                | ECA            |                         | Alive             | Yes             | No               |
| 16      | Lantieri               | Paris, France, 04/2011       | 41, man Ballistic trauma | Nose, mandible, maxilla          | Partial                | ECA            |                         | Deceased (suicide, 36 mo) | Yes             | No               |
| 17      | Pomahac                | Boston, Mass., 04/2011       | 30, man Electrical burn | Forehead, eyelids, nasal bone, check, lips | Full                  | Facial artery + ECA | Facial artery + ECA | Alive             | Yes             | No               |
| 18      | Pomahac                | Boston, Mass., 05/2011       | 57, woman Animal attack | Forehead, eyelids, eyes, nasal bone, lips, maxilla, mandible | Full                  | Facial artery + ECA | Facial artery + ECA | Alive             | Yes             | No               |
| 19      | Blondeel               | Ghent, Belgium, 12/2011      | 54, man Ballistic trauma | Eyes, eyelid, cheek, nose, maxilla, mandible, lips | Full                  | ECA            |                         | Alive             | Yes             | No               |
| 20      | Ozkan                  | Ankara, Turkey, 01/2012      | 19, man Burn            | Forehead, nose, cheeks, lips     | Full                  | ECA            |                         | Alive             | Yes             | No               |
| 21      | Nasir                  | Ankara, Turkey, 02/2012      | 25, man Burn            | —                             | Full                  | —              |                         | Alive             | —               | —               |
| 22      | Ozmen                  | Ankara, Turkey, 03/2012      | 20, woman Ballistic trauma | Nose, upper lip, teeth, maxilla, mandible | Partial                | —              |                         | Alive             | —               | —               |
| 23      | Rodriguez              | Baltimore, Md, 05/2012       | 37, man Ballistic trauma | Forehead, eyelids, nose, cheek, lips, zygoma, maxilla, mandible | Full                  | ECA            |                         | Alive             | Yes             | No               |
| 24      | Ozkan                  | Ankara, Turkey, 05/2012      | 35, man Thermal burn     | Forehead, eyelids, nose, cheeks, lips | Full                  | ECA            |                         | Alive             | Yes             | No               |
| Patient | Surgical Team | Location, Date of Transplant | Recipient (Age, Gender) | Indication | Extent of Defect | Allograft Type | Allograft Vascular Pedicle | Status (COD, TFT) | Acute Rejection | Chronic Rejection |
|---------|---------------|-----------------------------|-------------------------|------------|-----------------|----------------|--------------------------|------------------|----------------|------------------|
| 25      | Devauchelle, Dubernard | Amiens, France, 09/2012 | woman, 25 | Vascular tumor | Lower eyelid, mandible, maxilla, tongue | Partial | — | Alive | Yes | No |
| 26      | Pomahac       | Boston, Mass., 02/2013     | woman, 44 | Chemical burn | Nose, lips, eyelids, forehead, cheek, ears, eyes, neck | Full | — | Alive | Yes | Yes |
| 27      | Maciejewski   | Gliwice, Poland, 05/2013   | man, 32 | Blunt trauma | Nose, lips, eyelid, cheek, maxilla | Partial | ECA | Alive | Yes | No |
| 28      | Ozkan         | Ankara, Turkey, 07/2013    | man, 26 | Ballistic trauma | Forehead, eyelids, left eye, nose, cheek, mandible | Full | ECA | Alive | Yes | No |
| 29      | Ozkan         | Ankara, Turkey, 08/2013    | man, 54 | Ballistic trauma | Scalp, forehead, eyelids, nose, left eye, maxilla, mandible, tongue | Full | ECA | Yes | No |
| 30      | Maciejewski   | Gliwice, Poland, 12/2013   | woman, 28 | NF | Forehead, eyelids, nose, maxilla, lips, mandible | Full | ECA | Alive | Yes | No |
| 31      | Ozkan         | Ankara, Turkey, 12/2013    | man, 22 | Ballistic trauma | Forehead, lips, nose, maxilla, mandible | Partial | ECA + Facial artery | Alive | Yes | No |
| 32      | Pomahac       | Boston, Mass., 05/2014     | man, 39 | Ballistic trauma | Forehead, nose, lips, lower face | Full | — | Alive | Yes | No |
| 33      | Papay         | Cleveland, Ohio, 09/2014   | man, 44 | TINI | Scalp, forehead, eyelids, nose, eye, maxilla, cheeks | Partial | ECA | Alive | Yes | No |
| 34      | Pomahac       | Boston, Mass., 10/2014     | man, 31 | Ballistic trauma | Forehead, mandible, maxilla, lips and nose | Full | Facial artery | Alive | Yes | No |
| 35      | Barret        | Barcelona, Spain, 02/2015  | man, 45 | AVM | Lower face, neck, lips, tongue, pharynx | Full | — | Alive | — | — |
| 36      | Volokh        | Saint-Petersburg, Russia, 05/2015 | man, 22 | Electrical burn | Forehead, nose, lips | Partial | ECA | Alive | Yes | No |
| 37      | Rodriguez     | New York, N.Y., 08/2015    | man, 41 | Thermal burn | Scalp, forehead, eyelids, nose, cheeks, lower face, ear, lips, neck, maxilla, central mandible | Full | ECA | Alive | Yes | No |
| 38      | Tormwall      | Helsinki, Finland, 02/2016 | man, 34 | Ballistic trauma | Nose, maxilla, mandible, central mandible | Partial | ECA + facial artery | Alive | No | No |
| 39      | Mardini       | Rochester, Minn., 06/2016  | man, 32 | Ballistic trauma | Nose, maxilla, mandible, cheeks, salivary glands, lower face | Partial | — | Alive | Yes | No |
| 40      | Papay         | Cleveland, Ohio, 05/2017   | woman, 21 | Ballistic trauma | Scalp, forehead, eyelids, orbit, nose, cheeks, maxilla, mandible | Full | — | Alive | — | — |
| 41      | Rodriguez     | New York, N.Y., 01/2018    | man, 25 | Ballistic trauma | Eyelids, nose, cheek, lips, maxilla, mandible, zygoma, right orbital floor | Partial | ECA | Alive | Yes | No |
| 42      | Lantieri      | Paris, France, 01/2018     | man, 43 | CR of previous FT | — | Full | — | Alive | — | — |
| 43      | Lasus         | Helsinki, Finland, 03/2018 | man, 58 | Ballistic trauma | Maxilla, mandible, full face soft tissue | Full | — | Alive | No | No |
| 44      | Borsuk        | Montreal, Canada, 05/2018  | man, 64 | Ballistic trauma | Maxilla, mandible, nose, lower 2/3 of face | Partial | — | Alive | — | — |
| 45      | Santanelli, Longo | Rome, Italy, 09/2018  | woman, 49 | NF | — | — | — | — | — | — |
| 46      | Pomahac       | Boston, Mass., 07/2019     | man, 68 | Thermal burn | Lips, nose, facial skin | Full | — | Alive | — | — |
| 47      | Pomahac       | Boston, Mass., 07/2020     | woman, 52 | CR of previous FT | — | Full | — | Alive | — | — |
| 48      | Rodriguez     | New York, N.Y., 08/2020    | man, 21 | Thermal burn | Forehead, eyelids, ears, nose, lips | Full | ECA | Alive | No | No |

AVM, Arteriovenous malformation; CCA, Common carotid artery; COD, Cause of Death; CR, Chronic rejection; ECA, External carotid artery; FT, Face transplant; HCC, Hepatocellular carcinoma; NF, neurofibromatosis; ORN, osteoradionecrosis; TFT, Time from transplantation; TINI, Trauma-induced necrotizing inflammation.
achieving an acceptable donor–recipient color match proved difficult.33 This case underscores the well-established ethnic and racial disparity observed in willingness to donate both solid organ and VCA, and further echoes the limited availability of skin-containing allografts for people of color.32 Despite the paucity of long-term outcome reports, the data available indicate that most FT recipients remain alive to this day (81.2%), while 8 (16.7%) have died (Table 3).

### Computerized Surgical Planning

The feasibility of FT is now widely established and the focus of the field has shifted to optimizing safety and outcomes, with the integration of new surgical technologies into cadaveric and clinical procedures.14,31 The application of computerized surgical planning (CSP) and computer-aided design and manufacturing (CAD/CAM) of patient-specific devices has been instrumental to allow FT teams to adopt a customized approach to various clinical scenarios and achieve superior functional and aesthetic outcomes, including optimized operative flow and cephalometric and occlusal relationships after transplantation.34 At least 8 other FT teams have relied on various forms of three-dimensional (3D) imaging and CAD/CAM for preparation and execution of their FTs.3,13,15,28,35,36 Nonetheless, CSP should serve as a guide for FT surgeons, rather than dictate intraoperative decision-making; deviating from the computerized plan may be necessary in real time.

Intraoperative surgical navigation (ISN) provides real-time 3D guidance with 1- to 2-mm precision, and its use in craniomaxillofacial surgery has been extensively documented.37 To date, 2 clinical FTs have utilized ISN as an adjunct to CSP, allowing intraoperative guidance of LeFort III osteotomies in the first patient and image-guided allograft inset and fixation in the second patient.34 Mixed reality (MR) technology has recently been proposed as a complementary option for use in FT planning and intraoperative visualization.38 In addition to the perceived benefits of MR, including enhanced visualization and easier maintenance of sterility, costs and surgical planning time have been cited as advantages of the holographic model over CSP and CAD/CAM. Further clinical comparative studies between the 2 modalities should be conducted to evaluate the role of MR in future FTs.

### POST-TRANSPLANTATION CONSIDERATIONS

#### Immunosuppression and Management of Allograft Rejection

Lifelong immunosuppression, allograft surveillance, and management of rejection ultimately dictate allograft survival. To date, 6 cases of CR have been reported, and nearly all FT recipients have had at least 1 incidence of acute rejection (AR) (Table 2). Immunosuppression induction regimens generally consist of anti-thymocyte globulin (ATG) or anti-IL-2 receptor antibody in combination with tacrolimus, mycophenolate mofetil (MMF), and steroids. Other reported induction protocols include a combination of steroids with either ATG, ATG with anti-CD20, ATG with MMF, or anti-CD52.40,41,42 Maintenance therapy traditionally consists of triple therapy with corticosteroids, MMF, and tacrolimus, although some groups have used dual therapy with MMF and tacrolimus.67 Appropriate antimicrobial prophylaxis is necessary because immunosuppression increases susceptibility to opportunistic infections, particularly given the unique craniomaxillofacial flora (Table 4).41

Given the composite nature of tissue transplanted in FT, different methods of allograft surveillance have been proposed, with skin biopsy remaining the gold standard.65 Although the use of oral mucosal biopsy has been frequently described, its clinical utility remains unclear, as high rates of discordance with skin biopsy have been noted. Additionally, compared with the oral mucosa, skin histology is more likely to confirm clinical suspicion of rejection.43,44 Some groups have advocated additional use of sentinel flaps for clinical monitoring, although the benefits of this approach are unclear.14,45 Noninvasive methods to detect rejection have also been reported, including ultrasound biomicroscopy, epidermal skin-stripping, and circulating donor-derived cell-free DNA; however, clinical application of these methods remains under investigation.33–37 Ultimately, we recommend close clinical follow-up and visual inspection of the allograft to detect clinical signs of AR followed by histologic confirmation with skin biopsy depending on clinical suspicion, as opposed to routine surveillance biopsy.14,46

Management protocols for AR in FT remain nonstandardized and underreported.65 Most groups have reported successful use of pulse-dose corticosteroids, with or without topical agents and/or increased maintenance doses of immunosuppression.66 Other therapies described include a combination of plasmapheresis, intravenous immunoglobulins, extracorporeal photopheresis, ATGs, eculizumab, and bortezomib.36,40,45 Successful management of AR has been proposed as a rationale for the relatively low incidence of CR in FT. Although reports are beginning...

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**Table 3. Summary of the 48 Face Transplants Performed to Date**

| Face Transplant Recipient Characteristics (n = 48) | n (%) |
|-----------------------------------------------|-------|
| **Demographics** | |
| Men | 38 (79.1) |
| Women | 10 (20.8) |
| Mean Age ± SD | 57.2 ± 12.4 |
| **Indications** | |
| Ballistic injury | 21 (43.7) |
| Burn | 12 (25) |
| Neurofibromatosis | 5 (10.4) |
| Animal attack | 3 (6.25) |
| Tumor | 2 (4.2) |
| Blunt trauma | 1 (2.1) |
| Trauma-induced necrotizing inflammation | 1 (2.1) |
| Arteriovenous malformation | 1 (2.1) |
| Re-transplantation for chronic rejection | 2 (4.2) |
| **Allograft type** | |
| Partial | 24 (50.0) |
| Full | 25 (47.9) |
| Unknown | 1 (2.1) |
| **Status** | |
| Alive | 39 (81.2) |
| Deceased | 8 (16.7) |
| Unknown | 1 (2.1) |

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Table 4. Common Pathogens and Antimicrobial Prophylaxis/Treatment in Facial Transplantation

| Pathogen | Origin | Prophylaxis/Treatment |
|----------|--------|----------------------|
| **Virus** |        |                      |
| HSV-1    | Oral cavity, oropharynx | Acyclovir for the first 4 weeks after transplant |
| VZV      | Skin | Varicella vaccine* more than 4 weeks before transplantation/induction of immunosuppression |
| Influenza | Paranasal sinus | Yearly influenza vaccine |
| CMV      | — | Prophylaxis/treatment: valgancyclovir or gancyclovir |
| EBV      | — | Treatment: reduction of immunosuppression, chemotherapy, and anti-B-cell therapies, such as rituximab. |
| **Bacteria** |        |                      |
| MRSA     | Skin, oral cavity, oropharynx | Empiric treatment: vancomycin |
| Anaerobes | Oral cavity | Ampicillin-sulbactam perioperatively** |
| Staphylococcus | Paranasal sinus | Updated pneumococcal vaccinations |
| Pneumococcus | Skin, ororal cavity, oropharynx | Ampicillin-sulbactam perioperatively** |
| Streptococcus pyogenes | — | Ampicillin-sulbactam perioperatively** |
| **Fungus** |        |                      |
| Candida   | Skin, oral cavity, oropharynx | Prophylaxis/treatment: nystatin or clotrimazole |
| Coccioidoides | Paranasal sinus | Avoid gardening, farming, construction, home remodeling, and landscaping |
| **Pneumocystis carinii** | — | Prophylaxis: trimethoprim-sulfamethoxazole*** for at least 3 months posttransplant |
| **Others** |       |                      |
| Toxoplasma gondii, Isospora belli | — | Prophylaxis: trimethoprim-sulfamethoxazole*** for at least 3 months posttransplant |
| Cyclospora cayetanensis | — | |

*Zoster vaccine if transplant candidate is above 50 years old.
**If no penicillin allergy.
***If allergy to trimethoprim-sulfamethoxazole: dapsone, atovaquone, or pentamidine.

CMV, Cytomegalovirus; EBV, Epstein-Barr Virus; HSV, Herpes Simplex Virus; MRSA, Methicillin-Resistant Staphylococcus Aureus; VZV, Varicella Zoster Virus.

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To emerge, the timeframe for CR remains unknown and expert consensus on CR management and allograft failure has not been established. Clinical findings range from early fibrotic changes such as facial skin thinning and/or accelerated wrinkling, telangiectasia, dyschromia and skin sclerosis with allograft dysfunction, to frank necrosis. In the event of allograft loss, surgical salvage strategies are necessary and both autologous reconstruction and retransplantation have been reported.

Allograft Revisions

Due to the en bloc nature of FT, restoration of multiple facial subunits can be achieved in a single surgery. Aesthetic and functional outcomes can be further refined with allograft revisions. Despite the inherent risks of additional surgeries related to immunosuppression, potential vascular compromise, and triggering of AR, secondary allograft procedures are nearly ubiquitous and can be successfully performed at various timepoints in the post-transplant course. The range of indications is wide, including emergent return to the operating room, elective aesthetic surgery, unplanned functional corrections, and end-stage salvage procedures. Overall, facial allograft revisions allow optimization of functional and aesthetic outcomes after FT (Table 5).

Quality of Life

Quality of life (QoL) of FT recipients’ remains the ultimate measure of FT success. Currently, there is a lack of consistent reporting using validated measures for QoL, with most FT centers only offering subjective assessments. Among the teams that report using objective assessments, more than 25 unique instruments have been employed, and none have been validated for use in FT. This underscores the need for standardized, FT-specific patient-reported outcomes measures (PROMs). Although robust quantitative analyses are currently limited by the relatively small number of FTs, further qualitative studies may continue to inform the development of standardized PROMs. Open collaboration between teams and consensus on outcomes reporting will be critical to advance the field.

Data on functional outcomes remain largely underreported, and have included assessments of olfaction, breathing, facial motor and sensory functions, speech, and eating. Comparison of postoperative functional outcomes across the FT recipient cohort is further nuanced by patient-specific variations in preoperative functional status, mechanism of injury, and allograft composition. Facial tracking technology, video analysis software, and facial surface electromyography have been used to non-invasively track recovery of speech, eyelid function, and facial expression, with results showing at least partial restoration of function after FT and the potential for personalized rehabilitation. Additionally, objective measures such as timing to tracheostomy decannulation, gastrosomy tube removal and resumption of regular oral diet are important parameters to report for QoL assessment.

FUTURE OF FACIAL TRANSPLANTATION

Advances in Facial Transplantation

Two unsuccessful attempts at combined FT-DHT have been reported in the past. Ongoing postoperative infectious complications ultimately resulted in death of the first recipient on postoperative day (POD) 65, and vascular complications necessitated removal of the second recipient’s upper extremities on POD 5. In August 2020, the world’s first successful combined FT-DHT was performed amidst the COVID-19 pandemic in a 21-year-old man who
### Table 5. Categorization of the Most Commonly Performed Secondary Revisions after Facial Transplantation

| Soft Tissue                                      | Craniofacial Skeleton, Dental                                      | Oro-nasal Cavity, Salivary Glands, Facial Nerve | Ocular                                      | Additional                                      |
|--------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------|------------------------------------------------|
| Indication                                      | Example                                                           | Indication                                      | Example                                     | Example                                      |
| Allograft augmentation                           | Fat grafting                                                      | Malocclusion                                    | LeFort III osteotomy                        | Fistula                                       |
|                                                  | Alloplastic implant placement                                      | Midface advancement                            | Omental advancement of floor-of-mouth       | Orbital floor fistula repair                  |
|                                                  |                                                                    | Hardware removal                                | Hyoid and genioglossus advancement          | Medial canthal fistula repair                 |
|                                                  |                                                                    |                                                 | Wound debridement                           |                                                |
| Facial contouring                                | Fat grafting or lipectomy                                          | TMJ-related complications                      | BT injection                                | Vascular revisions                            |
|                                                  | Tissue removal                                                    | Coronoidectomy                                  | Drainage                                    | Vascular thrombectomy                         |
|                                                  | Scar revision                                                     | Condylotomy                                     | Stenting of Stensen ducts                   | Arterial repair (iatrogenic injury)           |
|                                                  | Local tissue rearrangement                                         | Superficial Muscular Aponeurotic System         | Fluid collection, necrotic tissue          | Anastomotic revision                         |
| Tissue resuspension                             | Allograft resuspension and advancement                            | Dental                                          | Eyelid revisions                            | Hematoma evacuation                          |
|                                                  | Rhytidectomy with SMAS plication                                  | Tooth extraction Osseointegrated dental implant placement | Ectropion repair                            | Abscess drainage                             |
|                                                  |                                                                    | Facial nerve revisions                           | Blepharoplasty                              | Debridement and washout                      |
|                                                  |                                                                    | Revision of nerve coaptation                    | Canthoplasty                                |                                                |
|                                                  |                                                                    | Nerve transfer with interposition graft         | V-Y AF of medial canthus                    |                                                |
|                                                  |                                                                    | Eyebrow ptosis                                  | Levator muscle plication                    |                                                |
|                                                  |                                                                    | Chronic rejection                               | Allograft removal                           |                                                |
|                                                  |                                                                    |                                                | Free flap reconstruction                    |                                                |
|                                                  |                                                                    |                                                | Facial re-transplantation                   |                                                |

AF: advancement flap; BT: Botulinum Toxin; SMAS: Superficial Muscular Aponeurotic System; TMJ: Temporomandibular joint.

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had sustained an 80% total body surface area burn injury. Advances in technology, surgical technique, transplant immunology, and expertise gained through 15 years of clinical FT experience, coupled with meticulous preparation and strict adherence to COVID testing and guidelines culminated in the safe execution of this procedure, the most comprehensive VCA to date.31

In concert with the field’s expansion, cross-sex facial transplantation (CSFT) has been proposed as a method of expanding the restricted VCA donor pool. Successful outcomes have been observed in clinical extremity transplantation, including 4 upper extremity transplants and 1 lower extremity transplant.50,60 Although it has yet to be performed in the clinical setting, CSFT has shown promising results in cadaveric simulations, and survey data show acceptance of the practice among members of the general public as well as by the ethics community.22,61,62

Despite a trend toward increasingly complex reconstructive undertakings, the inclusion of certain anatomic structures within the facial allograft has yet to be described. To date, only 1 clinical FT involved a unilateral condyle.63 As trauma to the craniofacial skeleton and subsequent reconstructive attempts can lead to temporomandibular joint (TMJ) ankylosis, FT candidates can experience TMJ-related complications after FT, even with normal TMJ anatomy on pretransplant imaging.64 For FT candidates with TMJ pathology, either preexisting or as a result of their injury, inclusion of bilateral condyles in the allograft could in theory represent a potential option to restore TMJ function. Three methods of TMJ harvest have been explored in cadaveric simulations, with full passive mandibular range of motion obtained posttransplant.65,66 However, important clinical considerations for TMJ-containing FT remain largely unaddressed, including TMJ dynamics after FT, occlusion, and long-term development of TMJ-related complications.

New Ethical Considerations

With FT recipients now living longer posttransplant, we must prepare for an increasing number of CR and allograft failure. Thus far, re-transplantation appears technically feasible; however, acceptance of the practice may depend on patient-specific determinations of its impact on QoL, as in primary FT. Among FT experts, a majority believe re-transplantation should be considered in cases of graft loss.50 In theory, re-transplantation may carry increased immunological risks due to recipient sensitization to the primary allograft, which could lead to earlier rejection of a new allograft. Altered recipient vessel architecture from previous anastomoses might contribute to technical complexity. Careful monitoring will inform the long-term implications of this surgical intervention.

To date, no pediatric FT has been documented, although 62% of survey respondents at an international ethics conference were in favor, given appropriate indications.64 Ethical concerns surrounding consent, immunological risks, and ongoing development of children and adolescents weigh against enhanced QoL, psychosocial well-being, social integration, and restoration of function.87 Nonetheless, discussions addressing donor availability, a dynamic consent process, treatment adherence, and procedural considerations are underway.68,69

Facial Transplantation in the Post-COVID-19 World

The COVID-19 pandemic and associated global economic crisis have placed an unprecedented strain on healthcare systems throughout the world. Financing schemes for FT differ significantly across countries and healthcare systems. In European countries, FTs have typically been financed by the national health care system or public research programs.15,70 Most FTs in the United States continue to be performed using a combination of institutional resources and research grants from agencies such as the Department of Defense. In 2018, the first FT to be partially supported by an employer-mediated third-party private insurer was performed.14 Financial, regulatory, and access-related considerations have pushed some patients to seek VCA care in countries other than their own, but this may become less feasible as travel restrictions, infection-control practices, and resource allocation measures tighten in the aftermath of the COVID-19 pandemic.71 Select teams have already engaged in long-distance follow-up care of FT recipients living in areas far from their VCA centers.72 This approach may gain traction in the post-COVID-19 era, as the challenges imposed by the pandemic meet an accelerated integration of telemedicine throughout the field of plastic and reconstructive surgery.73,74 Standardization of monitoring practices with quality control measures are necessary to maximize the benefit of remote patient interactions. Clinical evaluation using photography, serial documentation of signs and symptoms of rejection, and monitoring for medication-related adverse events must all be incorporated.75

CONCLUSIONS

Over the past 15 years, landmark achievements have shaped the field of FT as a feasible, sometimes preferable reconstructive option for otherwise irreparable craniofacial defects. The field is expanding, and outcomes are encouraging. With some facial allografts beginning to succumb to CR, FT teams were challenged to innovate with re-transplantation to overcome new hurdles. Most recently, the world’s first successful combined FT-DHT established the feasibility of simultaneous VCA, marking the entry of FT into a new phase in caring for patients with extensive composite defects. In this new decade, amidst a global pandemic, we are now presented with a novel set of challenges as we strive to further the field. Continued research efforts will be necessary to validate the feasibility of CSFT. Community outreach, education, and connectedness with local OPOs will set the stage for expansion of the donor pool. Finally, transparency and standardization of clinical protocols and outcomes reporting will be fundamental to the maturation of the field.

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