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Vascularized Composite Allotransplantation: Medical Complications

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Abstract The objective of this review is to summarize the collective knowledge regarding the risks and complications in vascularized composite tissue allotransplantation (VCA), focusing on upper extremity and facial transplantation. The field of VCA has entered its second decade with an increasing experience in both the impressive good outcomes, as well as defining challenges, risks, and experienced poor results. The limited and selective publishing of negative outcomes in this relatively new field makes it difficult to conclusively evaluate outcomes of graft and patient survival and morbidities. Therefore, published data, conference proceedings, and communications were summarized in an attempt to provide a current outline of complications. These data on the medical complications of VCA should allow for precautions to avoid poor outcomes, data to better provide informed consent to potential recipients, and result in improvements in graft and patient outcomes as VCA finds a place as a therapeutic option for selected patients.

Keywords Vascularized composite allotransplantation · Vascularized composite allograft · Facial transplantation · Hand transplantation · Complications · Renal failure · Rejection · Malignancy · Mortality

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Introduction

The first successful hand transplant was performed in 1998 [1••], and the first partial face transplant was performed in 2005 [2]. Since then, an estimated 32 face transplants have been done worldwide and 75 patients were recipients of 111 upper extremity transplants [3–6]. The benefits of vascularized composite allotransplantation (VCA) are both functional and cosmetic. VCA immunological, functional, psychological, and aesthetic outcomes have been reported and have demonstrated objective successes [7–10]. Nonetheless, these transplants are associated with a unique set of characteristics and complications in addition to the better defined risks of transplantation. VCA has also expanded to other grafts including lower extremity, abdominal wall, uterus, larynx, penis, and other composite tissues. These transplants are few in number and less well-described; therefore, this review will focus on upper extremity and facial transplantation.

Skin containing VCA have demonstrated survival over a decade despite early and near universal, episodes of acute rejection. Long-term survival requires chronic immunosuppression comparable to other highly antigenic allografts like heart, lung, and pancreas. Nonetheless, unlike solid organ transplantation (SOT), which is considered life-saving or life-prolonging, VCA is predominately life-changing. This major difference has aroused concerns about the exposure of otherwise young and healthy individuals to the sequelae of chronic immunosuppression.

VCA recipients have experienced all of the major complications seen in SOT: infection, malignancy, renal failure, graft loss, metabolic disorders, and death [11–13]. Bacterial, viral, and fungal infections have been common, resistant, and on occasion associated with sepsis and death. Malignant complications including post-transplant lymphoproliferative disease (PTLD), recurrence of previous malignancies, lymphomas,

and other de novo malignancies have been reported [14–18]. These patients have required systemic chemotherapy, graft removal, and in some cases have died. Renal dysfunction has required transition to non-calcineurin inhibitor-based regimens, temporary renal replacement therapy, and renal transplantation [19, 20]. Graft removal has also been described due to poor functional outcomes [5•, 21], rejection [5•, 22•], and non-compliance [5•, 21, 23].

The field of VCA has progressed from an experimental therapy to one demonstrating good outcomes stretching into two decades. This time interval has allowed for the observation of serious and life-ending complications. Consistent with other new surgical procedures or techniques, a period of intense observation and evaluation of outcomes is essential for the broader acceptance and wider application of VCA. The existing evidence of VCA risks and complications will be presented in this review (Table 1).

Table 1 Medical complications associated with vascularized composite tissue allotransplantation

Medical complications associated with VCA	
Preoperative comorbid conditions adversely affecting outcomes	Depression Post-traumatic stress disorder Substance abuse Lack of social support Lack of continuous medical support HIV positive CMV mismatch with donor Need for multiple VCA
Peri-, intra-operative complications	High transfusion requirement Hemodynamic instability Graft thrombosis Nosocomial infections Respiratory distress, ARDS Acute and chronic renal failure Acute rejection Metabolic disorders Graft edema Rhabdomyolysis
Rejection	Acute rejection Chronic rejection Development of donor specific antibodies
Infection	Nosocomial infections Pseudomonal graft infections Sepsis Hardware infections Osteomyelitis Pneumonia (aspiration, ventilator associated) Pulmonary aspergilloma Candida surgical site infections Tinea/noninvasive cutaneous fungal infections Viral infections (CMV, HSV, VZV, HPV)
Malignancy	Lymphoma Reoccurrence Cutaneous malignancies Hepatocellular carcinoma Lung cancer
Renal and metabolic	Acute and chronic renal failure Diabetes Metabolic syndrome Osteoporosis SIADH
Graft dysfunction	Poor outcome, non-functional graft Graft failure Graft loss

Patient Selection and Surgical Planning

Patient screening and selection are the initial steps in transplantation. The status of VCA as an emerging field with a distinctly different population from SOT warrants continuous review and discussion of inclusion and exclusion criteria. Complications can be best avoided by a thorough screening processes and the implementation of OPTN/UNOS approved criteria for VCA donors [24]. Early transplants driven by limited outcome data had strict inclusion/exclusion criteria for both donors and recipients. This reserved approach was warranted, especially in the early, uncharted experience of facial transplantation, with the threat of graft failure resulting in non-reconstructable defects (or death), and in fact, the first 11 face transplants were partial transplants [3, 25]. With progression of the field and the emergence of good results similar to SOT, recipient exclusion criteria have been loosened to include blind patients, self-inflicted injuries, oncologic defects, bilateral upper extremities, multiple VCA's (extremity with face), HIV positive patients, pre-sensitized patients, and other complex issues on a case by case basis [16, 26–30]. Many of these have had good outcomes, though concurrent bilateral hand and face transplantation, positive HIV status, and CMV mismatch have had poor outcomes to date and are advised against by many in the field [3, 16, 17, 28, 31].

Critical assessment of factors that could affect medical compliance including psychological health, social support structure, medical insurance, and a well-functioning medical team providing support for long-term follow-up and multidisciplinary care; similar to SOT. As an extreme example, a report from China described 15 hand allotransplants in 12 patients with graft failure requiring removal in seven patients; six of these were due to severe rejection after cessation of immunosuppression and lack of access to medications [21].

This early experience highlights that VCA requires medication compliance and lifelong commitment from both the patient and the medical teams' perspective. Given the various traumatic mechanisms of injury involved in many of these cases, patients may also be suffering from post traumatic stress disorder, depression, and social marginalization, which must

all be well controlled pre- and post-transplantation [32]. The observed associations of VCA recipients' mechanism of injury with PTSD requires increased attention to ongoing mental health therapy, with specific regards to associated depression and substance abuse history. Ongoing psychiatric and psychologic care may be necessary to prevent medical noncompliance or illness secondary to PTSD, depression, and substance abuse (including both alcohol and tobacco). Additionally, ethical concerns not limited to informed consent, donor confidentiality, lack of coercion, and societal burden of costs must be thoroughly addressed, with the definite understanding that sustained life-long care will be needed [33–35].

Perioperative Complications

High operative transfusion requirements were noted in all face transplants, with a median transfusion rate of 20 units [36, 37]. Higher transfusion requirements were necessary in recipients with extensive neurofibromatosis or whole face burns in contrast to more limited pathology. Associated hemodynamic instability required vasopressors in many cases. This requirement is concerning for the possibility of vasoconstriction leading to thrombosis in microsurgical flaps, although evidence for this phenomenon is inconsistent [38, 39]. Paralleling these concerns, high transfusion rates with hemoglobin levels >10 g/dL were undesirable due to elevated viscosity and microanastomotic thrombotic risk. Two cases of facial vein thrombosis have been reported, with one requiring reoperation [36]. Severe graft edema is present in most face transplant patients after receiving a median of 13 l of crystalloid.

A more theoretical concern associated with allogeneic transfusion requirements is transfusion immunomodulation (TRIM) [40]. Although allogeneic transfusions have historically been associated with improved renal transplantation outcomes, no routine transfusion practices have been applied or demonstrated as necessary in transplantation. Nonetheless, transfusions likely increase rates of postoperative bacterial infections [40–43]. Fresh frozen plasma (FFP) transfusion is associated with higher risk of nosocomial infection, including ventilator-associated pneumonia [44]. Allogeneic leukocytes may be the responsible mechanism, thus routine leukoreduction of blood products for transplant recipients may minimize these effects [40]. Severe respiratory failure and acute respiratory distress syndrome have been described in facial transplant recipients, where the median FFP transfusion is 20 units [36]. Many of these complications do not translate directly to upper extremity transplantation as transfusion and vasopressor requirements are considerably lower, although not as clearly reported in the literature [45, 46]. However, multiple cases of venous and arterial thrombosis in upper extremity allografts have been described and have required urgent surgical intervention to salvage these at risk grafts [47].

Acute postoperative kidney injury as well the development of chronic kidney disease has been seen in multiple cases of both upper extremity and face transplantation. One instance of rhabdomyolysis was noted in a facial transplant [36, 48]. Perioperative opportunistic and nosocomial infections are one of the most prevalent complications encountered in face and upper extremity transplantation along with acute rejection and metabolic disorders, these are topics will be explored in subsequent sections.

Rejection

Rejection in solid organs is categorized as hyperacute, acute, or chronic, according to chronologic and defined histopathology findings. In VCA, however, only acute rejection has been clearly defined. Banff criteria for VCA acute rejection have been developed and applied; although, these only apply to the skin component and continue to be discussed for ongoing modifications [49–51]. More recently, chronic rejection has been described as graft vasculopathy, although strict criteria are as yet being developed without universal consensus [14, 18, 22•, 52, 53]. Due to the heterogeneous composition of VCA tissues (i.e., skin, muscle, bone, nerve, and vessels,), rejection of one component may not equate to rejection of other tissues within the allograft [54]. The potential discordance between the histopathology of different VCA tissues and the context of clinical presentation result in significant clinical variation in the response to a diagnosis of rejection and choice of immunosuppressive therapy [6, 55, 56]. Potential overtreatment of mild VCA rejection as observed in face and hand transplantation may occur because of the obvious visibility of the graft as compared to SOT. All these clinical and histological factors affect the diagnosis of VCA rejection and subsequent treatment [6, 55, 56].

According to the International Registry of Hand and Composite Tissue Transplantation (IRHCTT) nearly 85 % of both hand and face transplant recipients experience one or more episodes of acute rejection during the first year, despite the use of potent T cell depleting induction therapies in almost all cases [57]. These cases are not progressive and have generally been treated with options including increased levels of existing immunosuppression and steroids, topical agents, antithymocyte globulin, Campath-1H, or other monoclonal biologic therapies [3]. Rates of acute rejection in solid organ transplant are much lower with approximately 10 % of patients having an episode of acute rejection during the first year for renal transplants and 15 % for liver transplants [58–60]. Given the high rate of acute rejection in VCA as compared to SOT, these rejection episodes and the treatments have been

relatively well documented despite the short history of VCA transplantation [61, 62].

Similar attempts at consolidating information on chronic rejection have been made; however, the limited number of possible cases and the lack of consensus have made this considerably more difficult [50, 53]. Preclinical models and isolated case reports in hand and knee transplantation predicted the appearance of chronic rejection as a clinical entity [22, 50, 51, 63, 64]. The features noted in these studies have included transplant vasculopathy with intimal hyperplasia in deep and medium-sized vessels, basal cell layer vacuolization and necrosis of the epidermis, tertiary lymphoid follicles, graft fibrosis, and edema. A more recent summary of cases from Louisville has shown newer findings of capillary thrombosis in two cases of hand transplantation after multiple episodes of acute rejection in one case and development of donor specific antibodies (DSAb) in another, with development of DSAb after removal of the graft in a second case [52]. The mechanism of capillary thrombosis is not thought to be antibody mediated rejection (AMR); yet, AMR has been seen de novo in a hand allograft and in a pre-sensitized patient in face transplantation [30, 65, 66]. No clinical cases of AMR with C4d deposition have been described in non-pre-sensitized face transplant recipients, although chronic rejection with C4d deposition has been seen in a preclinical non-human primate model [67]. Other preclinical models have not associated the development of chronic rejection with either DSAb of C4d positivity. Nonetheless, there are multiple VCA patients who have developed DSAb post-transplant, and emerging data suggests an association of DSAb with poor graft outcomes and loss.

Alternate chronic graft pathologies will also exist besides vasculopathies possibly associated with donor antibodies. One interesting case of chronic graft pathology occurred following the development of Epstein-Barr virus (EBV) + B cell lymphoma in a face transplant recipient [14]. Although initial treatment with rituximab was successful, EBV-associated post-transplant smooth muscle tumors developed in the liver requiring additional reduction of immunosuppression. Eventually scleroderma-like features with dyschromic aspects, resembling chronic GVHD, developed in the patient. Histology demonstrated a thin, atrophic, keratotic epidermis, with a sclerotic dermis, atrophy of epidermal adnexa and capillaries with thickened collagenous walls with reduced lumina. These studies indicate that new findings including epidermal and dermal thinning, sclerosis, and atrophy will be included as new cases of chronic rejection are defined in VCA grafts followed over a longer periods of time.

Infection

Infection is one of the leading postoperative complications of VCA and consists mostly of nosocomial, surgical site, and donor-derived infections in the early recovery period in both hand and face transplants. Severe bacterial and fungal infections are most likely to be life threatening in VCA. Two cases of sepsis in face with concurrent bilateral upper extremity transplants have resulted in one mortality from pseudomonal graft infection eventually leading to death during a secondary procedure, and one case requiring removal of both upper extremity grafts to salvage the face transplant after aspiration pneumonia [56, 68]. Hardware infections have occurred resulting in a mandibular abscess and osteomyelitis of the ulna. Both of these infections resolved after hardware removal and antimicrobial treatment [4, 13, 19]. Fungal infections were seen in the form of pulmonary aspergilloma in a Belgian face transplant recipient and candida surgical site infections in three additional face transplant patients, including the first face recipient [2, 13, 56, 69]. Hand transplant recipients saw cases of tinea and noninvasive cutaneous fungal infections, all treated successfully with topical antifungal agents.

Late infections are generally cases of viral reactivation. Mismatches in cytomegalovirus (CMV) and EBV status are significant contributors, associated with several cases of CMV viremia and one case of CMV gastritis. Two of these were resistant to ganciclovir and valganciclovir [7, 70]. EBV mismatch was associated with one case of EBV-related B cell lymphoma in a face transplant recipient who also endured multiple HSV1 infections, as well as one case of PTLD in a bilateral lower extremity recipient which required graft removal [14, 17]. These viral infections are of great concern in the postoperative period with reactivation of donor CMV and herpes family viruses being quite common in the multiple types of VCA; cases of varicella zoster and human papilloma virus infection have also been seen in hand transplantation [16, 71, 72]. It has also been proposed that CMV infection increases the risk of acute rejection episodes in these grafts [3, 73, 74].

It is important to note that face allografts may include lymph nodes, mucosal surfaces, and sinuses, all which can be highly colonized by various organisms. This puts face transplant patients on par with the infectious risks involved in lung transplantation. Many of the infections seen in VCA and some of the cases are presented in more detail along with treatment modalities in recently published review articles [4, 75, 76].

Malignancy

Similar to SOT unresolved malignancy with or without metastasis is one of the exclusion criteria for VCA, not

including skin cancers. Three face transplants have been performed for oncologic reconstruction. The first was for a Chinese patient with advanced melanoma, with a graft involving the scalp and both ears [77]; the long-term outcome is unknown. Another was a tongue transplant alone, for a patient with advanced squamous cell carcinoma (SCC) of the base of the tongue; this patient had untreatable recurrence at 13 months [15]. The last case was a face transplant in a Spanish 42-year-old male who was HIV positive. The graft involved transplanting the tongue, floor of the mouth, and most of the mandible for a defect cause by radiation therapy of a SCC of the tongue [78]. This was the first face transplant in a HIV-positive patient, also initially considered an exclusion criterion. Pseudosarcomatous spindle cell proliferation was diagnosed 11 months postoperatively and successfully treated; however, at a later date, the patient developed lymphoma that would prove fatal.

It is well established that long-term immunosuppression increases the risk of developing de novo malignancies, most commonly cutaneous malignancies, especially squamous and basal cell carcinoma [79]. Virus-induced cancers such as lymphoproliferative disorders (most commonly B-cell non-Hodgkin lymphoma or EBV-associated PTLD), anogenital cancers including cervical cancer, and Kaposi sarcoma also have a higher incidence in the transplant patient population [80]. The total incidence of all cancers (including skin) at 10 years in cadaveric renal transplant (CRT) recipients was estimated at 26 % in one study, compared to 1 % for those on dialysis, and 3 % in the patient population with failed transplants [81, 82]. One face transplant recipient patient was diagnosed with nodular-pigmented basal cell carcinoma of the native facial skin 6 years post-transplant; while one double hand recipient was diagnosed with a disseminated premalignant lesion, superficial actinic porokeratosis [18]. Although these lesions are not life threatening if detected early and treated appropriately, their prevalence highlights the importance of incorporating education on prevention and regular screening in VCA patients.

PTLD has been described both in preclinical and clinical VCA [14, 17, 83]. The first bilateral lower extremity transplant was EBV donor negative and recipient positive, and went on to develop central nervous system PTLD requiring cessation of immunosuppression and graft removal [17]. One additional case of B cell lymphoma was seen in a face transplant recipient who had multiple HSV1 infections in the postoperative period and a spontaneous asymptomatic EBV infection at 6 months. Immunosuppression was decreased and rituximab was used initially, but 11 months later a relapse required treatment with rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone (R-CHOP). After successful treatment, post-transplant related smooth muscle tumors in the liver appeared, initially progressed, and then plateaued [14].

Other cases of hepatocellular and lung cancers resulting in patient mortalities have been presented but not yet reported. Additional less serious cases of premalignant or malignant lesions have been described including cervical dysplasia treated with hysterectomy in the first face transplant recipient and in situ cervix carcinoma in another patient treated with cervical conization.

Renal and Metabolic Complications

One case of renal transplantation after bilateral hand transplantation has occurred although it is stated that this was for preexisting renal disease [20]. Complications have also been seen in face transplantation including development of hyperglycemia, SIADH, osteoporosis leading to vertebral fractures, hypertension, and nephrotoxicity leading to acute and chronic renal failure [9, 13]. Most of these are side effects of various pharmacological therapies required for immunosuppression or antimicrobial therapy. However, renal dysfunction can progress from acute to chronic with the use of calcineurin inhibitors (tacrolimus), prompting many groups to switch to mTOR inhibitors such as sirolimus and everolimus [66], including one case where conversion to belatacept and sirolimus was successful when the patient was facing multiple rejection episodes with renal failure [84]. In some cases, mTOR inhibitor conversions or the addition of belatacept resulted in episodes of rejection, indicating that development of suitable immunosuppression regimens is an ongoing endeavor [66, 85]. Experimental therapies involving donor bone marrow infusions have taken place in hopes of reducing or eliminating the required amounts of immunosuppression; however, tolerance has not been achieved and any other benefits are unclear due to the limited number of cases [86, 87••]. At the current time, the individual case of renal transplantation and multiple cases of immunosuppressive therapy changes in efforts to preserve renal function highlight the necessity of screening candidates for adequate renal function to tolerate calcineurin inhibitor therapy.

Metabolic complications of VCA, similar to SOT, are also associated with the requirement for immunosuppression. Early results reported in the IRHCTT indicated that nearly 90 % of upper extremity recipients experienced metabolic complications including hyperglycemia both transient and irreversible leading to diabetes, renal failure which required hemodialysis in one case, arterial hypertension, Cushing's syndrome, osteopenia, osteoporosis, and osteonecrosis of the hip requiring prosthesis [4, 19, 57, 89, 90]. Hyperglycemia tends to be transient in the postoperative period, primarily thought to be due to steroid and tacrolimus use, with some

examples of long-term insulin requirements developing. Without the establishment of immunologic tolerance, these regimens will continue to be necessary, though ongoing work continues to make progress toward minimizing immunosuppression in the long-term [91].

Graft Dysfunction

The concept of graft dysfunction or non-function in VCA is fundamentally different from SOT. In SOT, graft function can easily be quantified as a life-supporting metabolic equation (creatinine, prothrombin time, and oxygenation) or a set of physical parameters (cardiac output and tidal volume). Graft function is poorly defined in face transplantation, where the value of the allograft is often primarily cosmetic and only secondarily functional: blink protection, olfaction, and mastication. These outcomes are hard to quantify and defining priority of cosmesis over functionality comes down to a case by case evaluation. There have been some serious reports of graft dysfunction in face transplant with one patient without a blink reflex putting their vision at risk [92].

Graft dysfunction in extremity transplantation is much more subtle, granular, and dependent on expectations based on level of the initial defect. Good functional results of extremity transplantation are associated with intensive physical and occupational therapy [89, 93]. Continuous long-term physical therapy for upper extremity transplants requires high compliance rates in a patient population often burdened by a history of trauma and unusual psychological stressors [32]. Fine motor skills recover well with therapy, but do not return to pre-injury performance and tend to decline over time after a peak level. Conversely, increasing evidence supports upper extremity graft dysfunction directly related to non-participation and non-compliance with therapies. Two hand transplant patients requiring graft removal had very poor function that was believed secondary to non-compliance with occupational and physical therapies [94].

Long-term declines in function may be associated with chronic rejection in upper extremity transplants, though this association has not yet been observed in facial transplantation [14, 22, 50, 52, 95]. Facial transplants have demonstrated functional success with emoting, chewing, lip function, speech, smell, sensation, and eyelid function—many of which cannot be restored using classical techniques [92, 96, 97]. Long-term declines in function have not been clearly defined in facial transplantation while cosmetic results for facial VCA have ranged from near normal appearances to significant remaining deformities.

Mortality and Graft Loss

The field of VCA does not yet have similar requirements for reporting outcomes as SOT; therefore, the actual 1- and 3-year results for graft and patient survival are not yet defined. However, the estimates presented in this review support VCA outcomes as overall superior to most other organ transplants.

Current estimates suggest seven mortalities/graft losses in recipients of facial VCA. This results in approximately a 20 % overall mortality for facial VCA. The first mortality occurred in China and was attributed to non-compliance by the patient who declined immunosuppressive medications for herbal medicine on multiple occasions [9]. The second mortality was in a recipient with extensive burn injuries who underwent a full face with bilateral hand transplantation. A pseudomonal graft infection required additional surgery, during which a fatal cardiac arrest occurred [68]. The third reported mortality was in a HIV-positive Spanish patient who developed lymphoma [16, 78]. An additional mortality was reported in Turkey, where a patient required facial graft removal due to severe infectious complications and eventually succumbed to multisystem organ failure [94]. Suicide was unfortunately the cause of death in one additional patient. Other known or suspected mortalities have not been formally reported.

In upper extremity transplantation, 24 graft losses and 4 mortalities have been reported [5]. Of these, three of these were in patients who underwent combination VCA (upper and lower limb or upper limb and face transplants) with fatal infectious complications [5, 57]. The fourth mortality was reported from Mexico in a patient who died immediately after an attempted bilateral hand transplantation [98]. In contrast to facial VCA, upper extremity transplantation has a much lower mortality rate estimated at 1 % for 1-year outcomes with isolated upper extremity and 4 % overall mortality. This is partly because graft removal after severe complications is possible without a major reconstruction requirement. Accordingly, cumulative upper extremity graft loss is estimated at 22 %.

Conclusion

Advances in immunomodulatory and immunosuppressive protocols, microsurgical techniques, and computer-aided surgical planning have enabled broader clinical application of VCA. Experience-driven improvements in psychological counseling, patient screening, and lifelong multidisciplinary care are fundamental to long-term success. However, VCA remains an experimental field without widespread consensus as a standard of care [99], though the recent addition of VCAs to regulatory oversight of the Organ Procurement and Transplantation Network in 2014 as well as databases such as the International Registry on Hand and Composite Tissue

Transplantation will bring some transparency to this field as reporting of outcomes especially complications has been incomplete [57, 100–103]. Inclusion in the Scientific Registry of Transplant Recipients could also pave the way for more cohesive cataloging of methods and outcomes. While reasonably safe VCA does have measurable risks of morbidity, graft loss, and patient death, many of which are related to chronic immunosuppression. Further efforts to reduce complications and increase acceptance of VCA as a life-changing (but not life-saving) procedure depend on continued research into identifying and developing approaches to minimize these complications.

Compliance with Ethical Standard

Conflict of Interest Arthur Nam, Rolf Barth, Jhade Woodall, Mehmet Uluer, Philip Brazio, and Stephen Bartlet declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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