



Review

Pre-transplant management and sensitisation in vascularised composite allotransplantation: A systematic review



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KEYWORDS

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Hand transplantation;
Facial transplantation;
Transplantation
immunology;
Graft rejection

Summary **Introduction:** Vascularised composite allotransplantation (VCA) permits like-for-like reconstruction following extensive soft tissue injuries. The initial management of extensive soft tissue injury can lead to the development of anti-HLA antibodies through injury-related factors, transfusion and cadaveric grafting. The role of antibody-mediated rejection, donor-specific antibody formation and graft rejection in the context of VCA remains unclear. This systematic review aimed to determine whether pre-transplant management strategies influence immunological outcome following VCA.

Methods: A systematic review of MEDLINE, EMBASE and CINAHL using a PRISMA-compliant methodology up to February 2019 was conducted. Pre-transplant, procedural and long-term outcome data were collected and recorded for all VCA recipients on an individual patient basis.

Results: The search revealed 3,847 records of which 114 met inclusion criteria and reported clinical data related to 100 patients who underwent 129 VCA transplants. Trauma (50%) and burns (15%) were the most frequent indications for VCA. Of all 114 studies, only one reported

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acute resuscitative management. Fifteen patients were sensitised prior to reconstructive transplantation with an 80% incidence of acute rejection in the first post-operative year. Seven patients demonstrated graft vasculopathy, only one of whom had demonstrated panel reactive antibodies.

Conclusions: Currently employed acute management strategies may predispose to the development of anti-HLA antibodies, adding to the already complex immunological challenge of VCA. To determine whether association between pre-transplant management and outcomes exists, further refinement of international registries is required.

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Introduction

Transplantation of vascularised composite allografts (VCAs) enables reconstruction of extensive soft tissue defects with functional tissue units, permitting like-for-like restoration of form and function. Currently, a universally adopted consensus for the selection and management of VCA recipients is yet to be established, with much variation in patient selection and immunosuppressive therapies existing between VCA centres. Allograft size, colour and donor gender must be considered in conjunction with human leukocyte antigen (HLA) matching status, given the requirement for optimal functional and aesthetic outcomes.¹

The principal obstacle to the widespread clinical application of VCA transplantation is the high risk of rejection and requirement for chronic immunosuppression.² The development of donor specific anti-HLA antibodies (DSAs) is also recognised as a potential cause of chronic graft vasculopathy in VCA transplantation.^{3, 4} The distinct immunological challenge posed by VCA is highlighted by the 80% in-

cidence of acute rejection in the first post-operative year, compared with a 7% incidence of acute rejection in renal allografts using modern immunosuppression.^{5, 6}

A multitude of sensitising events are known to predispose to the development of DSAs, however much of this evidence is derived from solid organ transplantation. HLA-sensitisation is widely considered a risk factor for early and late antibody-mediated rejection (AMR), with further evidence to suggest accelerated development of chronic nephropathy following renal allotransplantation.⁷ HLA-sensitisation occurs following exposure to non-self HLA molecules following transfusion, transplantation and during pregnancy.⁸⁻¹⁰ Anti-HLA antibodies can also arise *de novo* in patients without known sensitising events.¹¹

Candidates for reconstructive transplantation often have extensive injuries that mandate emergent intensive care with therapies which may lead to allosensitisation. Indeed, extensive burns, red cell transfusion⁷, and cadaveric skin grafting¹² all have a significant association with HLA sensitisation in limited clinical studies.^{8, 12, 13} However, the

role of allosensitisation in the context of AMR and chronic vasculopathy remains equivocal, despite a growing number of clinical reports.¹⁴ There is a growing global experience with reconstructive transplantation, however conventional resuscitative and pre-transplant practice may inadvertently preclude access to VCA due to allosensitising events that result in the development of pre-transplantation DSAs.

The aim of this systematic review is to determine whether pre-transplant management strategies influence sensitisation and outcomes following VCA transplantation performed in both adult and paediatric populations.

Methods

This systematic review was developed and conducted using guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement¹⁵ and the protocol was registered in the prospective register of systematic reviews (PROSPERO; CRD42017084261).

Eligibility criteria

All randomised controlled trials, clinical studies, comparative studies, case series and case reports were eligible for study inclusion. Review articles, meta-analyses and descriptions of operative technique without accompanying novel clinical data were excluded.

Participants

All studies examining patients, both adult and paediatric, who have undergone vascularised composite allotransplantation regardless of underlying aetiology were included. Participants who underwent definitive reconstruction with autologous grafting alone and those who had reported underlying autoimmune conditions before transplantation were excluded. Sensitised patients were defined as those with demonstrated panel reactive antibodies or donor-specific antibodies prior to VCA.

Interventions and Comparators

Any form of VCA was eligible for inclusion. VCA was defined in line with nine criteria proposed by the United States Department of Health and Human Services.¹⁶ In short, we considered a VCA to be any allograft that is primarily vascularised, contains skin and other tissues, and harvested as a structural unit that is susceptible to both ischaemic and immunological complications of rejection. Thus, composite allografts devoid of skin, such as uterine and tracheal transplants, were not included in the current review. Details of the type of VCA performed were extracted along with relevant pre-transplant management strategies used in resuscitative care and for temporary soft tissue coverage. Multiple comparisons were made:

- Comparisons between early management strategies (resuscitative and soft tissue coverage).

- Comparisons between cohorts with known sensitising events before transplantation.
- Comparisons regarding underlying aetiology and type of VCA performed.
- Comparisons between immunologically distinct cohorts (as defined by the degree of HLA mismatch and the presence of DSAs).

Institutions were contacted directly for further information regarding pre-transplant resuscitation treatment if not explicitly stated.

Outcomes

The primary outcome assessed was development of rejection. Specifically, the incidence of acute rejection, the number of acute rejection episodes, the grade of acute rejection episodes (as per the Banff Criteria for Acute Skin Rejection in VCA)¹⁷ and the incidence of chronic rejection (defined as graft vasculopathy occurring due to myointimal proliferation and narrowing of luminal diameter).¹⁷ The treatment given for rejection episodes was recorded when appropriately reported. Secondary outcomes assessed included the development of infectious and neoplastic complications related to the VCA.

Search Strategy

Search strategies were developed using index and free text terms, in conjunction with a search strategist. The literature search was limited to human studies, full search strategies are given in [Appendix 1](#). They were applied to Medline & In Process (1946-December 2017), EMBASE (1947-December 2017) and CINAHL (1981- December 2017). A secondary search was performed up until February 2019. The reference lists of included articles were hand searched for further relevant publications.

Study Selection

After pooling and electronic de-duplication, two authors (LG, MAK) independently screened all abstracts against pre-specified stepwise inclusion criteria (see [Figure 1](#), PRISMA flow chart). Disagreements were resolved by discussion with a third author (AS).

Data Extraction and Statistical Analysis

Relevant data extracted included demographics, type of VCA, indication for VCA, resuscitation and soft tissue coverage modalities prior to VCA, time to VCA, procedural length, degree of HLA matching, pre-transplant panel reactive antibody (PRA) status, incidence and grade of acute rejection episodes, incidence and treatment of chronic rejection, incidence of infectious and neoplastic complications. Differences in continuous variables were evaluated using an independent t-test or Mann-Whitney U test depending on data distribution. Differences in nominal data were analysed using Fisher's exact test. Significance was set at the level of

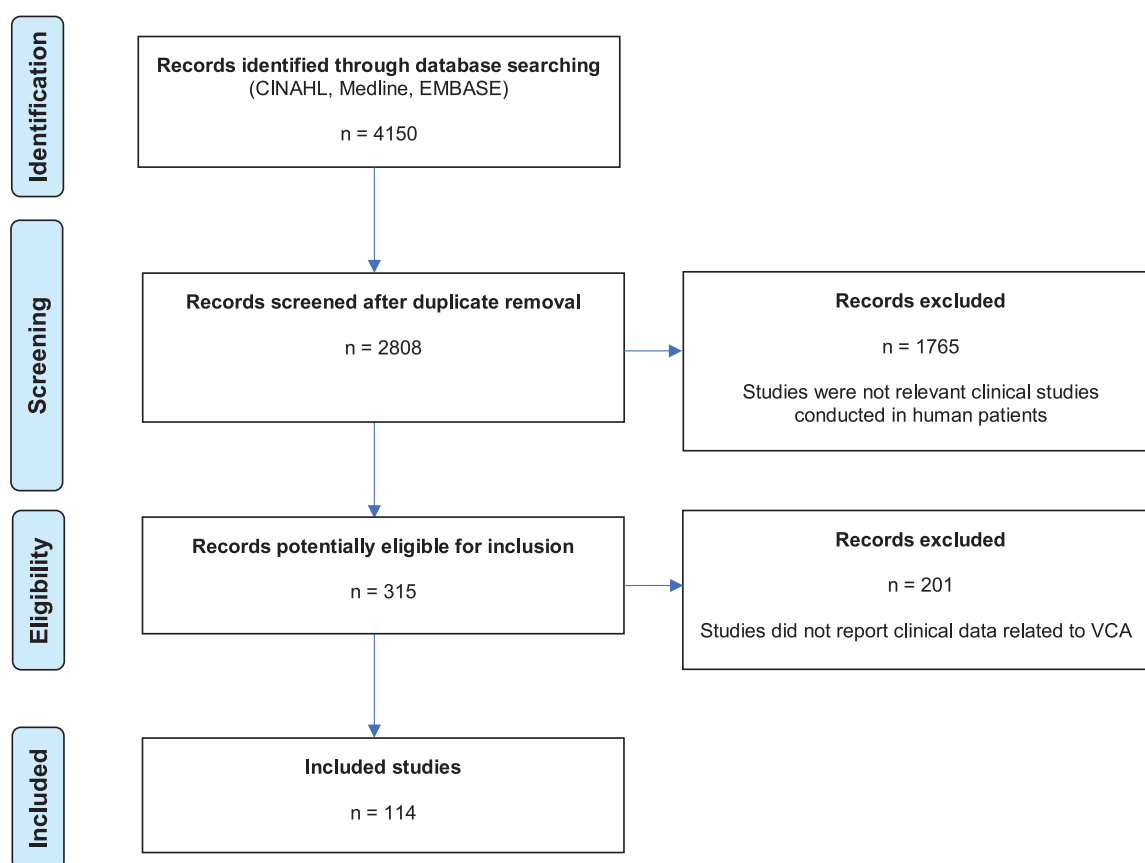


Figure 1 PRISMA flow chart detailing results of the search strategy.

$P \leq 0.05$ and analysis was performed using SPSS version 26 (IBM, USA).

Results

Search results

3,847 records were identified through database screening, including 1,687 from EMBASE, 1,402 from Medline and 758 from CINAHL. A secondary electronic search performed in February 2019 yielded an additional 333 studies. Collectively, the combination of searches provided 4,180 studies. After removing duplicates, 2,808 were screened. Overall, 315 studies were fully assessed for eligibility with 114 meeting inclusion criteria. The combination of both primary and secondary searches is summarised in [Figure 1](#). All included studies were retrospective case series or case reports.

Demographics and interventions

In the 114 included studies, 100 patients underwent 129 VCA transplants ([Table 1](#)). Collectively, 87 patients were male with a mean age of 37.2 (range: 0.25-68) years at transplantation. The upper limb was the most frequent type of allograft with 27 unilateral and 25 bilateral upper-limb transplants reported. Trauma (50%) and burns (15%) were the most frequently cited indications for VCA transplantation in

included studies. The underlying indication for VCA was not reported in eleven studies. The mean time to VCA from initial injury was 99 ± 119 months. The mean procedure length was 16.6 ± 5 hours with a mean cold ischaemia time of 310.7 ± 177 minutes.

Sensitising events

Acute resuscitative measures following initial injury were briefly reported in a single paper.¹⁸ Four of the contacted authors provided additional information regarding resuscitative treatment modalities implemented prior to VCA transplantation. Twenty-seven articles reported that patients underwent surgical procedures prior to reconstructive transplantation, all were autologous reconstructive procedures, and none reported the use of cadaveric skin grafting as a temporary coverage modality. Previous allogenic solid organ transplantation was reported in one patient who had undergone previous combined renal and pancreatic transplantation prior to a subsequent combined scalp, skull, pancreas and renal transplant from a single donor, however PRA prior to transplantation were reported as 0.¹⁹

Of the 15 female patients, 13 were at or above childbearing age on the date of their VCA procedures, 1 was below childbearing age and 1 patient's age at time of VCA was not reported. Of the 13 patients at or above childbearing age, gravidity at the point of VCA was only reported in one patient (two successful pregnancies).¹⁸

Table 1 Demographic information of included patients

	N
Part transplanted	
Face	28
Unilateral hand	27
Bilateral hand	25
Knee	6
Abdo wall and bowel	5
Femoral diaphysis	3
Penis	2
Face and bilateral hand	2
Scalp, kidney and pancreas	1
Liver and rectus fascia	1
Indication for VCA	
Trauma	50
Burn	15
Not recorded	11
Sepsis and gangrene	6
Congenital	4
Animal bite	3
Cancer	2
Crohn's disease	2
Frostbite	1
Kawasaki	1
Osteomyelitis	1
Mesenteric infarction	1
Metabolic disorder	1
Radiation enteritis	1
Cancer and osteomyelitis	1

Pre-transplant immunological status

The degree of HLA mismatch was reliably reported for 60 patients. There were no fully matched transplants. The median mismatch in our cohort was 5/6 (range 1-6/6) across HLA-A, -B and DRB1 alleles. Fifteen patients were sensitised prior to transplantation with a mean PRA status of 27% (range 5-99%, [Table 2](#)).^{18, 20-38} Individual patient-specific data from the cohort of unsensitised patients is available on request from the authors. One patient presented with 99% PRA prior to transplantation and underwent treatment with Protein A immunoabsorption therapy which reduced PRA to 5%.³² Three acute rejection episodes were reported at 3, 5- and 17-months post-transplant however these were all successfully treated with increased dosages of tacrolimus, pulsed methylprednisolone and a reducing dosage of prednisone.

Outcomes

Overall, 73 patients experienced at least one episode of acute rejection within the first post-operative year. Within the cohort of sensitised patients, the incidence of acute rejection was 80% (12 patients). The median number of acute rejection episodes experienced was 3 (range 1-4) in this cohort. In the unsensitised cohort, the incidence of acute rejection was 71.8% (61 patients) with a median number of acute rejection episodes of 2 (range 1-16). There was no

significant difference between sensitised and unsensitised cohorts ([Table 3](#)). Comparison of the severity of acute rejection episodes was not possible due to inconsistent reporting of formal clinical or histological grading systems.

Chronic rejection, defined by the presence of graft vasculopathy, was reliably reported in 7 cases. The median number of acute rejection episodes in those who experienced chronic rejection was 3 (range 0-5 episodes). The median time to chronic rejection was 37.5 months (range 9-156 months) and five grafts were lost due to necrosis.

Of those who experienced chronic rejection, all were unsensitised prior to VCA. One patient developed de novo alloantibodies with 27% PRA to class I HLA on post-operative day 7. One-year post transplant, the patient demonstrated evidence of vasculopathy on magnetic resonance angiography and was treated with IVIG and plasmapheresis following a diagnosis of antibody mediated rejection. The patient was then maintained on belatacept and sirolimus. Vascular studies demonstrate reduced velocities in VCA ulnar and radial arteries however the graft is still viable to the best of the authors knowledge without further signs of rejection.³⁹

Overall, forty-two patients suffered from infectious complications and 4 patients developed neoplastic complications following VCA. No significant differences were noted between sensitised and unsensitised cohorts ([Table 3](#)).

Discussion

In this study we examined whether resuscitative and pre-transplantation management strategies influence the development of HLA-sensitisation prior to VCA. Of the 114 studies that met inclusion criteria, none adequately detailed the resuscitative and early post-injury management strategies.

Patients with extensive soft tissue deficits are likely to become sensitised due to resuscitative efforts and subsequent management during intensive care. A portion of these patients are likely to be eligible for VCA transplants as their definitive reconstructive treatment. Approximately 40% of all donors after brainstem death (DBD) currently meet the united Network for Organ Sharing criteria for eligible VCA donation.⁴⁰ Estimates from the USA alone indicate that 185,000 individuals undergo extremity amputation each year, of which approximately 100,000 are due to vascular disease and 83,000 are due to traumatic injury.⁴¹ A further 3 million craniofacial injuries present to emergency departments annually, of which 15,000 are catastrophic disfiguring injuries.⁴² Despite the fact that 90% of trauma-related deaths occur in low- and middle-income countries where VCA services are not currently established, conservative estimates from the USA alone indicate a further potential 1000 VCA candidates each year.⁴³ The latest 2017 report from the International Registry on Hand and Composite Tissue Allotransplantation indicate that 66 upper extremity transplantations have been performed in 21 centres and 30 partial or full facial transplantations have been performed in 11 centres worldwide, although many more have been reported outside the registry.⁴⁴ Due to limited clinical experience with VCA, the impact of pre-transplantation care on sensitisation and post-transplant outcomes remains unknown.

Table 2 Demographic, transplant-specific and outcome data for all sensitised patients.

Patient number	References	Transplantation centre	Age	Gender (parity)	VCA type	HLA mismatch	Pre-VCA PRA	DSA	Aetiology	Acute resuscitative measures	Acute rejection (number and Banff Grade)	Chronic rejection (time of diagnosis and outcome)
1	<i>Brandacher et al., 2009</i> ¹⁶ <i>Piza-Katzer et al., 2002</i> ¹⁷ <i>Schneeberger et al., 2013</i> ¹⁸ <i>Schneeberger et al., 2006</i> ¹⁹ <i>Weissenbacher et al., 2014</i> ²⁰	Austria	47	M	Bilateral upper limb	6/6	5%	Not present	Bomb blast	One autologous reconstructive procedure.	3 (Grade I-II)	Not reported
2	<i>Iglesias et al., 2014</i> ²¹	Mexico	52	M	Bilateral upper limb	5/6	30%	Not present	Electrical burns	Three autologous procedures. 8 units PRBC.	4 (1 grade I; 3 grade II)	Not reported
3	<i>Lantieri et al., 2011</i> ²² <i>Lantieri et al., 2016</i> ²³	Paris	27	M	Face (lower 2/3)	6/6	6%	Not present	GSW	Not reported	1 (Grade III)	Not reported
4	<i>Lantieri et al., 2011</i> ²² <i>Lantieri et al., 2016</i> ²³	Paris	33	M	Face (lower 2/3)	5/6	6%	Not present	GSW	Not reported	5 (2 grade II, 2 grade III, 1 grade IV)	Not reported
5	<i>Lantieri et al., 2011</i> ²² <i>Lantieri et al., 2016</i> ²³	Paris	35	M	Face (full)	6/6	2%	Not present	Neurofibromatosis	Not reported	7 (1 grade I; 4 grade II; 2 grade III)	Not reported
6	<i>Lantieri et al., 2011</i> ²² <i>Lantieri et al., 2016</i> ²³	Paris	45	M	Face (lower 2/3)	5/6	1%	Not present	GSW	Not reported	1 (Grade II)	Not reported
7	<i>Lantieri et al., 2011</i> ²² <i>Lantieri et al., 2016</i> ²³	Paris	41	M	Face (lower 2/3)	5/6	1%	Not present	GSW	Not reported	No episodes reported	Not reported

(continued on next page)

Table 2 (continued)

Patient number	References	Transplantation centre	Age	Gender (parity)	VCA type	HLA mismatch	Pre-VCA PRA	DSA	Aetiology	Acute resuscitative measures	Acute rejection (number and Banff Grade)	Chronic rejection (time of diagnosis and outcome)
8	<i>Pomohac et al., 2012²⁴</i> <i>Janis et al., 2015²⁵</i> <i>Kueckelhaus et al., 2016²⁶</i> <i>Fischer et al., 2015²⁷</i>	Boston	25	M	Face	Unknown	68%	Not present	Electrical burns	Not reported	1 (Grade III)	Not reported
9	<i>Guo et al., 2008²⁸</i>	China	30	M	Face (partial)	3/6	99% (5% post treatment)	Not present	Animal bite	Not reported	3 (unknown grade)	Not reported
10	<i>Fischer et al., 2015²⁷</i> <i>Win et al., 2017²⁹</i> <i>Chandraker et al., 2014³⁰</i>	Boston	44	F (2)	Face full	6/6	98%	Not present	Chemical burns	Multiple transfusions	4 (Grade II-III)	Not reported
11	<i>Dwyer et al., 2013³¹</i>	Melbourne	65	M	Unilateral upper limb	6/6	6%	Not present	Meningococcal sepsis	Not reported	1 (Grade II)	Not reported
12	<i>Fischer et al., 2017³²</i>	Boston	33	M	Face (lower 2/3)	5/6	33%	Present against HLA-A1 (resolved 6 months post-transplant)	GSW	13 previous autologous procedures. 5 units PRBC, 2 units FFP.	2 (Grade II and III)	Not reported
13	<i>Zheng et al., 2004³³</i>	China	39	M	Unilateral hand	3/6	<10%	Not present	Not reported	Not reported	Not reported	Not reported
14	<i>Zheng et al., 2004³³</i>	China	27	M	Unilateral hand	3/6	10.8%	Not present	Not reported	Not reported	Not reported	Not reported
15	<i>Lindford et al., 2019³⁴</i> <i>Lassus et al., 2018³⁵</i>	Finland	35	M	Face	4/6	33%	Present against HLA-B7	GSW	28 previous autologous procedures. Multiple transfusions.	No episodes reported	Not reported

DSA- Donor specific antibodies; FFP- Fresh frozen plasma; PRA- Panel reactive antibodies; PRBC- Packed red blood cells; VCA- Vascularised composite allotransplantation

Table 3 Comparative demographic and outcome data for sensitised and unsensitised patients

	Non-sensitised (n= 85)	Sensitised (n= 15)	Significance
Age	37.3 ± 13.9	36.6 ± 11.9	p= 0.86
Gender (% male)	83.5%	93.3%	p= 0.33
Incidence of acute rejection	71.8%	80%	p=0.80
Median number of acute rejection episodes	2	3	P=0.76
Median HLA mismatch	5/6	5/6	P=0.63
Incidence of chronic rejection	8.2%	0%	P= 0.59
Infectious complications	37.6%	60%	P=0.15
Neoplastic complications	4.7%	0%	P=1.00

HLA- Human leucocyte antigen.

To our knowledge, this study is the first that systematically reviews the available evidence for HLA sensitisation in view of pre-transplantation care. We did not identify any clinical evidence to suggest that pre-VCA management strategies influence the development of HLA-sensitisation. This may represent a perceived lack of importance regarding the role of pre-transplantation care in the setting of VCA alloimmunisation, which may be compounded further by a lack of standardised reporting guidelines. The unique cellular and architectural features of composite allografts must also be considered. The inherent antigenicity of the skin component of VCAs was initially thought to represent a significant immunological challenge for reconstructive transplantation.⁴⁵ However, skin does not induce a greater T-cell response compared to solid organ transplantation, and the skin component of VCAs is more susceptible to rejection, rather than being more antigenic in nature.⁴⁶ Larger tissues have been shown to have a survival advantage due to operational tolerance secondary to the development of an antigenic sink.⁴⁷ Further, the transplantation of bone marrow within the composite graft may contribute to the development of a tolerogenic chimaeric state, although there is a lack of clinical evidence in VCA recipients at present, perhaps owing to limited worldwide experience.⁴⁸⁻⁵⁰

Duhamel et al., demonstrated a significant association between the number of packed red blood cell units administered, a history of pregnancy, the use of cryopreserved skin grafts, the percentage total burn surface area and HLA-sensitisation through bivariate analysis.¹² Extensively burned patients had a significantly higher PRA compared to patients on the renal transplant waiting list with a relative risk of hyperimmunisation in the burns cohort of 3.3 (2.3-4.9). Hyun et al., demonstrated significantly higher sensitisation rates in solid organ transplant recipients who underwent previous transplantation, transfusion or pregnancy compared with controls.⁵¹ In allograft-naïve solid organ recipients, erythrocyte transfusion is associated with a 4.1 relative risk of sensitisation in contrast to non-transfused patients.⁵² This is likely due to the fact that large numbers of erythrocytes, which express low levels of HLA class I, are transfused post-operatively.⁵³ Several randomised controlled trials have demonstrated that restrictive transfusion strategies are as safe or safer than liberal transfusion strategies.⁵⁴⁻⁵⁶ Indeed, clinical practice guidelines from the Amer-

ican Association of Blood Banks recommend a red blood cell transfusion threshold of 70 g/L for haemodynamically stable critically ill patients and a threshold of 80 g/L for those undergoing orthopaedic or cardiac surgery.⁵⁷

Cadaveric skin allografts are frequently used to achieve temporary wound coverage in patients with extensive burns and soft tissue damage. Skin allograft, particularly when cryopreserved, has been associated with the development of HLA sensitisation in the setting of acute burns.¹² Win et al., demonstrated that in patients with extensive burns treated with skin allografts, the average PRA score was 87.7%, however there was no significant correlation between antigenic load (as measured by allograft surface area) and the level of allosensitisation.¹³ This may be due to the limited cohort size of 14 individuals. A further prospective study by Lindford et al., demonstrated that glycerol-preserved skin allograft may have a greater potential to sensitise burn patients than erythrocyte transfusion.⁵⁸ The use of cadaveric allografts in burns has been associated with prolonged hospitalisation and an increased number of procedures compared to non-allograft recipients.⁵⁹ Indeed, a recent national study demonstrated that allografted patients had a significantly higher inpatient mortality, greater length of hospital stay, more complications and a higher total cost of care.⁶⁰ There is currently no consensus for the use of cadaveric allograft.⁶¹ If the extent of soft tissue defects precludes the use of autografted dressings, animal-based and synthetic dressings may be seen as a viable temporising measure to achieve wound coverage.⁶²

The presence of DSAs may result in graft and life-threatening complications. In the setting of VCA transplantation, alloantibodies can disrupt graft microvasculature through complement-mediated cytotoxicity with deposition of activated complement component. In our series, twelve patients were sensitised prior to VCA, all of whom had varying exposure to sensitizing events and differing post-operative courses. Chandraker et al., describe the case of a full facial allograft performed in a mother of two suffering with 80% chemical burns with a 6/6 HLA mismatch and 98% pre-VCA PRA status.¹⁸ Despite initial treatment with plasmapheresis, she developed AMR on post-operative day five. In our series of sensitised patients, no evidence of graft vasculopathy was reported. The risk factors for graft vasculopathy and chronic rejection in VCA are equivocal,

although rodent studies suggest that multiple acute rejection episodes result in endothelial damage, myointimal proliferation and eventual graft vasculopathy.⁶³ Similar clinical observations have been made in a recent review of graft vasculopathy in human VCA recipients.¹⁴

Desensitisation protocols are currently being developed for facial transplant patients.⁶⁴ Antibody mediated rejection can be prevented from developing by removing alloantibodies through immunoadsorption or plasmapheresis whereas treatment of established antibody-mediated rejection is achieved through high dose intravenous immunoglobulins. The long-term efficacy of such therapies in sensitised VCA recipients is currently unknown. Novel therapies such as the IgG-degrading endopeptidase derived from *Streptococcus Pyogenes* (IdeS) has shown promise in highly sensitised renal allograft recipients: through inhibition of complement and antibody-dependent cellular cytotoxicity, IdeS has been shown to permit HLA-mismatched transplantation in 96% of highly sensitised patients (n= 24/25).⁶⁵ Further evidence from large phase III studies is required to determine efficacy and safety in renal allograft recipients prior to experimental use in VCA recipients.

The current evidence base for sensitising events and outcomes in reconstructive transplantation is limited. Evidence from current studies suggests that VCA transplantation is not contraindicated in the setting of HLA-sensitisation. Of those with demonstrated evidence of graft vasculopathy, only one patient identified in the present review had positive PRA. Limited evidence from solid organ transplantation and in vitro studies suggests that pre-transplant management may influence antigenic load and sensitisation prior to VCA. To determine whether significant association exists, further refinement of VCA databases is required. Pragmatically this could be achieved through inclusion of proven and potentially sensitising events in international registries.¹ A data-driven approach is required to determine association between pre-transplant management and outcomes in VCA given the inherent challenges to conducting clinical trials in this evolving field. Demonstrated association between pre-transplant variables and outcomes can then be used to inform the design of management pathways that widen access to VCA from the point of initial injury.

SUPPORTING INFORMATION: Additional supporting information may be found online in the supporting information tab for this article.

Declaration Competing of Interest

The authors disclose no conflicts of interest related to the current work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.bjps.2020.05.010](https://doi.org/10.1016/j.bjps.2020.05.010).

Appendix 1: Search strategies for respective databases

Medline and EMBASE

- 1 ((Hand* or upper limb*) adj transplant*).mp.
- 2 (Face transplant* or facial transplant*).mp.
- 3 Abdominal wall transplant*.mp.
- 4 ((Leg* or lower limb*) adj transplant*).mp.
- 5 Penis transplant*.mp.
- 6 Vasculari?ed Composite Allotransplantation.mp.
- 7 exp Vascularized Composite Allotransplantation/
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7

CINAHL

- 1 Hand* transplant* or upper limb* transplant* or Face transplant* or facial transplant* or Abdominal wall transplant* or Leg* transplant* or lower limb* transplant* or Penis transplant* or Vasculari?ed Composite Allotransplantation (MH "Facial Transplantation")
- 2 1 or 2

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