Review Article

Blood banking in solid organ transplantation

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Abstract: Over 150,000 organ transplants are performed annually worldwide, and transfusion medicine support is crucial for each patient. Liver transplants have posed the greatest challenge for transfusion support, including 4–9% rates of preoperative red blood cell (RBC) alloimmunization, and higher-end blood use is associated with adverse outcomes. However, with effective patient blood management, means/medians of 4–9 allogeneic RBC units per case and 75th percentiles of 7–12 units or lower are reported. Heart or lung transplant RBC transfusions averaged around 3 units, but COVID-19 lung transplants needed a median 8 units (75th percentile 15) due to dense adhesions. Passenger lymphocyte syndrome due to donor anti-A/B induce hemolysis after 6% of ABO-unmatched kidneys, 19% of livers and 29% of intestinal transplants. ABO-incompatible transplants are achieved by desensitization, A subgroup organs, or tolerance in infants. However, interlaboratory reproducibility of anti-A/B titers in these patients remains problematic. ABH structures are predominantly type 2 in RBCs and hearts, type 4 in kidneys and secretor-dependent type 1 in liver bile ducts and arteries. These anatomic differences suggest that anti-A/B assessments and therapeutic adsorptions might be improved by using organ-tailored ABH glycans. Therapeutic plasma exchange (TPE) and extracorporeal photopheresis (ECP) are widely employed for antibody removal and rejection treatment. As organ transplantation expands globally, transfusion medicine will continue to be integral to patient care.

Keywords: Blood transfusion; organ transplantation; ABO blood group; passenger lymphocyte syndrome; therapeutic apheresis

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Introduction

Organ transplantation is now performed worldwide in over 80 countries. The Global Observatory on Donation and Transplantation (GODT), a collaboration of the World Health Organization and the Spanish Organización Nacional de Trasplantes, estimated that in the year 2019 there were 100,097 kidneys (+44% from their first report in 2008), 35,784 livers (+76%), 8,722 hearts (+64%), 6,800 single or double lungs (+104%), 2,323 pancreases (–2%) and 153,863 total organs transplanted (+52%) (1,2). On a per-capita basis, the top 5 countries in 2019 were the United States (US), Spain, France, Korea and Canada (83–123 transplants per million population). However, in absolute numbers the top 5 were the US [40,621], China [19,462], India [12,666], Brazil [9,232] and France [5,910], just ahead of Turkey [5,763]. In the US, 2020 totals kept pace with 2019 despite the COVID-19 pandemic (3).

Current one-year patient survivals in US data are 89–91% for heart, lung and pancreas transplants, 94% for livers, and 96–99% for deceased donor (DD) and living donor (LD) kidneys (*Table 1*). However, waitlists are 1 to 4 times the annual transplant totals for most organs. Waitlist mortality rates for lung, heart and liver candidates are 9–15% and 5% for DD kidney candidates. These statistics help illustrate the impetus to expand organ access, including ABO-incompatible (ABO-i) organs.

Organ transplant patients require comprehensive transfusion medicine support throughout their full course, from evaluation of candidates with ABO typing and antibody titers to the treatment of rejection with therapeutic apheresis. The purposes of this narrative review

Table 1 US Organ Transplants, Waitlists and Survivals

Parameters	Kidneys	Kidney-pancreas	Livers	Hearts	Lungs
LD	5,234	0	491	0	0
% LD	23%	–	6%	–	–
DD	17,583	827	8,415	3,658	2,539
Total in 2020	22,817	827	8,906	3,658	2,539
1 yr patient survival in 2019	96–99%	97%	94%	91%	90%
Waitlist on 9/30/21	97,806	1,855	11,982	3,540	1,014
Ratio waitlist : 1 yr transplants	4.3×	2.2×	1.3×	1.0×	0.4×
Waitlist mortality during 2019–2021	5% DD	4%	12%	9%	15%

US Organ Procurement and Transplantation Network (OPTN) data, October 1, 2021 (3). Accessed at https://optn.transplant.hrsa.gov/data/. LD, living donor; DD, deceased donor.

are to summarize current knowledge of blood transfusion requirements, red blood cell (RBC) alloantibody problems, passenger lymphocyte antibodies, the laboratory support of ABO-i transplants including antibody titers, and therapeutic apheresis indications. Selected reviews in these areas are cited for more focused information.

Perioperative transfusions

Table 2 shows perioperative blood component usage in numerous liver transplant programs. The earliest data from Pittsburgh in 1981 is shown for historical comparison. The Nashville program demonstrated significant transfusion reductions by instituting transfusion guidelines, education, intraoperative RBC salvage and viscoelastometric testing (5). Their post-intervention usage and most of the other series were in the range of 4–8 mean or median intraoperative RBCs and a similar number of units of plasma. The 75th-percentile levels for RBCs ranged from 7–12 units. Intraoperative RBC salvage is commonly used, with 700 mL (mean) and 1,300 mL (median) transfused in Pittsburgh 2013–2014 and in Nashville's intervention phase (5,7). Mean or median intraoperative platelet needs were 1 to 1.5 doses per case. The Toronto and Pittsburgh experiences are of interest because workers published two series at different times, and both programs tended to use less RBCs and plasma in later years (6-9). *Table 3* and *Table 4* show six studies which sought risk factors for higher blood use. Anemia, thrombocytopenia and elevated international normalized ratios or viscoelastometry clotting times were frequently cited, reinforcing the benefits of preoperative patient blood management measures to correct cytopenias and coagulopathies. The Detroit experience was useful because it included preoperative (–1 week) and postoperative (+2 weeks) transfusions in addition to intraoperative usage (12). Across this perioperative period, these patients received approximately twice as many units as in the surgery itself.

In North America and Europe, LD for adult livers are in the minority (6% in the US, *Table 1*), usually selectively arranged for patients with less advanced disease and lower DD priority scores. In this scenario blood needs in LD transplants may be significantly lower, as seen in Scottsdale (18). However, in other regions such as the Middle East, DD are infrequent, LD are used routinely, and blood usage such as in Chengdu and Cairo may be similar to routine DD cases elsewhere (19,20). In a large multicenter analysis, only 2% of 5,202 living liver donors needed RBC transfusions (26).

Melbourne's program described collecting blood from DDs for recipients (13). In donors who were ABO-matched, RhD-compatible, and cytomegalovirus (CMV)-status-compatible (avoiding CMV+ to CMV–), a RBC salvage reservoir full of heparinized donor blood (4 units) was retrieved with the liver, crossmatched with the recipient, washed and processed in the operating room cell salvage instrument, and transfused as needed. Patients receiving donor blood (median 3 units) used less intraoperative blood bank RBCs than propensity-matched patients who did not have donor blood available.

"Dead-icated" deceased blood donors and organ transplants have intersected before. The curious reader may consult Ramsey and Schmidt's historical essay for information about how cadaver blood collections in the Soviet Union in the 1930s–1960s were inspired by the first

Table 2 Transfusions in adult and pediatric liver transplant programs

Location	Year	n	RBC	Plasma	Platelets	Theme
Pittsburgh (4)	1981	17	36 (± NA)	36 (± NA)	5 (± NA)	Early experience
Nashville (5)	2010–2011	156	14±17	16±16	1.5±2.3	Before interventions
	2012–2013	125	7±9	11±12	1.1±1.4	After interventions
Pittsburgh (6)	2004–2006	475	9 [4–11]	7 [2–9]	1.6 (0–2.4)	No pulmonary embolism
Pittsburgh (7)	2013–2014	36	6 [3–9]	4 [3–6]	1 (0–2)	Hemostasis testing
Toronto (8)	1998–2004	460	5 [3–9]	9 [6–14]	1 (0–2)	High-use prediction
Toronto (9)	2002–2015	1,420	4 [1–7]	6–8 [3–11]	1–1.5 (0–5)	Tranexamic acid effect
Seattle (10)	2013–2015	207	5±4	NA	NA	High-use prediction
Baltimore (11)	2014–2016	200	6 [2–12]	7 [2–13]	NA	High-use prediction
Detroit (12)	2007–2017	970	6±7	10±9	2.0±1.8	Blood use
Melbourne (13)	2009–2018	175	3 (0–6)	0 (0–3)	0 (0–2)	No donor blood, paired
		175	2 (0–4)	1 (0–4)	0 (0–2)	Deceased donor blood
Essen (14)	2009–2010	266	2 (0–5)	0 (0–0)	0 (0–1)	Factor concentrates
Montreal (15)	2002–2013	500	0.5±1.3	0.2±1.1	0.1±1.0	Minimal transfusions
Los Angeles (16)	1999–2004	27	0	0	0	Jehovah's Witnesses
Pisa (17)	2007–2016	13	0	0	0	Jehovah's Witnesses
Scottsdale (18)	2001–2004	69 DD	2.9±2.7	2.5±2.4	1.2±1.0	Compared to LD
		27 LD	1.0±1.6	0.8±1.5	0.4±0.7	Lower use in LD cases
Chengdu (19)	2005–2012	218 LD	7.9±6.6	NA	NA	Blood use and outcomes
Cairo (20)	2005–2015	123 LD	9.5± (NA)	9.1± (NA)	2.9± (NA)	Blood use and outcomes
Bergamo (21)	2002–2009	243 (children)	1 (NA)	1.6 (NA)	0 (NA)	Blood use & outcomes
Paris (22)	2009–2014	84 (children)	0.6 BV (0–6)	NA	NA	High-use prediction
Pittsburgh (23)	2008–2017	278 (children)	0.2 BV (0–0.5)	NA	NA	High-use factors

Mean ± standard deviation (SD) or median (interquartile range). Transfusions were all intraoperative (IO) except IO plus 24 hr in Toronto. Pittsburgh 2004–2006 series was compared to 20 other patients with pulmonary embolism. Cairo transfusion means were calculated from their data in two groups. Platelets are expressed in apheresis units or pools (5 whole-blood derived units per pool if not specified). RBC, red blood cell; BV, blood volume; DD, deceased donor; LD, living donor; NA, not available.

kidney transplants there (27). That experience led a surgeon at a small Chicago-area hospital to secretly give cadaver blood transfusions in the 1930s, before one of his colleagues at the same facility later performed the first briefly functional DD kidney transplant in Western medicine in 1950.

Four liver transplant series were notable because of their unusually low transfusion needs. Kirchner *et al.* replaced plasma for clotting factors with factor concentrates and fibrinogen concentrate and gave very few units of plasma and platelets (14). Massicotte *et al.* described 500 liver transplants in Montreal which averaged 0.5 units of RBCs and <0.2 units of plasma and platelets intraoperatively (15). Eighty percent received no RBCs. They performed surgery with low central venous pressures, minimum volume replacement and avoidance of plasma and platelets until bleeding occurred. Jabbour *et al.* and Costanzo *et al.* described bloodless management in two cohorts of Jehovah's Witnesses in the US and Italy who did not permit transfusions (16,17).

Table 2 shows blood use information in pediatric liver transplants. Three series with transfusion data had different patient populations, judging from the patient ages. Younger

Table 3 Analyses of risk factors for increased RBC use in adult liver transplant surgery

Risk factor	Toronto (8)	Seattle (10)	Baltimore (11)
High use definition	≥6 U in 24 hr	>1.25 L & >2 L RBC IO	>10 U IO
Risk expression	Points	On–line calculator	Points
Patient factors	Age >40; Retransplant	Dialysis; Past spontaneous bacterial peritonitis	Liver-kidney transplant; Retransplant
Hematology tests	Hgb <10 g/dL; Platelets ≤70,000/μL; INR 1.2–2 or >2	Hgb; INR	Hgb <10 g/dL; Platelets <100,000/μL; TEG R >6 min
Other tests	Albumin ≤24 g/L; Cr >110 (F) or >120 (M) mmol/mL		

RBC, red blood cell; Cr, creatinine; F, female; Hgb, hemoglobin; INR, international normalized ratio; M, male; IO, intraoperative; TEG R, thromboelastography R value; U, units.

Table 4 Analyses of risk factors for increased RBC use in pediatric liver transplant surgery

Risk factor	Paris (18)	Boston (24)	Houston (25)
High use definition	>1 BV RBCs IO	>1 BV loss in 24 hr	>85th percentile blood use
Risk expression	Points	List	List
Patient factors	*Ex situ* liver transection Prior abdominal surgery		In hospital; split or reduced-sized graft
Hematology tests	Factor V ≤30%	Hgb <8.5 g/dL; platelets <100,000/μL	
Surgical		Surgery >10 hr	Operative time; use of plasma, cryoprecipitate

RBC, red blood cell; BV, blood volume; IO, intraoperative.

patients received proportionally higher RBCs/blood volume. These and other studies examined preoperative risk factors for higher blood use, and split livers used more blood in two studies (*Tables 3*,*4*). The Bergamo group found that patients receiving ≥3 RBC or plasma units intraoperatively (compared to medians of 1 and 1.6 U) had lower 1-year patient survivals (21).

Table 5 tabulates recent data on transfusions in heart transplants. Programs in Pittsburgh and Newcastle had median or mean transfusions of around 3 RBCs, 2–4 plasma units and 1 platelet unit. These studies found correlations between higher transfusions and increased postoperative complications such as graft dysfunction. Several centers including ours described introduction of 4-factor concentrates to reverse warfarin before surgery, showing not only reduced plasma usage but also sometimes reduced RBC transfusions. Transfusions in the 4-factor-concentrate patient groups were similar to the above numbers.

Table 5 displays data on blood use in lung transplants. The Newcastle program gave intraoperative medians of 3 RBCs, 2 plasmas and 1 platelet unit. Studies from Brisbane and Prague showed that intraoperative hemostasis testing reduced intraoperative and postoperative blood needs. Their average intraoperative transfusions guided by testing were around 2 RBCs and ≤0.2 units of plasma and platelets. These were all in bilateral lung transplants. Huddleston *et al.* did not report overall RBC usage, but from their Table 1 we calculated that 44% of single-lung patients received intraoperative RBCs compared to 87% of bilateral lung transplants (39). Initial experience at our institution and elsewhere with lung transplants in COVID-19 patients has seen higher intraoperative blood use due to dense pleural adhesions, with medians [interquartile ranges] of 8 [5–15] RBCs and 4 [3–7] plasma units (38).

Several lung transplant programs have correlated above-average transfusions with adverse outcomes in multivariate analyses controlling for other factors. In Newcastle, patients receiving >1 unit of platelets had decreased 1-year (but

Table 5 Transfusions in heart and bilateral lung transplants

Location	Years	n	Interval	RBC	Plasma	Platelets	Theme
All UK (28)	2012–2015	450	IO?	2.7	2	1.4	PGD & transfusions
	No PGD	287		2	2	1	
	PGD	163		4	2	2	
Pittsburgh (29)	2010–2016	197	IO + 24 hr	3 [1–5]	4 [1–8]	1 (0–2)	Transfusions & adverse events
Norfolk US (30)	2011–2015	12	IO + 24 hr	7	8	2.5	Warfarin-plasma
		13		3	4	2	Warfarin-4FC
Chicago (31)	2010–2015	39	IO	7 [4–9]	9 [6–13]	4 [2–6]	Warfarin-plasma
		21		3 [1–5]	4 [1–6]	4 [2–4]	Warfarin-4FC
Cleveland (32)	2010–2016	49	Day 0–2	6 [3–9]	8 [6–10]	2 [2–3]	Warfarin-plasma
		57		7 [4–11]	6 [4–8]	2 [1–3]	Warfarin-4FC
Boston (33)	2013–2016	42	IO	5 [3–7]	6 [4–8]	2 (1.5–2.5)	Warfarin-plasma
		32		2 [1–3]	1 (0–2)	2 (1.5–2.5)	Warfarin-4FC
Newcastle (34,35)	2003–2013	311 (lung)	24 hr	3 (NA)	2 (NA)	1 (NA)	Transfusions & outcomes
Brisbane (36)	2010–2014	47 (lung)	IO	4.4	3.6	1.4	Before POC testing
		46 (lung)		1.6	0.1	0.2	POC testing
Prague (37)	2018–2020	36 (lung)	IO + 24 hr	3.1	7.8	0.6	Before ROTEM
		31 (lung)		1.7	0	0.2	ROTEM
Multiple (38)	2020	12 (lung)	IO	8 [5–15]	4 [3–7]	NA	COVID-19 transplants

Mean ± SD or median (IQR). RBC, red blood cell; 4FC, 4-factor concentrate; BV, blood volume; IO, intraoperative; N, number; NA, not available; POC, point of care; PGD, primary graft dysfunction; ROTEM, rotational thromboelastometry; US, United States.

not 10-year) survival (34,35). In Minneapolis, patients receiving >15 units of RBCs had lower hazard-adjusted 30-day survival (39). In Durham, Seay *et al.* examined plasma:RBC ratios in patients receiving >4 units of RBCs in 72 hr, and when plasma units were >50% of RBC units, there was a higher rate of primary graft dysfunction (40). They instituted viscoelastometric testing late in their study period, so did not examine that impact on their findings.

Transfusions to lung donors might also adversely affect outcomes. This was examined in all US lung transplants from 1996 to 2014 (41). For the 6% of donors who received >10 units of RBCs, 30- and 90-day recipient multivariable-adjusted mortalities were 50% higher (approximately 6% *vs.* 4% at 30 days). This was linked to primary graft dysfunction, which has clinical similarities to transfusion-associated acute lung injury (TRALI), and the authors and the accompanying editorial speculated whether TRALI in donors might have contributed to these findings (41,42). During the latter part of this 18-year period, TRALI rates in the US declined substantially due to introduction of male-predominant plasma [2007] and human leukocyte antigen (HLA) antibody screening in parous plateletpheresis donors [2008–2009] (43). This decline leveled off after 2010 in the New York Blood Center's timeline analysis, but the AABB standard for apheresis platelet screening did not take effect until 2016. The donor-transfusion study compared eras and the 2010–2014 era was not statistically different from earlier years, but this question could be reexamined in the current framework of TRALI mitigation. Current policies from the US Organ Procurement and Transplantation Network (OPTN) for organ donors do not require information on donor transfusions other than for assessment of hemodilution of infectious-disease test specimens (44).

Intraoperative blood transfusion needs for kidney or pancreas transplants have not been studied in recent years, but are generally modest. The blood order schedule at Johns Hopkins Hospital recommends 2 RBCs crossmatched for kidney and kidney-pancreas transplants (45).

Special blood component needs

Ex situ machine perfusion of donor lungs, livers and kidneys is increasingly employed and often includes blood bank RBCs in oxygenated circuits. Callaghan *et al.* reviewed several issues for this practice with regard to blood group compatibility, unit disposition tracing and potential infection transmission (46).

Leukoreduced RBC and platelet transfusions were formerly a special requirement in most organ transplant candidates and patients for mitigation of HLA alloimmunization and CMV exposure, but near-universal leukoreduction is now standard in most countries performing organ transplants.

Leukoreduction also appears to reduce the risk of transfusion-associated graft-versus-host disease (TA-GVHD) in patients in risk groups who inadvertently received unirradiated blood, but irradiation is still the standard of practice when indicated (47). TA-GVHD has been reported in 5 organ transplant patients, as reviewed by O'Brien *et al.* when describing the most recent case in 2013 (48). In a 2014 US practice survey of over 2,000 laboratories, a significant minority (37%) irradiated blood for solid organ transplants (49). However, given the rarity of these events when most patients receive unirradiated blood, most published recommendations and guidelines do not include all organ transplants (50,51).

The manufacturer of alemtuzumab (anti-CD52), used widely in organ transplant immunosuppression protocols, recommended blood irradiation in patients receiving the drug as CAMPATH for chronic lymphocytic leukemia (CLL) (52). The same manufacturer's prescribing information for alemtuzumab as Lemtrada in smaller annual doses for multiple sclerosis does not recommend blood irradiation (53). In the 2014 survey, 29% irradiated blood for alemtuzumab recipients (49). In a 2015 review of TA-GVHD, all 3 author institutions irradiated blood for alemtuzumab patients (54).

The immunosuppressive risk from alemtuzumab for TA-GVHD was reexamined by Hui *et al.* in London (55). The drug manufacturer based their irradiation recommendation on one trial patient with CLL who had also received fludarabine, another drug with more established TA-GVHD risk. No other cases have been published. Hui *et al.* reviewed 647 renal transplant patients in their program who received alemtuzumab and were transfused with non-irradiated leukoreduced blood. No cases of TA-GVHD occurred. Based in part on these data, the British Society for Haematology removed alemtuzumab from their 2020 recommendations for blood irradiation (56).

RBC alloantibodies

Most RBC antibody information in organ transplants comes from liver transplants, in which blood bank support is most affected. *Figure 1* shows fairly constant RBC alloantibody rates in 10 cohorts of liver transplant patients over 30+ years. The preoperative median rate was 6.15% and the overall total median rate was 7.4%, with most series between 4–9%. The 1980s series had higher rates of postoperative antibodies, likely attributable to the higher blood use in that era. However, the overall rates have not changed over the entire period. In the series with gender information, male rates were 4–11% and female rates were 8–15%, and in individual series the female rates were 1.3 to 3 times the male rates. In adults this difference has been attributed to pregnancies, but even the Pittsburgh pediatric series showed the same trend, 4% in males and 8% in females (57).

We have examined the available data in these series for prevalence of difficult antibodies, defined as >3 antibodies or with <25% of donors antigen-negative, and 1–4% of all patients fit this criterion. When sufficient antigen-negative units may not be available, we have attempted to start with at least 10 compatible units, and as many more as possible, before switching to antigen-positive or antigen-untested units after some degree of antibody washout (65). We also take into account whether the antibody is currently detectable, although with some extra caution with historic Kidd antibodies. Clinicians are alerted to the possibility of a delayed hemolytic transfusion reaction. This approach generally has been successful for avoiding intraoperative hemolysis.

Antibodies to high-prevalence antigens pose special challenges when large numbers of RBCs may be needed. Case reports have described management of anti-PP_1P^k, anti-Jr^a and anti-Jk3 in liver and heart transplants (66-68). One liver transplant patient with anti-e received e+ RBCs in surgery and then a postoperative RBC exchange with e-negative RBCs when they became available (69).

In most RhD-negative patients receiving RhD+ RBCs, the general anti-D alloimmunization rate is 20–35% (70). However, we and others have documented that the immunosuppression administered in organ transplantation appears to significantly reduce new anti-D formation (71-73). This allows for switching to RhD+ RBCs if the RhD–negative RBC supply is low. We are still cautious in girls and women of child-bearing age.

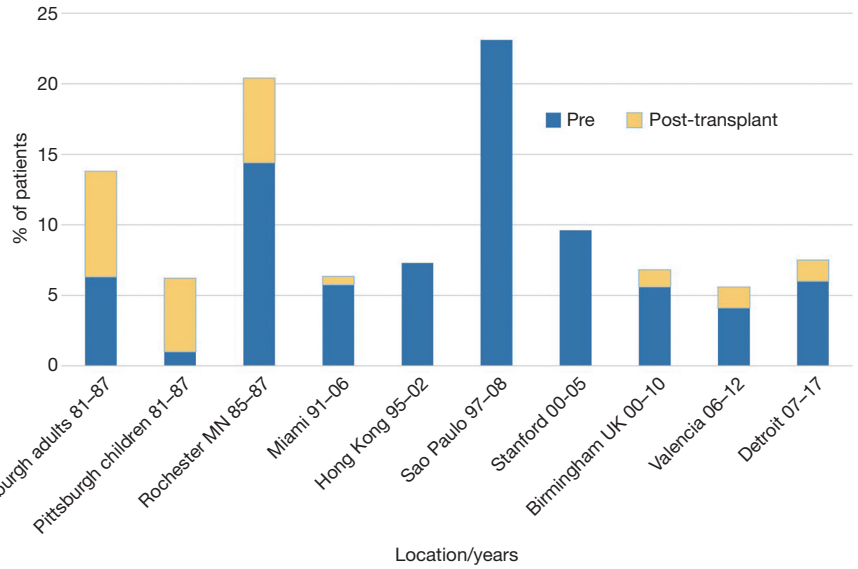

Figure 1 Frequency of RBC alloantibodies in liver transplant patients. Percentages of liver transplant patients with RBC alloantibodies. Pre, pre-transplant; Post-transplant, additional patients with antibodies developing post-transplant. References: Pittsburgh (57); Rochester, MN (58); Miami (59); Hong Kong (60); Sao Paulo (61); Stanford (62); Birmingham, UK (63); Valencia (64); Detroit (12).

Passenger lymphocyte syndrome

In the 1980s we and many others recognized that kidney (74) and liver (75) transplants, especially from ABO-unmatched grafts such as O donors to non-O recipients, sometimes produced RBC antibodies as a humoral graft-versus-host response. The term 'passenger lymphocyte syndrome' (PLS) was adopted for this phenomenon (74). Although these antibodies were usually short-lived, there were cases of severe and rarely fatal hemolysis. We reviewed the burgeoning literature in 1991 (76). In ABO-unmatched transplants, ABO-antibody and hemolysis frequencies were 40% and 29% for livers and 17% and 9% for kidneys, respectively. By then we and others also began to encounter cases of non-ABO RBC antibodies, usually from donors whose antibody screens were positive prior to organ donation (77).

In the 30 years since our first review, this literature has continued to grow and other examples of antibody transfer beyond blood groups have been recognized. *Table 6* shows key references for ABO PLS in more recent years, including several detailed reviews. For ABO, the authors of the post-1990 liver and kidney series mostly sought hemolysis, so their frequencies were more akin to hemolysis rates than to overall antibody rates. In 7 liver series since 1991, the aggregate hemolysis rate was 19%, and in three kidney series, the aggregate hemolysis rate was 6%. Both were somewhat lower than the 1980s experience of 29% and 9%, respectively. Thomas *et al.* recently reported a 12-year experience with ABO-unmatched intestinal and intestine-containing multivisceral transplants; 9 of 31 patients (29%) had PLS hemolysis (92). They also reviewed 7 previously reported intestinal cases. Presumably the larger lymphoid burden in intestinal transplants makes PLS more likely. Additional cases from lung and heart transplants were reported by Aujayeb *et al.* (91). In many centers, ABO-unmatched deceased-donor transplants are uncommon because of the need to provide group O patients with group O grafts. In the US in 2013–2015, 6% of DD adult liver transplants were ABO-unmatched, about 265 per year (93). Only 12% of these were O-to-A, the combination with the highest rate of hemolysis in our 1991 review. However, living-donor kidneys and liver segments are frequently ABO-unmatched with potential for PLS.

Anti-D was transferred in >30 cases (*Table 7*). In a series of 97 lung transplants in Toronto, the only two donors with anti-D both transferred the antibodies to their 3 recipients (100). Other donor-derived RBC antibodies in the Rh, Kell, Kidd, Duffy and MNS blood groups have been seen. The US OPTN does not require determination of donor RBC antibody status, and transfusion services usually do not know who will become a deceased organ

Table 6 ABO passenger-lymphocyte antibodies from transplanted organs

Organ	Reference	N or rate of hemolysis
Reviews		
Kidney	Nadarajah 2013, (78)	
Liver	Romero 2015, (79)	
All 2009–2019	Moosavi 2020, (80)	
Liver	Ramsey 1991 review, (76)	33/115, 29% hemolysis; 36/90 with anti-A/B, 40%
	Triulzi 1992, (81)	5/9
	Kunimasa 1998, (82)	1/27
	Romero 2015, (79)	10/56
	ElAnsary 2015, (83)	2/11
	De Bruijn 2017, (84)	4/10
	Woolfson 2019, (85)	7/51 (pediatric)
	Brunetta 2020, (86)	5/16
Sum post 1991		34/180, 19% hemolysis
Kidney	Ramsey 1991 review, (76)	15/165, 9% hemolysis; 24/144 with anti-A/B, 17%
	Povlsen 1990, (87)	0/108 Aza, 2/34 CsA
	Elhence 1998, (88)	2/15
	Bakr 2009, (89)	10/214
	Achkar 2011, (90)	5/37
Sum post 1991		17/266, 6% hemolysis
Lung	Aujayeb 2014, (91)	6 cases
Heart	Aujayeb 2014, (91)	1 case
Intestine-containing	Thomas 2021, (92)	9/31, 29% hemolysis

Aza, azathioprine; CsA, cyclosporin A.

donor. However, when organ donors are found to have RBC antibodies, it seems prudent to notify the transplant service and type the recipient's RBCs for the cognate antigens so that potential PLS can be anticipated.

PLS antibodies typically develop 7–14 days after transplant and persist for a few weeks. Management usually consists of giving antigen-negative RBC transfusions. In severe PLS after intestinal transplantation, plasmapheresis and rituximab were employed (92). One liver transplant with anti-D was associated with profound reticulocytopenia (97).

Our 1991 review noted the first case of organ-transmitted immune thrombocytopenic purpura (ITP) (112) and speculated that transfer of other antibodies such as anti-CMV and anti-hepatitis C virus (HCV) was possible. Now to date, 7 cases of platelet autoantibody transfer (donor ITP) reviewed by Aranda Escaño *et al.* (113) and 6 cases of platelet alloantibody PLS (donor human platelet antigen antibodies) reviewed by French *et al.* (114), including one from our institution (115), have been reported (*Table 8*). There are also suspected cases of anti-HCV, anti-CMV and anti-HLA antibody transfers. One patient received factor VIII inhibitor antibody from a liver transplant (116).

PLS involves mostly but not exclusively IgG antibodies. Muller *et al.* recently reviewed 9 patients with IgE allergy transfer by organ transplants and investigated their own recipients of 3 donors who had died from anaphylaxis (121). One of their 3 donors transferred symptomatic peanut allergy to liver and lung recipients. In the 8 prior reports, 6 donors had died from anaphylaxis, and allergic reactions were acquired in liver, pancreas and lung (but not kidney)

Table 7 Non-ABO passenger-lymphocyte RBC antibodies from transplanted organs

Antibody & organ	Reference	Cases & antibodies
Reviews		
Anti-D	Ainsworth 2009, (94)	23 cases reviewed
Non-ABO RBC	Draper 2018, (95)	
Anti-D since 2009		
Liver	Turiño-Luque 2012, (96)	1
	ElAnsary 2015, (83)	1
	Romero 2015, (79)	2
	Gniadek 2017, (97)	1
	Tsang 2019, (98)	1
Kidney	Karanth 2014, (99)	1
Kidney-pancreas	Tsang 2019, (98)	1
Lung	Cserti-Gazdewich 2009, (100)	3
Other RBC antibodies		
Liver	Kim 1992, (101)	D-E
	Seltsam 2001, (102)	K-Fy^{a}
	Hareunevi 2002, (103)	Jk^{a}
	Grosskreutz 2008, (104)	D-C
	Shortt 2008, (105)	D-C-k
	De Luna 2011, (106)	E
	Koepsell 2013, (107)	Auto–anti-Kp^{b} (donor +)
	Draper 2018, (95)	D-C
	Tsang 2019, (98)	Jk^{a}
Kidney	Ramsey 1991 review, (76)	c [n=3], e
	Schwartz 1992, (108)	D-C
	Larrea 1997, (109)	E
	ElAnsary 2015, (83)	C (and B)
Kidney-pancreas	Seltsam 2001, (102)	K-Fy^{a}
	Hurtarte-Sandoval 2015, (110)	D-E
Multi-visceral	Makuria 2009, (111)	M

RBC, red blood cell.

recipients. Two of the 3 lung transplant transfers were especially long-lasting, with persistence of peanut allergy for 1.5 to 7 years. The authors recommended that recipients of lungs, livers and pancreases from fatally anaphylactic donors should have allergy evaluations and avoid known inciting antigens until cleared by testing and monitored challenges. These cases illustrate that the production of probably any clinically significant donor antibody can be transferred to organ transplant patients in a conducive setting.

ABO incompatibility

ABO compatibility is normally required for organ transplants to avoid ABO-antibody-mediated acute

Table 8 Non-RBC passenger-lymphocyte antibodies from transplanted organs

Antibody	Reference	Cases
Platelet autoantibodies (ITP)	Aranda Escaño 2020, (113)	7 cases reviewed
Platelet alloantibodies (HPA)	French 2020, (114)	6 cases reviewed
Factor VIII inhibitor	Hisatake 2003, (116)	Liver recipient
HLA alloantibodies	Maxfield 2015, (117)	Donor -> 2 kidneys
HLA alloantibodies	Kummrow 2019, (118)	Donor -> 5 organs
Anti-CMV	Koshizuka 2019, (119)	Lung recipient
Anti-HCV	Smibert 2018, (120)	4 lung recipients
IgE allergy transfer	Muller 2020 review, (121)	10 cases; 7/9 donors died of anaphylaxis

RBC, red blood cell; CMV, cytomegalovirus; HPA, human platelet antigens; HCV, hepatitis C virus; ITP, Immune thrombocytopenia.

rejection. Transplant recipient candidates and organ donors should have two independent typings to confirm their ABO blood group for listing and matching (44). The US OPTN published a guidance for blood type determination, summarizing for the transplant community familiar blood bank issues such as recent transfusions, allogeneic stem cell transplants, weak subgroups, acquired B-like antigens, and low ABO antibody levels (122). This document also discusses the ancillary use of DNA-based ABO phenotype prediction to assist with ambiguous typings caused by subgroups or massive transfusions. ABO genotyping test kits are not approved by the US Food and Drug Administration (FDA) but are available on a research-use-only basis employing technologies familiar to laboratories doing HLA typing. A Chinese group recently published their experience using ABO genotyping to resolve serologic typing discrepancies in 302 uremic patients with ABO subgroups (123). Although little to date has been published on ABO genotyping in organ donors, we can expect this area to grow.

As with blood transfusion, US OPTN policies require careful double-checking of correct and compatible organ and patient. A two-step process of preliminary and final time-out verification in the operating room is mandated before transplant. At our hospital the transfusion service enters each organ and its identification data into the laboratory information system as a "component", performs an electronic ABO crossmatch with the recipient, and issues a compatibility tag similar to a transfusion tag to the operating room for their time-out verifications (124). Since 2004, we have processed >7,000 organ transplants without ABO error using this procedure.

Evasion of the ABO barrier to expand organ availability has been pursued in two ways: (I) weak A subgroup organs to B or O patients, and (II) fully ABO-i transplants. These comprise a small fraction of all transplants, but the transfusion medicine support of these protocols is a significant aspect of laboratory testing and therapeutic apheresis at the centers performing them. Kidney paired donations, in which donor-recipient pairs swap donors for compatibility purposes, can help avoid fully ABO-i transplants but may include A subgroup donors.

Around 20% percent of European or African-ancestry group A or AB persons' RBCs are negative for the wild-type full-strength A_1 antigen as determined by *Dolichus biflorus* A_1 lectin (125). Most A_1-negative subjects have the A_2 genotype and express about 20% of the A_1 level of antigens on their RBCs and endothelium. Group A or AB A_1-negative organs (termed non-A_1 in OPTN policies), mainly kidneys, can be transplanted to B or O persons with reasonably equivalent success rates, as discussed below. In US OPTN policies for DDs, A_1 typing on two different specimens is required to confirm A_1-negative status in group A donors and is optional in AB donors, when not precluded by recent transfusions. Patients can be listed as candidates for A_1-negative organs if appropriate. A_1-negative phenotypes are much less common in Asia (123,126). In east Asia, weak B subgroups presenting with plasma anti-B discrepancies and characterized with ABO genotyping (123) may be a future area of organ transplant investigation.

Correct donor A subgroup typing is crucial for safely and effectively allocating A and AB kidneys with A subgroups (Asub and AsubB). Recently the US-based College of American Pathologists (CAP) ABO subgroup proficiency

Table 9 US OPTN policies for ABO antibody titers in ABO-incompatible organ transplants

Organ	Who	When	Titer limit
Kidney	B candidates for Asub or AsubB organs	Confirm eligible every 90 d	Program written policy for titer limit
Kidney paired donation	B candidates for Asub or AsubB organs	At listing	IgG <8
	O candidates for Asub organ		
Pediatric heart: at listing	<1 yr old, status 1A or 1B	In past 30 d	None specified
	1 yr to <2 yr old, status 1A or 1B	In past 30 d	≤16 and no recent titer reduction treatments
			If multiple titers/sample, report highest
Follow-up reports		Every 30 d	
		≤24 hr pre–transplant	
		Graft loss if <1 yr	
		Last before death if <1 yr	
Pediatric lung	All same as hearts, status priority 1		

Organ Procurement and Transplantation Network (OPTN) Policies (44). Asub, A subgroup.

testing program analyzed its results (127). A_1 and A_1B specimens were mistyped as A_1-negative in 0.8% of results, which in real life could lead to inadvertent transplantation of A1-incompatible organs, if not caught by second typings. Nearly 5% of Asub challenges were mistyped as A_1, which could lead to missed opportunities for A_1-negative transplants.

Beginning in 2014, group B renal candidates in the US were accorded preferential allocation of A_2 and A_2B kidneys. In the first 2 years of this protocol, 9% of group B patients (150/year) received A_2 or A_2B kidneys in 25% of US transplant centers (128). Transplant centers are required to have local policies addressing acceptable anti-A titers in these candidates (*Table 9*). Gilbert *et al.* and Azzi *et al.* have reviewed ABO issues in A_2-incompatible kidney transplants (129,130). Azzi *et al.* summarized 13 prior studies of A_2-incompatible deceased- or living-donor kidneys, finding that 8 studies used anti-A_1 titers and the rest anti-A_2 titers (see ABO antibody titers section below) (130). Most follow IgG titers although some centers also report IgM levels. Azzi *et al.* successfully used anti-A_2 IgG titers <16 as their acceptable level without plasma exchange. Outcomes in A_2-incompatible kidney transplants have been similar to standard ABO-compatible grafts, and some have come to think of them as ABO-compatible by comparison with fully incompatible transplants (131).

A_2-incompatible liver transplants are also performed in selected patients. They comprised 1% of deceased-donor adult liver transplants in the US in 2013–2015, or about 60 per year (93).

Fully ABO-i kidney transplantation was reviewed by Hourmant *et al.* (132). Most reports have sought a preoperative IgG anti-A_1 titer of <8, but some have used <16 or <32. One program successfully used IgM titers <4 regardless of IgG (133). A meta-analysis of 26 studies worldwide found that overall 1-year graft survival was 96% compared to 98% (P<0.001) in ABO-compatible transplants, and the rates of antibody mediated rejection were 10% *vs.* 2% (134). In the US, 1.3% of all living-donor adult renal transplants in 2000–2015 (930 cases, or about 60/year) were fully ABO-i (131). The absolute 1-year graft loss rate was not given but the adjusted hazard ratio was 2.34, similar to the literature meta-analysis of 4% *vs.* 2%. The 1-year prevalence of acute rejection episodes was 19% *vs.* 10%. Successful ABO-i kidney transplants undergo an incompletely understood process called accommodation in which graft function is maintained despite continued ABO antibody and C4d complement deposition. Mechanisms include downregulation of ABO plasma antibody and kidney ABO antigen levels and upregulation of renal complement regulatory molecules (135). Overall, good although not quite equivalent outcomes are achieved with ABO-i kidney transplants, and they expand organ availability for some patients such as those with broad HLA alloimmunization.

Infants do not produce RBC antibodies until at least 4 months of age and can become tolerant to antigens to which they are exposed at a young age. Because of the scarcity of neonatal and infant heart donors, fully ABO-i heart transplants for infants began in the 1990s and have become routine in some pediatric heart transplant programs. Kozik *et al.* examined US OPTN records from 2007–2018 (136). By the end of the period, 72% of heart transplant candidates under 2 years old were listed for ABO-i hearts and 25% of transplants were ABO-i. ABO-i heart recipients had survivals and 1-year rejection-episode rates equivalent to ABO-compatible recipients. Equivalent propensity-score-matched survivals were also seen in a large international registry of transplants from 1999 to 2018 (137). Infants receiving ABO-i hearts have long-term discrepancies in their ABO typings because of near-absence of ABO antibodies against the heart, and in particular some are missing antibodies to type 2 ABO glycans expressed in cardiac tissue (138).

OPTN policies for status 1A or 1B ABO-i pediatric heart transplant candidates are summarized in *Table 9*. No titer limit is specified for patients <1 year old. For patients between 1 and 2 years old, the anti-ABO titer threshold is <16 for listing. The titer method and whether IgG or IgM are not specified. If multiple titers are done on the same specimen, the highest titer must be reported. Dean *et al.* surveyed 21 US and Canadian transfusion services on their testing and transfusion practices in 2018 (139). Seventy-one percent performed both IgM and IgG titers. Half of the programs used cutoff titers other than 16 for antibody reduction therapy for high titers. Respondents were asked about whether they mitigated ABO antibody content of transfusions. About 50% gave washed or volume-reduced RBCs preoperatively or postoperatively, and 70% intraoperatively. Eighty percent to 90% gave plasma-rich products as group AB or for platelets, volume-reduced.

OPTN policies also permit priority 1 listing for ABO-i infant lung transplants, using the same criteria as for hearts. These are very uncommonly done. Costello *et al.* recently reviewed the limited available information (140).

Transfusion services supporting A_2- and A_1-incompatible transplants should have protocols in place to avoid giving plasma-rich blood components containing anti-A/B against the organ. Transplant services should notify the transfusion service when a patient is listed for ABO-i transplant so that ABO-appropriate plasma and platelets are given. Platelets can be washed or volume-reduced (2 hours processing time) for non-urgent needs if necessary. The small amount of plasma in additive-solution RBCs may not be significant except possibly in infants.

ABO antibody titers

ABO antibody titration in ABO-i organ transplant candidates and recipients is an important element of patient care. ABO antibody hemagglutination was the first clinical immunohematology test in the early 1900s and is one of the oldest laboratory tests still routinely performed. However, serial plasma dilutions, hemagglutinations and interpretations are all technique- and method-dependent. In manual tube titration, endpoints plus or minus one tube are generally accepted in blood banking as equivalent and within the limits of feasible precision. Exact titer thresholds such as those in the OPTN policies (*Table 9*) do not reflect this reality.

Group O persons usually have much higher IgG than IgM ABO titers, whereas group A and B persons have equal or higher IgM titers (141). As discussed in the transplant section, both IgG and IgM titers are often done in ABO-i transplant patients. Although IgG levels are most often monitored clinically, IgM antibodies more readily fix complement. Some laboratories titer IgG after IgM inactivation with dithiothreitol (142), but most do not (141).

The reproducibility of ABO titers across different laboratories is notoriously inexact. Proficiency testing (PT) programs receive a broad range of results for the same plasma. A US expert group studied this issue in 2008 and suggested a uniform method for reading endpoints (tube weak + antiglobulin phase) based on data from a referee panel (143). However, when this was applied for several years among >500 laboratories in a large PT program, agreement for the uniform method was no better than for others (144). Japanese and Korean laboratories went through analogous processes with more success, improving consensus on external quality assessments with standardized tube methods (142,145). Recently an Australasian pathology quality assurance program rediscovered widely variant titer results when external samples were tested across 24 laboratories with many different methods; e.g., anti-A_1 titers on the same plasma ranged from 8 to 1,024 (146). In the United Kingdom, facilities whose laboratories reported higher titers on external-assessment specimens performed more plasma exchange procedures for ABO-i kidney transplants (147).

To seek more objective readouts and reduce hands-on time compared to tube hemagglutination, other methods

Table 10 ABH antigen structures in RBCs and transplant organs

Structure	Type 1—secretors	Type 2	Type 3	Type 4	References
Locations	Endoderm; Secretions	Ectoderm; Endoderm; Secretions	Mucin; Glycolipids	Glycolipids	(154)
H precursors	H (Le^d) on Le^c	H (CD173)	H on T	Globo-H on P	(154)
RBC A_1	From plasma	Major	Minor-glycolipids	Minor	(154,155)
A_2	None*	Reduced	Weak or none	None	
B	From plasma	Major	None	None	
Kidney A_1	Trace (whole kidney)	Minor: distal tubules; collecting ducts	Minor (whole kidney)	Major: distal tubules; collecting ducts	(154,156-158)
A_2				Reduced	
B				Trace	
Heart A_1 & B	None	Positive	None	None	(155)
A_2		Reduced			
A_2B		No A detected			
Liver A_1 & B	Bile ducts, arteries	Some	Some		(157,158)
A_2	Reduced				

*, Jeyakanthan *et al.* examined stored reagent RBCs (155). RBC, red blood cell.

have been examined. Johns Hopkins Hospital in Maryland was an early proponent of manual IgG gel titers (148). More recently they reported that automated dilution and hemagglutination on the solid-phase platform gave results generally equivalent to manual dilution and manual gel; group A and B samples were slightly higher in gel (141). Adkins *et al.* found that IgM anti-A and anti-B automated gel titers were comparable to tube direct agglutination and were equivalent across instruments and between two laboratories (149). Shim *et al.* compared manual tube, manual gel and automated erythrocyte-magnetized technology (EMT) titers (150) (EMT pulls reagent RBCs coated with iron particles to the bottom of microwells by magnetic force instead of centrifugation before dispersal or hemagglutination is assessed.). All 3 methods were comparable for IgM but IgG patterns varied by blood type and method. Responding to growing interest in automated-platform antibody titers, the CAP introduced proficiency testing in 2020. Flow cytometry has been investigated for detecting binding of titered antibodies to RBCs (151,152) and for assessing ABO antibody levels after ABO immunoadsorption (153).

But are RBCs actually the best target to assess anti-organ ABO antibodies? A and B antigens are synthesized on four main H-precursor carbohydrate structures whose distributions vary among organs. *Table 10* compares A_1 and A_2 RBCs and organs with regard to ABH chain types. In the liver, the Type 1 ABH content of hepatic bile ducts is determined by secretor status. Type 2 structures are the major class on RBCs and in hearts. Most ABO antigens in kidneys are type 4, synthesized onto P antigens. RBCs have little type 4 antigen, and A_2 RBCs, which have been advocated for titers to monitor A_2-incompatible kidneys, have none.

The potential clinical significance of ABH structures is suggested by the work of Jeyakanthan *et al.*, who assessed antibodies in pediatric heart transplant patients using glycan microarrays (155). As noted earlier, children with ABO-i hearts have reduced levels of anti-A or-B against their organs. Jeyakanthan *et al.* found that group O patients who received group A hearts are specifically missing IgM and IgG antibody to type 2 antigens borne by their hearts, but still have antibodies to types 1, 3 and 4.

Another emerging tool is the ability to introduce ABH-chain-specific antigens into RBCs. Carbohydrate structures of interest have been linked by spacers to glycolipids. When these constructs are mixed with RBCs, the RBC membranes take up the molecules and the RBCs then express the added

Table 11 Indications for therapeutic apheresis in organ transplants: American Society for Apheresis (ASFA) guidelines

Organ	Indication	Procedures	Category	Grade
Kidney ABO-c	Desensitization LD	TPE/IA	I	1B
	Antibody mediated rejection	TPE/IA	I	1B
	Desensitization DD	TPE/IA	III	2C
Kidney ABO-i	Desensitization LD	TPE/IA	I	1B
	Antibody mediated rejection	TPE/IA	II	1B
Liver ABO-i	Desensitization LD	TPE	I	1C
	Desensitization DD	TPE	III	2C
	Desensitization	ECP	III	2C
Liver	Acute rejection	ECP	III	2B
	Immune suppression withdrawal	ECP	III	2B
	Antibody mediated rejection	TPE	III	2C
Heart	Rejection prophylaxis	ECP	II	2A
	Cellular/recurrent rejection	ECP	II	1B
	Desensitization	TPE	II	1C
	Antibody mediated rejection	TPE	III	2C
Lung	Bronchiolitis obliterans	ECP	II	1C
	Desensitization	TPE	III	2C
	Antibody mediated rejection	TPE	III	2C

From 2019 ASFA guidelines (161). Within each organ group, indications are listed from higher to lower categories and evidence grades. Categories: I, first-line therapy; II, second-line therapy; III, optimum role not established. Grade of evidence: recommendation strong [1] or weak [2]. Quality of evidence high (A), moderate (B) or low (C). ABO-c, ABO-compatible; ABO-I, ABO-incompatible; DD, deceased donor; ECP, extracorporeal photopheresis; IA, immunoadsorption; LD, living donor; TPE, therapeutic plasma exchange.

antigens. The manufacturer, Kode Biotech (Auckland, NZ), terms such RBCs kodecytes. Type-2-augmented RBCs were evaluated for titrating ABO antibodies in candidates for ABO-i renal transplants (159).

Lindberg *et al.* adsorbed plasma *ex vivo* with types 1, 2, 3 or 4 group A and B tetrasaccharides on Sepharose beads (160). Partial type-specific removal was seen for IgG, but not for IgM.

ABO-i kidney transplants are nearly as successful as ABO-compatible transplants. However, graft survival is slightly lower and patients have more infections under extra humoral immunosuppression, and more bleeding complications after preoperative plasma removal procedures (132). If ABO antibodies to organ-predominant ABO antigen structures—type 1 in livers, type 2 in hearts, type 4 in kidneys—could be assayed using targets like glycan arrays or modified RBCs, and reduced *in vivo* by more focused structure-specific immunoadsorption, perhaps outcomes could be improved with less adverse events and the ABO barrier could be overcome for more patients.

Therapeutic apheresis

Therapeutic apheresis (TA) is employed in organ transplantation to remove HLA or ABO antibodies before or after transplant or to treat graft rejection. At active transplant centers, these treatments constitute a significant portion of the apheresis program's activities. *Table 11* shows the current indications for apheresis in organ transplantation in guidelines of the American Society for Apheresis (ASFA) (161). Therapeutic plasma exchange (TPE) is mostly recommended for HLA donor-specific antibody (DSA) removal during pre- or post-transplant desensitization or to help treat antibody-mediated

rejection (AMR). Immunoadsorption (IA) removes antibodies by running plasma through devices which bind immunoglobulin (e.g., Staphylococcus protein A) or ABO antibodies (ABO glycans). (IA devices are not available in the US except in research protocols.) Extracorporeal photopheresis (ECP) is employed in liver, heart and lung transplants to treat or prevent rejection. TA is usually performed in conjunction with other measures to suppress humoral or cellular immunity as indicated.

Abbes *et al.* reviewed HLA antibody testing methods in the context of organ transplants and TA (162). Eighteen to 30% of candidates are HLA-sensitized and around 15% develop new antibodies post-transplant. Although cell-based cytotoxicity testing is still sometimes done, especially to assess complement fixation, most antibody testing utilizes solid-phase Class I and II antigens. Candidates are screened for HLA antibodies and evaluated for DSA when a transplant is considered. HLA laboratories have individualized methods for evaluating antibody levels with fluorescence intensities and titers.

Experts from the AABB Apheresis Committee provided a practical overview of TA practices in transplantation (163). For desensitization, pre-treatment ABO or HLA antibody titers help determine the feasibility and number of TA procedures needed. TPE is often performed every other day to allow for equilibration of extravascular IgG into plasma for the next procedure, although in acute AMR, some centers start with several daily procedures. Replacement fluid is usually albumin unless plasma is needed for hemostasis perioperatively or during bleeding.

In ECP, peripheral blood mononuclear cells (MNCs) are separated, exposed to 8-methoxypsoralen (8-MOP) either by administration to the patient or *ex vivo*, and irradiated with ultraviolet A (UVA) light to induce nucleic acid crosslinking by 8-MOP. ECP is done either by dedicated photopheresis instruments with in-line irradiation or by treating collected MNCs *ex vivo* and reinfusing separately. The treated MNCs then undergo apoptosis over 1 to 2 days.

In the US photopheresis devices are FDA-approved for treating cutaneous T-cell lymphoma. The mechanisms of immunomodulation for treatment of heart, liver or lung rejection are uncertain. Phagocytosis of apoptotic MNCs may induce a shift from inflammatory to anti-inflammatory cytokines and increased T-regulatory cells (164). Some UVA-irradiated MNCs may survive and become tolerogenic dendritic cells (165). ECP is often scheduled in a cycle of two treatments on consecutive days. Treatment courses are variable and response-dependent. ASFA guidelines give examples in cardiac rejection of cycles every 2–8 weeks for several months, and in lung-transplant bronchiolitis obliterans syndrome of 12 gradually spaced-out cycles over 6 months.

ECP is not included in the 2019 ASFA guidelines for renal transplants. In 2019 Tamain *et al.* reported retrospective experience with 33 cases of renal rejection treated with ECP because standard therapies failed or were contraindicated (Tamain). Patients initially received 1–2 treatments/week, tapered to monthly treatments as long as their graft survived. One-year graft survival was 61%. Of note were 6 patients with AMR in whom standard steroids, TPE and intravenous immune globulin (IVIG) or rituximab either failed (n=1) or became contraindicated by infection (n=5), and 1 patient who was switched from TPE to IVIG due to septicemia. All 7 grafts survived.

Conclusions

Some key conclusions can be drawn from this overview. The transfusion needs of liver, heart and lung transplant patients are usually manageable but sometimes challenging. As with other major operations, high transfusions are associated with adverse outcomes, and proactive patient blood management can reduce transfusions. ABO-i organ transplants are a very active area of development, especially for A_2- and A_1-incompatible kidneys. Anti-A/B titers are a key laboratory contribution, but more method standardization is needed. Because the predominant precursor ABH structures vary by organ—type 1 in livers, type 2 in hearts and type 4 in kidneys—future research is in order to determine whether structure-specific antibody levels and fine-specificity adsorption techniques can improve outcomes. Therapeutic apheresis plays a major role in preventing and treating organ rejection, but better understanding of how ECP works and how to best employ it could also be beneficial.

In the introduction we cited GODT's surveillance data that worldwide organ transplants had risen by 52% over the most recent 11 years of available data. Soberingly, we can conclude with their estimate that this still meets no more than 10% of the current global transplant needs. As the field of organ transplantation works to expands its reach and improve its successes, transfusion medicine will continue to have a vital role in its progress.

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