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REVIEW

Vaccinations in kidney transplant recipients: Clearing the muddy waters

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Abstract

Vaccine preventable diseases account for a significant proportion of morbidity and mortality in transplant recipients and cause adverse outcomes to the patient and allograft. Patients should be screened for vaccination history at the time of pre-transplant evaluation and vaccinated at least four weeks prior to transplantation. For non-immune patients, dead-vaccines can be administered starting at six months post-transplant. Live attenuated vaccines are contraindicated after transplant due to concern for infectious complications from the vaccine and every effort should be made to vaccinate prior to transplant. Since transplant recipients are on life-long immunosuppression, these patients may have lower rates of serological conversion, lower mean antibody titers and waning of protective immunity over shorter period as compared to general population. Recommendations regarding booster dose in kidney transplant recipients with sub-optimal serological response are lacking. Travel plans should be part of routine post-transplant assessment and pre-travel vaccines and counseling should be provided. More studies are needed on vaccination schedules, serological response, need for booster doses and safety of live attenuated vaccines in this special population.

Key words: Immunizations; Kidney transplant; Vaccines; Transplant outcomes; Serological response

Core tip: Vaccine-preventable disease can cause adverse patient and allograft outcomes

in kidney transplant recipients. Patients should be screened for vaccinations pre-transplant and catch up immunization should be provided at least four weeks prior to transplantation. For non-immune patients, catch-up immunization should start six months post-transplantation. Live attenuated vaccines are contra-indicated in transplant patients. There is limited data that suggests safety of live vaccines in selective population on low immunosuppression. Travel plans should be part of routine post-transplant assessment and pre-travel vaccines and counseling should be provided.

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BACKGROUND

With advancements in medicine and improved patient survival, there is a growing population of solid organ transplant (SOT) recipients[1]. Advanced immunosuppressive regimens have emerged and acute rejection rates have substantially declined[2]. Infection prophylaxis and rapid diagnosis of infectious complications have allowed patients to tolerate these more intense immunosuppressive regimens, yet vaccine preventable diseases still account for a significant proportion of morbidity and mortality in transplant recipients[2]. The Centers for Disease Control and Prevention (CDC) estimates that each year there are roughly 40000 cases and 4000 deaths attributable to invasive pneumococcal disease, which occurs in organ transplant recipients at a rate 25 times greater than in the general population[3]. It is estimated that the percentage of high-risk adults aged 18-64 vaccinated against pneumococcal disease to be only 21%[4]. Despite the burden of illness in this population, approved and recommended vaccinations remain underutilized[5,6].

The prevention of infection through vaccination is of paramount importance and of near equal importance is the timing of vaccination in relation to kidney transplantation (KT). Ideally, KT recipients (KTRs) should be vaccinated as early as possible as the response to vaccines is diminished in end-organ failure and in states of immunosuppression. In 2013, the guidelines of vaccination of adult solid organ transplant candidates and recipients were updated by the American Society of Transplantation (AST) and the Infectious Disease Society of America. They specify that vaccination is the responsibility of the primary care provider as well as the specialist or nephrologist. The vaccination status should be documented at the pre-transplant clinic and necessary immunizations must be administered as soon as possible thereafter[7,8]. When pre-transplant immunization is not possible, inactivated vaccines are generally considered safe after transplant. This review summarizes current evidence on the use of vaccination before and after KT, serological conversion rates in the setting of immunosuppression and the effect of vaccinations on kidney transplant outcomes.

PRE-TRANSPLANT VACCINATIONS

Patients with advanced chronic kidney disease (CKD) and dialysis dependent end stage renal disease (ESRD) on kidney transplant waitlist have high rates of infectious complications secondary to their already compromised immune systems. In this population, serological response to vaccinations may not be as optimal as in healthy individuals, but it is still better compared to post-transplant immunization. Hence, it is recommended to vaccinate patients with CKD, not requiring dialysis, so that they can mount an optimal immunological response. There is no consensus on the stage of CKD that would be ideal for administering vaccines. Too early-on administration might lead to "unnecessary" immunizations as many of these patients may never progress to ESRD. Dukes *et al*[9] conducted a prospective study in pre-dialysis patients (with serum creatinine > 2 mg/dL, mean serum creatinine 4.5 mg/dL) and found a favorable response to hepatitis B vaccine with subsequent booster dose as compared to dialysis patients historically[9]. Another prospective cohort study looked at rates of

seroconversion after hepatitis B immunization in CKD patients with mean serum creatinine of 3.4 +/- 1.5 mg/dL and mean estimated glomerular filtration rate (GFR) of 20 mL/min. They concluded that patient at higher GFR levels are more likely to respond to hepatitis B vaccination[10].

Some experts have recommended additional doses and/or boosters to improve serological response in CKD patients. García-Agudo *et al*[11] measured serological response in 155 CKD patients prospectively with two cycles of four double doses of conventional hepatitis B vaccine (at 0, 1, 2 and 6 mo), and additional four 20 mg dose of adjuvant vaccine in non-responders. Serological response was improved to 93.8% after the eighth dose compared to 75.9% after the fourth dose. Studies have shown that the humoral response to influenza vaccine is similarly better in hemodialysis patients compared to KTRs[12,13].

POST-TRANSPLANT VACCINATIONS

For those patients who are unable to obtain vaccinations pre-transplant, inactivated vaccines are considered safe when administered after kidney transplant. The optimal time for vaccination is not known but most transplant centers generally agree to wait at least 3-6 mo after transplantation or when patients are on stable maintenance levels of immunosuppressants. AST guidelines suggest avoiding all vaccinations, except influenza, within the first 6 mo post KT. Live-attenuated vaccinations (LAV) are contraindicated in KTRs due to risk of infection but family members of these patients can consider LAVs when appropriate to help provide herd immunity.

INFLUENZA VACCINE

Influenza is a common viral disease post-transplant and is associated with higher morbidity and mortality in immunosuppressed patients compared to a healthy host. Furthermore, influenza has been associated with increased risk of acute rejection after KT[14]. Although generally recommended to administer vaccination 3-6 mo after KT, the influenza vaccine may be given earlier than this time period if the transplantation occurs during the influenza season. Immunological response may be suboptimal with early vaccination; so patients may be revaccinated in the 3-6 mo period post KT if epidemiological risk for influenza exists based on the time of the year[7]. Thereafter, influenza vaccination should be offered yearly. Despite recommendations and safety profile of the influenza vaccine, this mode of protection against influenza is underutilized. Hurst *et al*[14] identified 51730 Medicare first-time KTRs from 2000 to 2006, of which 18.7% patients had influenza vaccination within the first year post-transplant and 43% of these patient received vaccines within the first 6 mo post-transplant. Multivariate analysis demonstrated that vaccination within the first year after transplant was associated with lower risk of allograft loss and death with adjusted hazard ratio of 0.77 ($P < 0.001$) and 0.82 ($P < 0.001$), respectively. Vaccination in the first 6 or 12 mo after transplant was not associated with increased risk for acute rejection[14].

Influenza vaccine preparations vary but both quadrivalent and trivalent vaccines can be used after KT. Only the LAV (FluMist) is contraindicated in transplant recipients and household members of transplant patients. One study investigated whether high-dose intradermal (ID) influenza vaccination would provide superior immunity to transplant patients compared to standard-dose intramuscular (IM) vaccine[15]. No significant difference was found in serological conversion rates between the high-dose ID and standard-dose IM vaccines. Similarly, there was no difference found in adverse effects between the two vaccines besides significantly higher rates of local adverse events including erythema, induration, tenderness, and pruritus with the ID vaccine[15].

Some studies have shown improved immunogenicity with higher doses of antigen in transplant recipients. Natori *et al*[16] showed significantly increased immunogenicity with high dose (60 mg) as compared to standard dose of influenza vaccine in SOT recipients. Since, high dose vaccine is not commercially available outside of North America, Mombelli *et al*[17] recently compared efficacy of double dose (30 mg) versus standard dose (15 mg) of inactivated trivalent influenza vaccine in SOT recipients and found a trend towards increased vaccine response and significantly higher rates of seroprotection with double dose, without any increase in vaccine-related serious adverse events. Another strategy that has been shown to be effective is to administer a booster dose five weeks after initial dose that led to significantly increased sero-conversion rates to all strains of influenza[18].

PNEUMOCOCCAL VACCINE

Infections from *Streptococcus pneumoniae* occur in SOT patients at an incidence rate of 146 infections per 100000 persons per year. Comparatively, the incidence rate of pneumococcal infections in the general population is 11.5 per 100000 persons per year[19]. There are two vaccines against *Pneumococcus*; the pneumococcal conjugate vaccine 13-valent vaccine (Prevnar 13® or PCV13) and the 23-valent polysaccharide vaccine (Pneumovax® or PPSV23). The CDC currently recommends administering PCV 13 followed by PPSV23 eight weeks later for immunocompromised patients including those with CKD, nephrotic syndrome, and SOT[20]. A booster dose of PPSV23 should be given at least five years after the first dose. If this booster dose is given before the age of 65, then a final dose of PPSV23 may be administered after 65 years of age, provided five years have elapsed since the previous dose. In the event, PPSV23 is administered prior to PCV 13; one should wait at least a year before giving PCV 13. Subsequent booster doses of PPSV23 may be administered as outlined earlier[21].

There have been no studies to date examining serological response or durability of response of PCV13 followed by PPSV23 in KTRs. However, some small randomized studies have explored the impact of the pneumococcal conjugate 7-valent (Prevnar-7 or PCV7) vaccine compared to PSSV23 in KTRs and did not find any improvement in duration of immune response[22,23]. Tobudic *et al*[24] found that immunogenicity was not improved when PPSV23 was boosted with PCV7. In this study, 62 patients were randomly assigned to PCV7 followed by PSSV23 after one year versus two doses of PSSV23 given one year apart. Immunogenicity of pneumococcal vaccination was not significantly different between the two strategies (87.5% for PCV7 *vs* 87.1% for PSSV23)[24].

DIPHTHERIA, TETANUS, PERTUSSIS VACCINE

Whooping cough, or pertussis, is a highly contagious infection caused by *Bordetella pertussis*. Recent outbreaks of pertussis are thought to be caused by waning pertussis immunity in adulthood. Therefore, a single dose of tetanus, diphtheria toxoid, and pertussis vaccine should be administered for all adults over the age of 18 to boost immunity to pertussis. Otherwise, tetanus and diphtheria is recommended every 10 years as an adult or when one sustains serious wounds including punctures, bites, scrapes, and burns[25].

HEPATITIS B VACCINE

Reactivation of hepatitis B after solid organ transplantation can rapidly cause severe hepatitis in the presence of potent immunosuppression[26]. Currently, the Advisory Committee on Immunization Practices (ACIP) recommends all hemodialysis (HD) patients be vaccinated for hepatitis B and to revaccinate this population when anti-HBs titers decrease to under 10 IU/mL[27]. Therefore, the majority of KTRs have been vaccinated to hepatitis B prior to transplant. The universal vaccination of HD patients has created an opportunity to expand the pool of possible deceased donor kidneys to include hepatitis B surface antigen (HBsAg) positive donors[28]. KTRs that are immune to hepatitis B either through vaccination or previous infection can be considered for HBsAg positive organs if the recipients' anti-HBs titers are above 10 IU/mL. There are several recent reports that showed patient and graft survival were similar to recipients with HBsAg-negative donors, with normal liver function and no evidence of HBV transmission[29,30]. Patients who receive living kidney transplants and pre-emptive transplants may require primary vaccination of hepatitis B after transplant[28,31-34].

HERPES ZOSTER VACCINE

Immunosuppression increases the incidence of herpes zoster infection approximately 7- fold compared to the immunocompetent host[35]. Until recently, the only vaccine available was a live-attenuated varicella zoster vaccine (Zostavax® or ZVL) which was contraindicated in KTRs. ZVL is FDA approved for prevention of herpes zoster in patients ≥ 50 years of age[36], however due to concerns about durability of the response, the ACIP recommends vaccination in ≥ 60 years of age. Comparatively, Shingrix® is a dead, recombinant zoster vaccine (RZV) which is approved to prevent

herpes zoster in patients ≥ 50 years[37]. RZV is a two dose vaccination given 2-6 mo apart and reduces the risk of shingles by more than 90%. Studies in healthy, non-transplant patients have demonstrated continued efficacy for three years post vaccination with 84.7% prevention of herpes zoster and reduced post-herpetic neuralgia in patients by 91.2%[38]. A Phase III randomized clinical trial found that humoral immunogenicity was significantly increased two months after vaccination in adult KTRs who received the RZV compared to placebo[39]. Further studies are required to determine the long term efficacy and safety of this vaccine in KTRs.

HPV VACCINE

Human papillomavirus (HPV) is a common sexually transmitted viral disease that is associated with cancers of the anus, penis, cervix, and vulva. Almost 14 million people are infected with HPV each year[40]. Three inactive HPV vaccines have been FDA approved for use in the United States. Both Gardasil® (4 valent vaccine) and Gardasil 9® (9-valent vaccine) are approved for use in females and males between 9 and 26 years of age[41,42]. Cervarix® is a bivalent HPV vaccine that is approved for use in females between the age of 9 and 25 years[43]. In the United States, only the 9-valent vaccine is currently available. The ACIP currently recommends that all patients with history of primary or secondary immunocompromising conditions, including SOT recipients, should receive a three dose series of HPV vaccine at months 0, 1-2, and 6 mo[40]. Serological and durability of immunological response post vaccination is unknown after kidney transplant.

MENINGOCOCCAL VACCINE

Menigococcal vaccine is indicated for KTRs who are travelling to highly endemic areas such as Sub-saharan Africa, Saudi Arabia or patients with history of splenectomy. It is also indicated for patients with atypical hemolytic uremic syndrome or antibody mediated rejection who are receiving eculizumab which is a complement inhibitor[44]. Effort should be made to administer meningococcal vaccine at least two weeks prior to the first dose of eculizumab. Patients should receive vaccination against meningococcal serogroups A, C, Y and W1235 by either Menactra or Menveo as well as vaccination against meningoccoal serogroup B with either Trumemba or Bexsero. Menactra or Menveo should be administered twice, at least 2 mo apart, with concurrent Trumemba or Bexsero vaccination. When Trumemba is given, three doses are required at 0, 1-2, and 6 mo while Bexsero is a two-dose series administered at least 1 mo apart. Vaccination should be repeated every 5 years for group A, C, Y, and W1235 with either Menactra or Menveo[21]. Immunogenic response to polysaccharide meningococcal vaccine is only 40% in SOT recepients with low titer antibodies developing only to menigococcus C. With conjugate vaccine, about half of the SOT recipients develop low antibody titers at least against one of the serogroups including A, C, Y and W-135. Two doses of conjugated quadrivalent menigococcal vaccine is recommended, followed by a booster every five years[45].

VACCINATION AGAINST CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is a double-stranded DNA virus that is ubiquitous with very high sero-prevalence. The virus can cause significant morbidity and mortality in immune-compromised organ transplant recipients. Anti-viral therapy currently used for CMV prophylaxis in SOT recipients is associated with adverse events including neutropenia. Hence, there is an unmet need for developing treatments with new mechanisms of action including effective vaccines. Earlier studies have shown variable impact on CMV immunogenicity with different vaccines administered pre transplant[46,47]. ASP0113 is a first-in-class bivalent DNA-based vaccine developed for preventing CMV infection in immuno-compromised transplant recipients. It contains equal quantities of the plasmids VCL-6365 and VCL-6368 encoding for glycoprotein B and phosphoprotein 65[48]. A phase I study demonstrated the immunogenicity and safety of ASP0113 in healthy adults[49]. In another randomized, double-blind placebo-controlled phase II study in allogeneic hematopoietic cell transplant (HCT) recipients, ASP0113 significantly reduced the occurrence and recurrence of CMV viremia with improved time to event and similar adverse events when compared to placebo[50]. A recently published phase-II placebo-controlled study randomized 149 CMV sero-negative recipients of kidneys from seropositive donors in a 1 : 1 manner to either 5

doses of ASP0113 or placebo on days 30, 60, 90, 120, 150 post-transplant. All patients received prophylactic valganciclovir/ganciclovir on days 10-100 after transplant. In this study, ASP0113 was not effective in preventing CMV viremia from day 100 through year one after first study vaccine injection but had a safety profile similar to placebo[51]. One possible reason for the lack of vaccine efficacy observed in this study could be related to the post-transplant administration of the vaccine when patients are heavily immunosuppressed resulting in a weak T-cell response. Future studies should follow a protocol that mandates pre-transplant use of ASP0113 when recipients likely have more robust T-cell response. Currently, an ongoing phase III study is evaluating the safety and efficacy of ASP0113 in CMV-seropositive allogeneic HCT recipients (NCT01877655).

LIVE ATTENUATED VACCINES

Despite several advantages of live-attenuated vaccines (LAV), it is not recommended to use these in immunocompromised host secondary to risk of vaccine-virus induced disease and uncontrolled replication of vaccine virus. There is scant data on safety of LAV in transplant recipients with stringent criteria such as need for minimal immunosuppression, with stable immunological parameters[52-54]. Live mumps, measles, rubella (MMR) vaccine is not recommended in KTRs. MMR serology should be checked prior to transplantation and non-immune patients should be vaccinated. If non-immune patients have exposure to measles, normal human immunoglobulin should be administered within six days of exposure[55,56]. When living KT is scheduled, pre-transplant non-immune patients should be vaccinated against Varicella Zoster using LAV with two doses at least 4-6 wk and 2-4 wk prior to transplant[57]. Generally, Herpes zoster vaccine Zostavax is contraindicated in KTRs secondary to risk of disseminated disease; however there is some data on the safety of Zostavax in pediatric patients with liver transplant[58,59]. In non-immune patients with risk exposure, administer Varicella zoster immunoglobulin within 96 h along with valacyclovir for 7 to 10 d[60].

While there are small studies suggesting no significant side effects with live attenuated yellow fever vaccines in transplant recipients traveling to sub-Saharan Africa and South America, it is still contraindicated post-transplantation secondary to risk of encephalitis[61-63]. In such patients, it is recommended to administer yellow fever vaccine pre-transplant in anticipation of travel to endemic areas. Other live vaccines to avoid in KTRs include oral typhoid vaccine, Bacille Calmette-Guerin vaccine and attenuated intra-nasal influenza vaccine[6,64-66].

INTERNATIONAL TRAVEL

A large number of immunocompromised patients including KTRs travel internationally to high risk destinations every year without adequate pre-travel advice and vaccinations[67-70]. These patients are at heightened risk of acquiring infections that could even lead to allograft rejection. Pre-travel vaccines could help in disease prevention or decrease the severity of disease in KTRs[64].

Preferably, patients should receive key vaccinations at least four weeks prior to undergoing transplantation but it may not be practical for area-specific travel vaccines for endemic diseases, especially, if travel plans are made post-transplantation. Some experts recommend restriction of travel within the first 12 mo post-transplantation[71]. During each physician encounter, specific questions should be asked about travel plans and referred to travel clinics ideally 12 wk prior to travel so that there is enough time for administration of required pre-travel vaccines, serological testing and additional boosters[45]. If travel is anticipated to endemic areas, then the recommended vaccinations are given in addition to routine vaccinations as listed in Table 1[45,64]. Since yearly influenza vaccine strains differ between different hemispheres and influenza seasons are in months of October-March in Northern hemisphere, April-September for southern hemisphere and all-year round in tropics, the ACIP recommends two vaccinations with hemisphere-specific trivalent influenza vaccines four weeks apart in immunocompromised patients crossing the hemispheres[72].

In endemic areas, mosquito-borne infections such as malaria and dengue may precipitate acute allograft rejections[73,74]. Traveler's diarrhea with organisms like *Escherichia coli*, *Campylobacter sp*, *Salmonella*, *Shigella*, *Giardia*, and *Entamoeba histolytica* are common especially in immunocompromised hosts. Patients should be advised to stay well hydrated as dehydration may also cause kidney dysfunction and calcineurin inhibitor toxicity. In addition to the pre-travel vaccines, KTRs should be counseled on

Table 1 Recommendations for various vaccines in kidney transplant recipients

Vaccine	Prior to transplant	After transplant	Prior to travel to endemic areas after transplant	Endemic areas	Antibody titers?
Hepatitis A	Yes	Yes	Yes		> 33 mIU/mL is protective
Hepatitis B	Yes	Yes	Yes		> 10 mIU/mL is protective
Pneumococcal	Yes	Yes	No		
Meningococcal	Yes	Yes	Yes	Sub-Saharan Africa, India, Philippines, Saudi Arabia	
Tdap	Yes	Yes	No		
Td	Yes	Yes	No		
MMR	Yes	No	No		
Varicella zoster	Yes	Only Shingrix may be given post-transplant	No		
Influenza	Yes	Yes - avoid live virus	No		
Rabies[1] only upon exposure	No	No	No		
Diphtheria	No	No	Yes[1]	SE Asia, Hajj travelers to Saudi Arabia	
Tick-borne encephalitis	No	No	No (live)		Can follow antibody titers
Japanese encephalitis	No	No	Yes, day 0 and 28	South, South East, and East Asia and part of Western Pacific	
Cholera	No	No	Yes, oral killed vaccine	South and South East Asia	
Yellow fever	No	No	No,	Sub-Saharan Africa, South America	
Typhoid	No	No	Yes, 2 wk prior to travel	South and South East Asia, Africa, Caribbean, Central and South America	

[1]Re-vaccination required if last vaccination was 10-15 years prior. MMR: Measles, mumps, rubella; TdaP: Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis, Td: Tetanus diphtheria.

food and water hygiene measures, use of insect and mosquito repellants and safe sex practice. Chemoprophylaxis for malaria should be offered and anti-parasitic regimen(s) offered based on susceptibility pattern at destination site. Atovaquone-proguanil or doxycycline is commonly offered medications for malaria prophylaxis in areas with chloroquine resistance.

SEROLOGICAL RESPONSE IN KIDNEY TRANSPLANT RECIPIENTS

Since KTRs are on life-long immunosuppression, these patients may not mount comparable serological response to vaccinations with lower rates of seroconversion, lower mean antibody titers and waning of protective immunity over shorter period as compared to general population[64,75]. Moreover, serological response might vary depending on type of immunosuppressive medications. Calcineurin inhibitors and mammalian target of Rapamycin (mTOR) inhibitors impair interleukin-2 dependent T-cell proliferation while mycophenolate mofetil and azathioprine inhibit antigen dependent T-and B-cell interaction and proliferation and response to vaccines[15,76-79]. Further studies have shown that cyclosporine treated patients have poorer response post-influenza vaccination as compared to azathioprine treated patients, and patients on mTOR-inhibitors had lower immune response to H1N1 vaccination[80,81]. Patients had decreased response rates if they had received anti-CD20 monoclonal antibody as a part of immunosuppression protocol[82]. The issue becomes more complex with contemporary powerful immunosuppression including the depleting antibodies such

as Thymoglobulin and alemtuzumab.

At present, we have limited data on the timing, dosing and efficacy of vaccinations in organ transplant population. With the advent of new biologics as immunosuppressants and approval of newer vaccines, the waters have become muddier with respect to providing direction for vaccinations in KTRs. Beil *et al*[83] followed antibody titers in 94 pediatric KTRs who had vaccinations and found that titers were low in 31% with tetanus, 25% with diphtheria and 68% with hepatitis B virus immunization. Eckerle *et al*[82] systematically reviewed published data on the vaccination response in SOT recipients and found that they had 10%-16% less response rate as compared to general population. They found encouraging serological responder rates with tetanus, diphtheria, rabies, hepatitis A and polio vaccination, though antibody titers declined over time for diphtheria and hepatitis A vaccination. Efficacy of repeated hepatitis B vaccination is also reduced to 32%-36% as compared to 90%-95% in healthy controls[84-86]. Recommendations regarding booster dose in pediatric or adult KTRs with sub-optimal serological response are lacking. L'Huillier *et al*[87] published a strategy utilizing serology based immunization in pediatric liver transplant patients with some success.

HEALTHCARE WORKERS AND CLOSE CONTACTS OF TRANSPLANT RECIPIENTS

Since there is risk of transmission of infections in immunocompromised KTRs, it is of critical importance to fully immunize persons in close contact with KTRs. This helps in building herd immunity and protects KTRs from diseases. Annual influenza vaccination in all healthcare workers and all indicated age appropriate vaccinations including LAVs such as MMR, rotavirus vaccine and varicella vaccine should be administered to the children of transplant recipients[44,82]. Since there is virus shedding post-vaccination, patients and contacts should be counseled about strict hand washing at least for two weeks after administration of live vaccines[88-90]. Live oral polio vaccine is contra-indicated in close contacts; therefore, inactivated polio vaccine should be administered. Living-organ donors should avoid LAV at least 3-4 wk prior to transplantation[53,91].

EFFECTS OF VACCINATIONS ON TRANSPLANT OUTCOMES

There have been concerns about adverse effects of influenza vaccination on allograft function by upregulation of human leukocyte antigen (HLA) alloantibodies after vaccination. During Influenza A/ H1N1 pandemic in 2009, some studies had demonstrated anti-HLA antibodies post vaccination with AS03-adjuvanted monoclonal H1N1 vaccine but this did not translate in adverse clinical outcomes[92,93]. Many other clinical studies did not show increased risk of acute rejections or allograft dysfunction after influenza vaccination[94-97]. In fact, Hurst *et al*[14] had shown reduced risk of allograft loss if influenza vaccination is administered in the first post-transplant year. Influenza vaccination is deemed safe and should be recommended to all KTRs.

Lindemann *et al*[98] showed no increase in HLA antibodies after pneumococcal vaccination in KTRs. Mulley *et al*[99] recently published no effect on the development of de novo donor-specific antibodies and no increase in episodes of acute rejection or graft loss post-vaccination in SOT recipients based on a systematic review and meta-analysis of 90 studies involving 15645 vaccinated patients and 42924 controls. Further high-quality, controlled studies for assessing the post-vaccination outcomes in transplant recipients are needed.

CONCLUSION

KTRs are at increased risk of infectious complications in the setting of prolonged, chronic immunosuppression with increased morbidity and mortality. Awareness about vaccine-preventable diseases, administration of vaccines preferably prior to kidney transplantation and to close contacts could lower the burden of complications post-transplant. If the opportunity for pre-transplant primary vaccination is missed, patients should be offered immunization 6 mo post-transplantation. Patients should also be offered pre-travel endemic area specific vaccinations. LAVs are generally

contraindicated in KTRs. More studies are needed on vaccination schedules, serological response, need for booster doses and safety of LAVs in this special population. The emergence of newer data from such studies would enable transplant community to make more evidence based recommendations and further clear the muddy waters.

REFERENCES

1 **Matas AJ**, Smith JM, Skeans MA, Thompson B, Gustafson SK, Stewart DE, Cherikh WS, Wainright JL, Boyle G, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2013 Annual Data Report: kidney. *Am J Transplant* 2015; **15** Suppl 2: 1-34 [PMID: 25626344 DOI: 10.1111/ajt.13195]

2 **Karuthu S**, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 2012; **7**: 2058-2070 [PMID: 22977217 DOI: 10.2215/CJN.04410512]

3 **National Vaccine Program Office**. Adult Immunization Plans. Available from: URL: http://www.hhs.gov/nvpo/national-adult-immunization-plan/

4 **Williams WW**, Lu PJ, O'Halloran A, Bridges CB, Kim DK, Pilishvili T, Hales CM, Markowitz LE; Centers for Disease Control and Prevention (CDC). Vaccination coverage among adults, excluding influenza vaccination - United States, 2013. *MMWR Morb Mortal Wkly Rep* 2015; **64**: 95-102 [PMID: 25654611]

5 **Kumar D**. Pre-transplant vaccination: a model for optimal patient care. Available from: URL: http://www.ishlt.org/ContentDocuments/2014FebLinks_Kumar.html

6 **Chow J**, Golan Y. Vaccination of solid-organ transplantation candidates. *Clin Infect Dis* 2009; **49**: 1550-1556 [PMID: 19842980 DOI: 10.1086/644734]

7 **Danziger-Isakov L**, Kumar D; AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 311-317 [PMID: 23465023 DOI: 10.1111/ajt.12122]

8 **Rubin LG**, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014; **58**: e44-100 [PMID: 24311479 DOI: 10.1093/cid/cit684]

9 **Dukes CS**, Street AC, Starling JF, Hamilton JD. Hepatitis B vaccination and booster in predialysis patients: a 4-year analysis. *Vaccine* 1993; **11**: 1229-1232 [PMID: 8256504 DOI: 10.1016/0264-410X(93)90047-2]

10 **DaRoza G**, Loewen A, Djurdjev O, Love J, Kempston C, Burnett S, Kiaii M, Taylor PA, Levin A. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. *Am J Kidney Dis* 2003; **42**: 1184-1192 [PMID: 14655190 DOI: 10.1053/j.ajkd.2003.08.019]

11 **García-Agudo R**, Aoufi Rabih S, Araque Torres P, Dolores Fraga Fuentes M, Carlos Valenzuela Gámez J, Mancha Ramos J, María Tenías Burillo J. Efficacy of a hepatitis B vaccination schedule with two cycles of four double doses of conventional vaccine and four doses of adjuvanted vaccine in chronic kidney disease patients evaluated for renal transplantation. *Transplant Proc* 2012; **44**: 2532-2534 [PMID: 23146445 DOI: 10.1016/j.transproceed.2012.09.046]

12 **Broeders NE**, Hombrouck A, Lemy A, Wissing KM, Racapé J, Gastaldello K, Massart A, Van Gucht S, Weichselbaum L, De Mul A, Brochier B, Thomas I, Abramowicz D. Influenza A/H1N1 vaccine in patients treated by kidney transplant or dialysis: a cohort study. *Clin J Am Soc Nephrol* 2011; **6**: 2573-2578 [PMID: 21921153 DOI: 10.2215/CJN.04670511]

13 **Mulley WR**, Visvanathan K, Hurt AC, Brown FG, Polkinghorne KR, Mastorakos T, Lewicki MC, Stuart RL, Tan SJ, Chean R, Kerr PG, Kanellis J. Mycophenolate and lower graft function reduce the seroresponse of kidney transplant recipients to pandemic H1N1 vaccination. *Kidney Int* 2012; **82**: 212-219 [PMID: 22495292 DOI: 10.1038/ki.2012.106]

14 **Hurst FP**, Lee JJ, Jindal RM, Agodoa LY, Abbott KC. Outcomes associated with influenza vaccination in the first year after kidney transplantation. *Clin J Am Soc Nephrol* 2011; **6**: 1192-1197 [PMID: 21511837 DOI: 10.2215/CJN.05430610]

15 **Baluch A**, Humar A, Eurich D, Egli A, Liacini A, Hoschler K, Campbell P, Berka N, Urschel S, Wilson L, Kumar D. Randomized controlled trial of high-dose intradermal versus standard-dose intramuscular influenza vaccine in organ transplant recipients. *Am J Transplant* 2013; **13**: 1026-1033 [PMID: 23406320 DOI: 10.1111/ajt.12149]

16 **Natori Y**, Shiotsuka M, Slomovic J, Hoschler K, Ferreira V, Ashton P, Rotstein C, Lilly L, Schiff J, Singer L, Humar A, Kumar D. A Double-Blind, Randomized Trial of High-Dose vs Standard-Dose Influenza Vaccine in Adult Solid-Organ Transplant Recipients. *Clin Infect Dis* 2018; **66**: 1698-1704 [PMID: 29253089 DOI: 10.1093/cid/cix1082]

17 **Mombelli M**, Rettby N, Perreau M, Pascual M, Pantaleo G, Manuel O. Immunogenicity and safety of double versus standard dose of the seasonal influenza vaccine in solid-organ transplant recipients: A randomized controlled trial. *Vaccine* 2018; **36**: 6163-6169 [PMID: 30181045 DOI: 10.1016/j.vaccine.2018.08.057]

18 **Cordero E**, Roca-Oporto C, Bulnes-Ramos A, Aydillo T, Gavaldà J, Moreno A, Torre-Cisneros J, Montejo JM, Fortun J, Muñoz P, Sabé N, Fariñas MC, Blanes-Julia M, López-Medrano F, Suárez-Benjumea A, Martinez-Atienza J, Rosso-Fernández C, Pérez-Romero P; TRANSGRIPE 1-2 Study Group. Two Doses of Inactivated Influenza Vaccine Improve Immune Response in Solid Organ Transplant Recipients: Results of TRANSGRIPE 1-2, a Randomized Controlled Clinical Trial. *Clin Infect Dis* 2017; **64**: 829-838 [PMID: 28362949 DOI: 10.1093/cid/ciw855]

19 **Kumar D**, Humar A, Plevneshi A, Green K, Prasad GV, Siegal D, McGeer A; Toronto Invasive Bacterial Diseases Network, McGeer A. Invasive pneumococcal disease in solid organ transplant recipients--10-year prospective population surveillance. *Am J Transplant* 2007; **7**: 1209-1214 [PMID: 17286615 DOI: 10.1111/j.1600-6143.2006.01705.x]

20 **Centers for Disease Control and Prevention (CDC)**. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2012; **61**: 816-819 [PMID:

23051612]
21 **Kim DK**, Riley LE, Hunter P; Advisory Committee on Immunization Practices. Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2018. *Ann Intern Med* 2018; **168**: 210-220 [PMID: 29404596 DOI: 10.7326/M17-3439]
22 **Kumar D**, Rotstein C, Miyata G, Arlen D, Humar A. Randomized, double-blind, controlled trial of pneumococcal vaccination in renal transplant recipients. *J Infect Dis* 2003; **187**: 1639-1645 [PMID: 12721944 DOI: 10.1086/374784]
23 **Kumar D**, Welsh B, Siegal D, Chen MH, Humar A. Immunogenicity of pneumococcal vaccine in renal transplant recipients--three year follow-up of a randomized trial. *Am J Transplant* 2007; **7**: 633-638 [PMID: 17217436 DOI: 10.1111/j.1600-6143.2007.01668.x]
24 **Tobudic S**, Plunger V, Sunder-Plassmann G, Riegersperger M, Burgmann H. Randomized, single blind, controlled trial to evaluate the prime-boost strategy for pneumococcal vaccination in renal transplant recipients. *PLoS One* 2012; **7**: e46133 [PMID: 23029408 DOI: 10.1371/journal.pone.0046133]
25 **Liang JL**, Tiwari T, Moro P, Messonnier NE, Reingold A, Sawyer M, Clark TA. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2018; **67**: 1-44 [PMID: 29702631 DOI: 10.15585/mmwr.rr6702a1]
26 **Hibberd PL**, Rubin RH. Approach to immunization in the immunosuppressed host. *Infect Dis Clin North Am* 1990; **4**: 123-142 [PMID: 2106550]
27 **Weinbaum CM**, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, Neitzel SM, Ward JW; Centers for Disease Control and Prevention (CDC). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 2008; **57**: 1-20 [PMID: 18802412]
28 **Pilmore HL**, Gane EJ. Hepatitis B-positive donors in renal transplantation: increasing the deceased donor pool. *Transplantation* 2012; **94**: 205-210 [PMID: 22430067 DOI: 10.1097/TP.0b013e31824e3db4]
29 **Sumethkul V**, Ingsathit A, Jirasiritham S. Ten-year follow-up of kidney transplantation from hepatitis B surface antigen-positive donors. *Transplant Proc* 2009; **41**: 213-215 [PMID: 19249516 DOI: 10.1016/j.transproceed.2008.09.056]
30 **Berber I**, Aydin C, Yigit B, Turkmen F, Titiz IM, Altaca G. The effect of HBsAg-positivity of kidney donors on long-term patient and graft outcome. *Transplant Proc* 2005; **37**: 4173-4175 [PMID: 16387070 DOI: 10.1016/j.transproceed.2005.10.094]
31 **Chancharoenthana W**, Townamchai N, Pongpirul K, Kittiskulnam P, Leelahavanichkul A, Avihingsanon Y, Suankratay C, Wattanatorn S, Kittikowit W, Praditpornsilpa K, Tungsanga K, Eiam-Ong S. The outcomes of kidney transplantation in hepatitis B surface antigen (HBsAg)-negative recipients receiving graft from HBsAg-positive donors: a retrospective, propensity score-matched study. *Am J Transplant* 2014; **14**: 2814-2820 [PMID: 25395260 DOI: 10.1111/ajt.12921]
32 **Fabrizi F**, Martin P, Dixit V, Kanwal F, Dulai G. HBsAg seropositive status and survival after renal transplantation: meta-analysis of observational studies. *Am J Transplant* 2005; **5**: 2913-2921 [PMID: 16303005 DOI: 10.1111/j.1600-6143.2005.01113.x]
33 **Huprikar S**, Danziger-Isakov L, Ahn J, Naugler S, Blumberg E, Avery RK, Koval C, Lease ED, Pillai A, Doucette KE, Levitsky J, Morris MI, Lu K, McDermott JK, Mone T, Orlowski JP, Dadhania DM, Abbott K, Horslen S, Laskin BL, Mougdil A, Venkat VL, Korenblat K, Kumar V, Grossi P, Bloom RD, Brown K, Kotton CN, Kumar D. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. *Am J Transplant* 2015; **15**: 1162-1172 [PMID: 25707744 DOI: 10.1111/ajt.13187]
34 **Len O**, Garzoni C, Lumbreras C, Molina I, Meije Y, Pahissa A, Grossi P; ESCMID Study Group of Infection in Compromised Hosts. Recommendations for screening of donor and recipient prior to solid organ transplantation and to minimize transmission of donor-derived infections. *Clin Microbiol Infect* 2014; **20** Suppl 7: 10-18 [PMID: 24476053 DOI: 10.1111/1469-0691.12557]
35 **Pergam SA**, Forsberg CW, Boeckh MJ, Maynard C, Limaye AP, Wald A, Smith NL, Young BA. Herpes zoster incidence in a multicenter cohort of solid organ transplant recipients. *Transpl Infect Dis* 2011; **13**: 15-23 [PMID: 20636480 DOI: 10.1111/j.1399-3062.2010.00547.x]
36 **Merck Co**. Zostavax. Available from: URL: https://www.merck.com/product/prescription-products/home.html
37 **GlaxoSmithKline**. Shingrix. Available from: URL: https://www.shingrix.com/index.html
38 **Dooling KL**, Guo A, Patel M, Lee GM, Moore K, Belongia EA, Harpaz R. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. *MMWR Morb Mortal Wkly Rep* 2018; **67**: 103-108 [PMID: 29370152 DOI: 10.15585/mmwr.mm6703a5]
39 **Vink P**. Immunogenicity and safety of a candidate subunit adjuvanted herpes zoster vaccine (HZ/su) in adults post renal transplant: A Phase III randomized clinical trial. *Open Forum Infectious Diseases* 2017; **4**: S417 [DOI: 10.1093/ofid/ofx163.1044]
40 **Meites E**, Kempe A, Markowitz LE. Use of a 2-Dose Schedule for Human Papillomavirus Vaccination - Updated Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2016; **65**: 1405-1408 [PMID: 27977643 DOI: 10.15585/mmwr.mm6549a5]
41 **Merck Co**. Gardasil®. Available from: URL: https://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_ppi.pdf
42 **Merck Co**. Gardasil-9. Available from: URL: https://www.gardasil9.com
43 **GlaxoSmithKline**. Cervarix. Available from: URL: https://www.gsk.com/en-gb/media/press-releases/glaxosmithkline-update-on-fda-review-of-cervarix/
44 **Kumar D**. Immunizations following solid-organ transplantation. *Curr Opin Infect Dis* 2014; **27**: 329-335 [PMID: 24945614 DOI: 10.1097/QCO.0000000000000078]
45 **Uslan DZ**, Patel R, Virk A. International travel and exposure risks in solid-organ transplant recipients. *Transplantation* 2008; **86**: 407-412 [PMID: 18698243 DOI: 10.1097/TP.0b013e31817c0673]
46 **Plotkin SA**, Smiley ML, Friedman HM, Starr SE, Fleisher GR, Wlodaver C, Dafoe DC, Friedman AD, Grossman RA, Barker CF. Towne-vaccine-induced prevention of cytomegalovirus disease

after renal transplants. *Lancet* 1984; **1**: 528-530 [PMID: 6142252 DOI: 10.1016/S0140-6736(84)90930-9]

47 **Griffiths PD**, Stanton A, McCarrell E, Smith C, Osman M, Harber M, Davenport A, Jones G, Wheeler DC, O'Beirne J, Thorburn D, Patch D, Atkinson CE, Pichon S, Sweny P, Lanzman M, Woodford E, Rothwell E, Old N, Kinyanjui R, Haque T, Atabani S, Luck S, Prideaux S, Milne RS, Emery VC, Burroughs AK. Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial. *Lancet* 2011; **377**: 1256-1263 [PMID: 21481708 DOI: 10.1016/S0140-6736(11)60136-0]

48 **Smith LR**, Wloch MK, Chaplin JA, Gerber M, Rolland AP. Clinical Development of a Cytomegalovirus DNA Vaccine: From Product Concept to Pivotal Phase 3 Trial. *Vaccines (Basel)* 2013; **1**: 398-414 [PMID: 26344340 DOI: 10.3390/vaccines1040398]

49 **Wloch MK**, Smith LR, Boutsaboualoy S, Reyes L, Han C, Kehler J, Smith HD, Selk L, Nakamura R, Brown JM, Marbury T, Wald A, Rolland A, Kaslow D, Evans T, Boeckh M. Safety and immunogenicity of a bivalent cytomegalovirus DNA vaccine in healthy adult subjects. *J Infect Dis* 2008; **197**: 1634-1642 [PMID: 18444883 DOI: 10.1086/588385]

50 **Kharfan-Dabaja MA**, Boeckh M, Wilck MB, Langston AA, Chu AH, Wloch MK, Guterwill DF, Smith LR, Rolland AP, Kenney RT. A novel therapeutic cytomegalovirus DNA vaccine in allogeneic haemopoietic stem-cell transplantation: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis* 2012; **12**: 290-299 [PMID: 22237175 DOI: 10.1016/S1473-3099(11)70344-9]

51 **Vincenti F**, Budde K, Merville P, Shihab F, Ram Peddi V, Shah M, Wyburn K, Cassuto-Viguier E, Weidemann A, Lee M, Flegel T, Erdman J, Wang X, Lademacher C. A randomized, phase 2 study of ASP0113, a DNA-based vaccine, for the prevention of CMV in CMV-seronegative kidney transplant recipients receiving a kidney from a CMV-seropositive donor. *Am J Transplant* 2018; **18**: 2945-2954 [PMID: 29745007 DOI: 10.1111/ajt.14925]

52 **Kamei K**, Miyazono A, Sato M, Ishikawa T, Fujimaru T, Ogura M, Ito S. Efficacy and safety of attenuated live vaccines in children with renal disease receiving immunosuppressants. *Jpn Soc Pediatr Nephrol* 2011; **24**: 179-186 [DOI: 10.3165/jjpn.24.179]

53 **Chaves SS**, Haber P, Walton K, Wise RP, Izurieta HS, Schmid DS, Seward JF. Safety of varicella vaccine after licensure in the United States: experience from reports to the vaccine adverse event reporting system, 1995-2005. *J Infect Dis* 2008; **197** Suppl 2: S170-S177 [PMID: 18419393 DOI: 10.1086/522161]

54 **Zamora I**, Simon JM, Da Silva ME, Piqueras AI. Attenuated varicella virus vaccine in children with renal transplants. *Pediatr Nephrol* 1994; **8**: 190-192 [PMID: 8018498 DOI: 10.1007/BF00865476]

55 **Centers for Disease**. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. *MMWR* 2006; **55**: RR-16

56 **Centers for Disease Control and Prevention**. Measles. Available from: URL: http://www.cdc.gov/measles/hcp/index.html

57 **Burroughs M**, Moscona A. Immunization of pediatric solid organ transplant candidates and recipients. *Clin Infect Dis* 2000; **30**: 857-869 [PMID: 10852737 DOI: 10.1086/313823]

58 **Weinberg A**, Horslen SP, Kaufman SS, Jesser R, Devoll-Zabrocki A, Fleckten BL, Kochanowicz S, Seipel KR, Levin MJ. Safety and immunogenicity of varicella-zoster virus vaccine in pediatric liver and intestine transplant recipients. *Am J Transplant* 2006; **6**: 565-568 [PMID: 16468967 DOI: 10.1111/j.1600-6143.2005.01210.x]

59 **Shinjoh M**, Miyairi I, Hoshino K, Takahashi T, Nakayama T. Effective and safe immunizations with live-attenuated vaccines for children after living donor liver transplantation. *Vaccine* 2008; **26**: 6859-6863 [PMID: 18930096 DOI: 10.1016/j.vaccine.2008.09.076]

60 **Suga S**, Yoshikawa T, Ozaki T, Asano Y. Effect of oral acyclovir against primary and secondary viraemia in incubation period of varicella. *Arch Dis Child* 1993; **69**: 639-42; discussion 642-3 [PMID: 8285774 DOI: 10.1136/adc.69.6.639]

61 **Azevedo LS**, Lasmar EP, Contieri FL, Boin I, Percegona L, Saber LT, Selistre LS, Netto MV, Moreira MC, Carvalho RM, Bruno RM, Ferreira TC, David-Neto E. Yellow fever vaccination in organ transplanted patients: is it safe? A multicenter study. *Transpl Infect Dis* 2012; **14**: 237-241 [PMID: 22093046 DOI: 10.1111/j.1399-3062.2011.00686.x]

62 **Visser LG**. The immunosuppressed traveler. *Infect Dis Clin North Am* 2012; **26**: 609-624 [PMID: 22963773 DOI: 10.1016/j.idc.2012.06.003]

63 **Duchini A**, Goss JA, Karpen S, Pockros PJ. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. *Clin Microbiol Rev* 2003; **16**: 357-364 [PMID: 12857772 DOI: 10.1128/CMR.16.3.357-364.2003]

64 **Aung AK**, Trubiano JA, Spelman DW. Travel risk assessment, advice and vaccinations in immunocompromised travellers (HIV, solid organ transplant and haematopoeitic stem cell transplant recipients): A review. *Travel Med Infect Dis* 2015; **13**: 31-47 [PMID: 25593039 DOI: 10.1016/j.tmaid.2014.12.007]

65 **Sester M**, Gärtner BC, Girndt M, Sester U. Vaccination of the solid organ transplant recipient. *Transplant Rev (Orlando)* 2008; **22**: 274-284 [PMID: 18684606 DOI: 10.1016/j.trre.2008.07.001]

66 **Rubin LG**, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014; **58**: 309-318 [PMID: 24421306 DOI: 10.1093/cid/cit816]

67 **Roukens AH**, van Dissel JT, de Fijter JW, Visser LG. Health preparations and travel-related morbidity of kidney transplant recipients traveling to developing countries. *Clin Transplant* 2007; **21**: 567-570 [PMID: 17645721 DOI: 10.1111/j.1399-0012.2007.00691.x]

68 **Schwartz BS**, Rosen J, Han PV, Hynes NA, Hagmann SH, Rao SR, Jentes ES, Ryan ET, LaRocque RC; Global TravEpiNet Consortium. Immunocompromised Travelers: Demographic Characteristics, Travel Destinations, and Pretravel Health Care from the U.S. Global TravEpiNet Consortium. *Am J Trop Med Hyg* 2015; **93**: 1110-1116 [PMID: 26304922 DOI: 10.4269/ajtmh.15-0185]

69 **Bialy C**, Horne K, Dendle C, Kanellis J, Littlejohn G, Ratnam I, Woolley I. International travel in the immunocompromised patient: a cross-sectional survey of travel advice in 254 consecutive patients. *Intern Med J* 2015; **45**: 618-623 [PMID: 25827660 DOI: 10.1111/imj.12753]

70 **Kotton CN**, Hibberd PL; AST Infectious Diseases Community of Practice. Travel medicine and transplant tourism in solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 337-347 [PMID: 23465026 DOI: 10.1111/ajt.12125]

71 **Trubiano JA**, Johnson D, Sohail A, Torresi J. Travel vaccination recommendations and endemic infection risks in solid organ transplantation recipients. *J Travel Med* 2016; **23**: taw058 [PMID: 27625399 DOI: 10.1093/jtm/taw058]

72 **Centers for Disease Control and Prevention (CDC)**. Use of northern hemisphere influenza vaccines by travelers to the southern hemisphere. *MMWR Morb Mortal Wkly Rep* 2009; **58**: 312 [PMID: 19343012]

73 **Coster LO**. Parasitic infections in solid organ transplant recipients. *Infect Dis Clin North Am* 2013; **27**: 395-427 [PMID: 23714347 DOI: 10.1016/j.idc.2013.02.008]

74 **Franco-Paredes C**, Jacob JT, Hidron A, Rodriguez-Morales AJ, Kuhar D, Caliendo AM. Transplantation and tropical infectious diseases. *Int J Infect Dis* 2010; **14**: e189-e196 [PMID: 19647464 DOI: 10.1016/j.ijid.2009.04.021]

75 **Kotton CN**, Ryan ET, Fishman JA. Prevention of infection in adult travelers after solid organ transplantation. *Am J Transplant* 2005; **5**: 8-14 [PMID: 15636606 DOI: 10.1111/j.1600-6143.2004.00708.x]

76 **Löbermann M**, Boršo D, Hilgendorf I, Fritzsche C, Zettl UK, Reisinger EC. Immunization in the adult immunocompromised host. *Autoimmun Rev* 2012; **11**: 212-218 [PMID: 21621004 DOI: 10.1016/j.autrev.2011.05.015]

77 **Sahasranaman S**, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. *Eur J Clin Pharmacol* 2008; **64**: 753-767 [PMID: 18506437 DOI: 10.1007/s00228-008-0478-6]

78 **Egli A**, Kumar D, Broscheit C, O'Shea D, Humar A. Comparison of the effect of standard and novel immunosuppressive drugs on CMV-specific T-cell cytokine profiling. *Transplantation* 2013; **95**: 448-455 [PMID: 23274966 DOI: 10.1097/TP.0b013e318276a19f]

79 **Salles MJ**, Sens YA, Boas LS, Machado CM. Influenza virus vaccination in kidney transplant recipients: serum antibody response to different immunosuppressive drugs. *Clin Transplant* 2010; **24**: E17-E23 [PMID: 19758368 DOI: 10.1111/j.1399-0012.2009.01095.x]

80 **Versluis DJ**, Beyer WE, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation* 1986; **42**: 376-379 [PMID: 3532450 DOI: 10.1097/00007890-198610000-00009]

81 **Cordero E**, Perez-Ordoñez A, Aydillo TA, Torre-Cisneros J, Gavalda J, Lara R, Segura C, Len O, Cabral E, Gasch A, Pachon J, Perez-Romero P. Therapy with m-TOR inhibitors decreases the response to the pandemic influenza A H1N1 vaccine in solid organ transplant recipients. *Am J Transplant* 2011; **11**: 2205-2213 [PMID: 21831151 DOI: 10.1111/j.1600-6143.2011.03692.x]

82 **Eckerle I**, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. *PLoS One* 2013; **8**: e56974 [PMID: 23451126 DOI: 10.1371/journal.pone.0056974]

83 **Beil S**, Kreuzer M, Pape L. Course of immunization titers after pediatric kidney transplantation and association with glomerular filtration rate and kidney function. *Transplantation* 2012; **94**: e69-e71 [PMID: 23222744 DOI: 10.1097/TP.0b013e3182743d57]

84 **Michel ML**, Tiollais P. Hepatitis B vaccines: protective efficacy and therapeutic potential. *Pathol Biol (Paris)* 2010; **58**: 288-295 [PMID: 20382485 DOI: 10.1016/j.patbio.2010.01.006]

85 **Weinstein T**, Chagnac A, Boaz M, Ori Y, Herman M, Zevin D, Schmilovitz-Weiss H, Gafter U. Improved immunogenicity of a novel third-generation recombinant hepatitis B vaccine in patients with end-stage renal disease. *Nephron Clin Pract* 2004; **97**: c67-c72 [PMID: 15218332 DOI: 10.1159/000078403]

86 **Jacobson IM**, Jaffers G, Dienstag JL, Tolkoff-Rubin NE, Cosimi AB, Delmonico F, Watkins E, Hinkle C, O'Rourke S, Russell PS. Immunogenicity of hepatitis B vaccine in renal transplant recipients. *Transplantation* 1985; **39**: 393-395 [PMID: 3157246 DOI: 10.1097/00007890-198504000-00011]

87 **L'Huillier AG**, Wildhaber BE, Belli DC, Diana A, Rodriguez M, Siegrist CA, Posfay-Barbe KM. Successful serology-based intervention to increase protection against vaccine-preventable diseases in liver-transplanted children: a 19-yr review of the Swiss national reference center. *Pediatr Transplant* 2012; **16**: 50-57 [PMID: 22093802 DOI: 10.1111/j.1399-3046.2011.01600.x]

88 **Danzinger-Isakov L**, Kumar D; AST Infectious Diseases Community of Practice. Guidelines for vaccination of solid organ transplant candidates and recipients. *Am J Transplant* 2009; **9** Suppl 4: S258-S262 [PMID: 20070687 DOI: 10.1111/j.1600-6143.2009.02917.x]

89 **Kotton CN**. Immunization after kidney transplantation-what is necessary and what is safe? *Nat Rev Nephrol* 2014; **10**: 555-562 [PMID: 25072119 DOI: 10.1038/nrneph.2014.122]

90 **Ali T**, Scott N, Kallas W, Halliwell ME, Savino C, Rosenberg E, Ferraro M, Hohmann E. Detection of influenza antigen with rapid antibody-based tests after intranasal influenza vaccination (FluMist). *Clin Infect Dis* 2004; **38**: 760-762 [PMID: 14986264 DOI: 10.1086/382887]

91 **Miyairi I**, Funaki T, Saitoh A. Immunization practices in solid organ transplant recipients. *Vaccine* 2016; **34**: 1958-1964 [PMID: 26954107 DOI: 10.1016/j.vaccine.2016.03.001]

92 **Fairhead T**, Hendren E, Tinckam K, Rose C, Sherlock CH, Shi L, Crowcroft NS, Gubbay JB, Landsberg D, Knoll G, Gill J, Kumar D. Poor seroprotection but allosensitization after adjuvanted pandemic influenza H1N1 vaccine in kidney transplant recipients. *Transpl Infect Dis* 2012; **14**: 575-583 [PMID: 22999005 DOI: 10.1111/tid.12006]

93 **Schaffer SA**, Husain S, Delgado DH, Kavanaugh L, Ross HJ. Impact of adjuvanted H1N1 vaccine on cell-mediated rejection in heart transplant recipients. *Am J Transplant* 2011; **11**: 2751-2754 [PMID: 21906258 DOI: 10.1111/j.1600-6143.2011.03743.x]

94 **Vermeiren P**, Aubert V, Sugamele R, Aubert JD, Venetz JP, Meylan P, Pascual M, Manuel O. Influenza vaccination and humoral alloimmunity in solid organ transplant recipients. *Transpl Int* 2014; **27**: 903-908 [PMID: 24797932 DOI: 10.1111/tri.12345]

95 **Scharpé J**, Evenepoel P, Maes B, Bammens B, Claes K, Osterhaus AD, Vanrenterghem Y, Peetermans WE. Influenza vaccination is efficacious and safe in renal transplant recipients. *Am J Transplant* 2008; **8**: 332-337 [PMID: 18162092 DOI: 10.1111/j.1600-6143.2007.02066.x]

96 **Candon S**, Thervet E, Lebon P, Suberbielle C, Zuber J, Lima C, Charron D, Legendre C,

Chatenoud L. Humoral and cellular immune responses after influenza vaccination in kidney transplant recipients. *Am J Transplant* 2009; **9**: 2346-2354 [PMID: 19656126 DOI: 10.1111/j.1600-6143.2009.02787.x]

97 **Orcurto A**, Pascual M, Hoschler K, Aubert V, Meylan P, Manuel O. Impact of anti-T-cell therapy in the immunogenicity of seasonal influenza vaccine in kidney transplant recipients. *Transplantation* 2012; **94**: 630-636 [PMID: 22895612 DOI: 10.1097/TP.0b013e31825f7f82]

98 **Lindemann M**, Heinemann FM, Horn PA, Witzke O. Vaccination against Streptococcus pneumoniae does not induce antibodies against HLA or MICA in clinically stable kidney transplant recipients. *Hum Immunol* 2013; **74**: 1267-1270 [PMID: 23911739 DOI: 10.1016/j.humimm.2013.07.010]

99 **Mulley WR**, Dendle C, Ling JEH, Knight SR. Does vaccination in solid-organ transplant recipients result in adverse immunologic sequelae? A systematic review and meta-analysis. *J Heart Lung Transplant* 2018; **37**: 844-852 [PMID: 29609844 DOI: 10.1016/j.healun.2018.03.001]

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MINIREVIEWS

Machine perfusion of the liver: Which is the best technique to mitigate ischaemia-reperfusion injury?

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Abstract

Longstanding research describes the mechanisms whereby the restoration of blood flow and reoxygenation (reperfusion) aggravates the ischaemic injury caused by a period of anoxia to a donor liver. This phenomenon, called ischaemia-reperfusion injury (IRI), leads to parenchymal cell death, microcirculatory failure, and inflammatory immune response. Clinically, IRI is the main factor responsible for the occurrence of posttransplant graft dysfunction and ischaemic-type biliary lesions. While extended criteria donor livers are more vulnerable to IRI, their utilisation is required to address the shortfall in donor organs. Thus, the mitigation of IRI should drive the setting of a new benchmark for marginal organ preservation. Herein, strategies incorporating different modalities of machine perfusion of the liver to alleviate IRI are discussed in conjunction with advantages and disadvantages of individual protocols. Techniques leading to reperfusion of the liver during machine perfusion (*in situ* normothermic regional perfusion and *ex situ* normothermic machine perfusion) may mitigate IRI by shortening the ischaemic period of the organs. This benefit potentially escalates from the minimum level, obtained following just partial alleviation of the ischaemic period, to the maximum level, which can be potentially achieved with ischaemia-free organ transplantation. Techniques that do not lead to reperfusion of the liver during machine perfusion (hypothermic, subnormothermic, and controlled-oxygenated rewarming) optimise mitochondrial oxidative function and replenish cellular energy stores, thereby lowering reactive oxygen species production as well as the activation of

downstream inflammatory pathways during reperfusion. Further mechanistic insights into IRI may guide the development of donor-specific protocols of machine perfusion on the basis of the limitations of individual categories of extended criteria donor organs.

Key words: Machine perfusion of the liver; Ischaemia-reperfusion injury; Liver transplantation; Organ preservation; Organ reconditioning

Core tip: Hepatic ischaemia-reperfusion injury (IRI) is the main culprit of post-transplantation graft dysfunction and ischaemic-type biliary lesions. Despite the increased demand, extended-criteria donor livers are more vulnerable to IRI, thereby presenting inferior postoperative outcomes. Hence, the mitigation of IRI should drive the setting of a new benchmark for extended-criteria donor organ preservation. Machine perfusion of the liver has the potential to mitigate IRI *via* a shortening of the ischaemic period of the livers or the reconditioning of their bioenergetic status. Interventions to further alleviate IRI, such as pharmacological or nonpharmacological metabolic modulation of donor organs, may amplify this effect.

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INTRODUCTION

Ischaemia-reperfusion injury (IRI) is the phenomenon whereby the hypoxic damage imposed on an organ is aggravated during the reestablishment of the blood flow along with reoxygenation[1]. This biphasic detrimental process affects donor livers during liver transplantation (LT) and is the main responsible factor for the occurrence of graft dysfunction (primary nonfunction and delayed graft function) after the procedure[2,3]. Additionally, IRI is associated with the occurrence of ischaemic-type biliary lesions (ITBL) posttransplantation, which, in turn, leads to high rates of graft loss and retransplantation[4,5]. During ischaemia, the absence of oxygen interrupts the shuttling of electrons through the mitochondria electron transport chain (ETC), as oxygen is the terminal electron acceptor during cellular respiration. The affected ETC interrupts the transfer of protons (H^+) across the inner mitochondrial membrane, thereby hampering the generation of the proton motive force required for oxidative phosphorylation and adenosine triphosphate (ATP) synthesis. The cellular ATP stores are then rapidly consumed and the process of anaerobic glycolysis is commenced in order to produce energy to the cells using the glycogen stores and the glucose available in the surrounding fluid. Activation of the former metabolic pathway results in lactate accumulation with local tissue acidosis as well as failure of the Na^+/K^+-ATPase pump with depolarisation of the cell membrane and influx of Ca^{2+}/Na^+ to the cytosol of the endothelial and Kupffer cells, leading to cell swelling. Additionally, the presence of vasoconstrictive substances such as endothelin and thromboxane-A2 not balanced by the vasodilatory nitric oxide (NO) can cause endothelial cell dysfunction with vasoconstriction and microcirculatory failure[2]. On reperfusion, when the blood flow is re-established, the damage caused by the ischaemic period is aggravated by the reoxygenation. This is initiated by the mitochondrial release of reactive oxygen species (ROS) due to an inhibited ETC causing the activation of Kupffer cells, which in turn will release proinflammatory cytokines, such as tumour necrosis factor-alpha/interleukin 1-beta, recruiting neutrophils and inducing the expression of adhesion molecules on sinusoidal endothelial cells. Activated neutrophils produce more ROS, perpetuating the inflammatory response that ultimately results in tissue damage and the initiation of cell death programs such as necrosis, apoptosis, or autophagy[2,3,6].

Donor organs with steatosis, organs that have been exposed to prolonged preservation times, organs from elderly donors, or organs from donation after

circulatory death (DCD) are all more vulnerable to IRI and therefore are referred to as marginal or extended criteria donor (ECD) organs[7]. The defining parameters of ECD organs can vary slightly amongst centres[8], although, consistently, ECD-LT is associated with high rates of graft dysfunction and lower patient and graft survival posttransplantation[9-11]. Despite inferior outcomes, the utilisation of ECD livers is required to tackle the shortfall of donor organs for transplantation. Whilst transplant surgeons do not have control over these donor features, they can consider alternatives to better preserve or even recondition ECD livers. The wider utilisation of ECD livers has exceeded the preservation capacities of traditional static cold storage (SCS), and machine perfusion (MP) of the liver is considered to be a possible alternative preservation method. The use of this technique may offer several advantages in comparison with SCS, including superior organ preservation, limiting ischaemia; the assessment of organ function prior to transplantation; and the possibility of improving or repairing highly vulnerable organs[12]. Nevertheless, benefits may vary between different modalities of MP (Table 1); therefore, those protocols are frequently seen as divergent or even competitive at this time. Herein, the advantages and limitations of each individual technique in relation to the possibility of IRI mitigation are briefly discussed in an attempt to identify which is the best technique of MP of the liver.

STUDY ANALYSIS

Machine perfusion of the liver and ischaemia-reperfusion injury

Considering its clinical significance, the mitigation of IRI should drive the setting of a new benchmark for ECD organ preservation. In accordance, the approach to this question might take into consideration how the different modalities of MP address IRI (Figure 1). For study purposes, these different modalities were categorised on the basis of either the occurrence of reperfusion of the liver during MP or not.

Techniques leading to reperfusion of the liver during machine perfusion

The common feature of this group of MP techniques is the abbreviation of the hypoxic period *via* reperfusion of the organ within physiological temperatures to support cellular metabolic function during preservation. This approach avoids further depletion of ATP stores and the accumulation of metabolic waste products, although experimental models have suggested that, even without the presence of leukocytes and platelets in the circuit, reperfusion during NMP induces oxidative tissue injury and the activation of the inflammatory immune response[13,14].

Ex situ normothermic MP (NMP) can be employed as a preservation method, fully replacing SCS; hence, it has the potential to limit the hypoxic injury to the minimum period required for organ preparation and the setting of the machine. Additionally, the presence of a constant flow of fluids in the vessels during organ preservation is advocated to improve the expression of vasoprotective endothelial genes alleviating the microcirculatory failure associated with IRI[15]. The benefits of this technique were recently shown in the largest clinical trial to date that compared this modality of NMP and SCS[16]. Nasralla *et al*[16] reported the results of transplantation of 121 donor livers following preservation NMP. The authors found a 50% decrease in the release of aspartate transaminase (AST) in the recipient within the first seven postoperative days in comparison with grafts that had SCS[16]. Nevertheless, the former study did not show superiority of NMP in terms of the occurrence of ITBL. This finding suggests that the limitation of hypoxic injury *per se* is not enough to prevent ITBL formation; thus, the etiopathogenesis of these lesions should rely also on the reperfusion injury, which is supported by an *in vitro* study[4]. The strongest evidence supporting the advantages of limiting IRI is the newly developed ischaemia-free organ transplantation (IFOT) technique[17], described by He *et al*[17], whereby complete elimination of hypoxia *via* continuous NMP was shown to prevent postreperfusion syndrome and vasoplegia after revascularisation of a severely steatotic donor liver. Moreover, NMP can also be performed after a period of SCS in an end-ischaemic approach. Whilst end-ischaemic NMP is logistically less challenging, it restrains the NMP's ability to shorten the time of hypoxic injury to the organs. Finally, NMP may take advantage of the nearly physiological environment to assess the function of the organ prior to transplantation and to offer therapeutic approaches, such as cytoprotective and/or metabolic-modulating agents, for the treatment of IRI during NMP. This option is still underexplored thus far, although experiments involving pharmacological modulation of the lipid metabolism during NMP exemplify the benefits of this approach[18].

In situ normothermic regional perfusion (NRP) re-establishes the delivery of

Table 1 Advantages and disadvantages of different modalities of machine perfusion of the liver

	Advantage	Disadvantage
Machine perfusion of the liver (All modalities)	Continuous circulation-improved preservation of the microcirculation; Nutrients and oxygen delivery for cellular metabolism; Removal of metabolic waste products; Delivery of cytoprotective agents and/or metabolic-modulating agents	Costly procedure; Requires specialised team
Techniques leading to reperfusion of the liver during machine perfusion (*In situ* normothermic regional perfusion; *Ex situ* normothermic machine perfusion)	Support organ full metabolism; Assessment of organ viability Assessment of hepatocellular injury; Potential to extend the period of organ storage; Possibility to shorten the ischaemic period of the livers	Persuade reperfusion on the machine; Risk of organ injury in case of organ failure or unrecognised problems with cannulation of the vessels; Require the use of an oxygen carrier in the perfusate
Techniques that do not lead to reperfusion of the liver during machine perfusion (Hypothermic oxygenated machine perfusion; dual-vessel hypothermic oxygenated perfusion; subnormothermic machine perfusion; controlled oxygenated rewarming)	Assessment of hepatocellular injury; Enhancement of mitochondrial function and replenishment of cellular energy stores; Lower rates of intra-hepatic biliary complications post-transplantation; Does not require oxygen carriers in the perfusate	Limited metabolic rate of the organs does not favour assessment of organ viability; Definition of the biomarkers to individualise perfusion times and assess responses to treatment in real-time is still pending
Ischaemia-free organ transplantation	Potential to abolish completely ischaemia-reperfusion injury	Limited application to donation after brainstem death thus far; Challenging procedure; Logistically challenging in a multivisceral retrieval setting; Just a single case reported

oxygen to the organs following asystole in DCD donors and, thus, limits the injury associated with a longer warm ischaemia period. Additionally, NRP may have a preconditioning effect, which could revert the detrimental mechanisms of warm injury[19,20]. While animal experiments involving dogs revealed that NRP is able to negate endothelial cell damage in livers harvested after 20 min of cardiac arrest[21], studies providing an in-depth analysis of the mechanistic effects of the procedure on the metabolism of human donor organs remain lacking.

Techniques that do not lead to reperfusion of the liver during machine perfusion

This category encompasses the hypothermic and subnormothermic techniques of MP as well as controlled oxygenated rewarming. All of them share as a common feature the absence of organ reperfusion, as perfusate temperatures do not exceed 20 °C. Within this category, the vast majority of mechanistic studies were performed so far on hypothermic oxygenated perfusion (HOPE) by the Zurich group. It has been proposed that the delivery of oxygen at hypothermic temperatures enhances the mitochondrial oxidative function, replenishing the cellular ATP stores prior to reperfusion[14]. This hypothesis is sustained by experimental studies that found a decrease in the expression of markers indicating oxidative tissue damage and the activation of Kupffer cells and leukocytes. In addition, these studies reported a lower release in the perfusate of markers of mitochondrial injury, damage-associated molecular patterns, and cytokines in livers after reperfusion following the HOPE procedure[13,14,22]. The Groningen group has been working on dual-vessel (hepatic artery and portal vein) hypothermic oxygenated perfusion (D-HOPE) and reported similar mechanistic findings to those obtained using HOPE[23,24].

Subnormothermic MP (SMP) is performed usually at around 20 °C with active oxygenation of the perfusion fluid. Transplant animal models suggest that SMP can positively impact mitochondrial function, increase organs' ATP stores, decrease the release of markers of tissue injury (*e.g.*, transaminases and cytokines), and improve graft function postoperatively[25,26]. Defenders of this technique advocate that the increase in the organ's metabolic rate that occurs as a result of the increase in temperature (from 10 °C to 20 °C) is sufficient for viability testing[25]. Minor *et al*[27] proposed a variant of the SMP technique called the controlled oxygenated rewarming (COR) method. In a reperfusion porcine model using *ex situ* NMP, as compared with hypothermic MP or SMP alone, COR was found to increase cellular ATP stores and decrease the release of lipid peroxides and markers of hepatocellular injury (AST and ALT) in the perfusate after reperfusion[27]. During NMP, organs that had undergone COR exhibited increased bile production, lower vascular resistance, and decreased expression of proinflammatory genes (*e.g.*, intercellular adhesion molecule 1, toll-like receptor 4, and tumour necrosis factor alpha)[27].

Which is the best technique of machine perfusion of the liver to mitigate ischaemia-reperfusion injury?

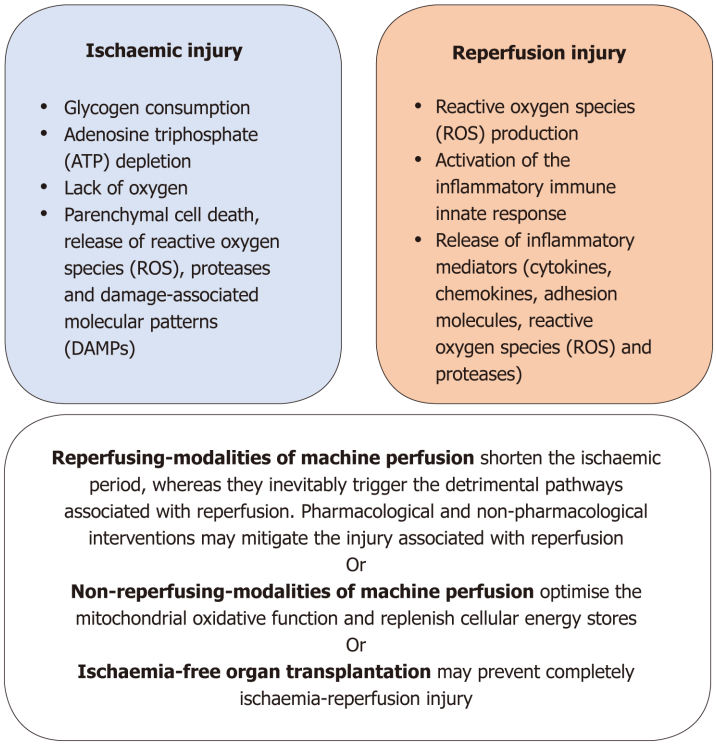

Figure 1 Mechanistic characteristic of the different periods of the ischaemia-reperfusion injury and the role of the diverse techniques of machine perfusion of the liver. Techniques leading to reperfusion of the liver during machine perfusion include *in situ* normothermic regional perfusion and *ex situ* normothermic machine perfusion; techniques that do not lead to reperfusion of the liver during machine perfusion include hypothermic machine perfusion, subnormothermic machine perfusion and controlled oxygenated rewarming.

Contemporary scientific evidence supports the concept that techniques of MP of the liver leading to organ reperfusion may mitigate IRI by shortening the ischaemic period. This benefit escalates from the minimum level, obtained following just partial alleviation of ischaemic injury during end-ischaemic NMP, to the maximum level, which can be potentially achieved with IFOT. However, these modalities of MP inevitably lead to ROS production, oxidative injury, and activation of the inflammatory immune response, with some degree of cell damage occurring during reperfusion[13]. Whilst this former detrimental phenomenon may not affect organs with enough metabolic reserve to overcome this injury, it can be a decisive factor when considering high-risk organs with limited metabolic reserve[28,29]. Consequently, most of the evidence accumulated thus far supports the advantages of NMP over SCS regarding organ preservation and viability assessment, although the resuscitative capacity of NMP *per se* is still unclear.

Mounting data suggest that techniques of MP of the liver that do not lead to organ reperfusion are able to mitigate IRI by way of optimisation of the mitochondrial oxidative function and replenishment of the cellular ATP stores during MP. The enhanced mitochondrial oxidative function decreases ROS production as well as the subsequent activation of downstream inflammatory pathways during reperfusion[30]. These mechanistic effects were shown to have a positive impact on the recovery of the metabolic function of discarded human donor livers submitted to NMP for viability assessment following the use of hypothermic oxygenated techniques of MP[29]. Conversely, the lower metabolic rate of the organs during hypothermic MP does not favour their functional assessment prior to transplantation. Arguably, strategies to evaluate mitochondrial metabolism and the energetic recovery of the organs, in real time, may warrant further promising studies be performed on this subject[22].

Despite the complex interaction between cells and signal molecules during IRI, future investigations determining the susceptibility of each individual cell population of the liver to the different periods of liver IRI (*i.e.*, warm ischaemia, cold ischaemia, and reperfusion) might help with driving the allocation of donor organs to specific MP techniques. Thus far, existing evidence associates warm ischaemia mainly with Kupffer-cell-mediated hepatocellular injury, whereas cold ischaemia damages primarily sinusoidal endothelial cells[2,31]. Cholangiocytes have been reported to be less vulnerable to anoxia than hepatocytes; however, during reperfusion, they produce higher amounts of ROS, leading to cell death[4]. If exposure of the organ to an

ischaemic period is unavoidable, the careful consideration of strategies to alleviate the local immune activation during reperfusion is desirable, such as employing preceding short periods of non-normothermic perfusions as a therapeutic approach or incorporating the delivery of pharmacological agents during NMP[29].

To conclude, whilst all techniques of MP of the liver have the potential to mitigate IRI, they offer different benefits and present diverse limitations. Therefore, there is no solid evidence yet to suggest the superiority of one technique over the others. A better mechanistic understanding of the intricate pathways of IRI may guide the development of personalised protocols of MP for groups of ECD organs, such as DCD livers, steatotic livers, or organs with prolonged cold ischaemia times.

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REFERENCES

1 **Collard CD**, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. *Anesthesiology* 2001; **94**: 1133-1138 [PMID: 11465607 DOI: 10.1097/00000542-200106000-00030]
2 **Peralta C**, Jiménez-Castro MB, Gracia-Sancho J. Hepatic ischemia and reperfusion injury: effects on the liver sinusoidal milieu. *J Hepatol* 2013; **59**: 1094-1106 [PMID: 23811302 DOI: 10.1016/j.jhep.2013.06.017]
3 **Zhai Y**, Petrowsky H, Hong JC, Busuttil RW, Kupiec-Weglinski JW. Ischaemia-reperfusion injury in liver transplantation--from bench to bedside. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 79-89 [PMID: 23229329 DOI: 10.1038/nrgastro.2012.225]
4 **Noack K**, Bronk SF, Kato A, Gores GJ. The greater vulnerability of bile duct cells to reoxygenation injury than to anoxia. Implications for the pathogenesis of biliary strictures after liver transplantation. *Transplantation* 1993; **56**: 495-500 [PMID: 8212138 DOI: 10.1097/00007890-199309000-00001]
5 **Guichelaar MM**, Benson JT, Malinchoc M, Krom RA, Wiesner RH, Charlton MR. Risk factors for and clinical course of non-anastomotic biliary strictures after liver transplantation. *Am J Transplant* 2003; **3**: 885-890 [PMID: 12814481 DOI: 10.1034/j.1600-6143.2003.00165.x]
6 **Eltzschig HK**, Eckle T. Ischemia and reperfusion--from mechanism to translation. *Nat Med* 2011; **17**: 1391-1401 [PMID: 22064429 DOI: 10.1038/nm.2507]
7 **Routh D**, Naidu S, Sharma S, Ranjan P, Godara R. Changing pattern of donor selection criteria in deceased donor liver transplant: a review of literature. *J Clin Exp Hepatol* 2013; **3**: 337-346 [PMID: 25755521 DOI: 10.1016/j.jceh.2013.11.007]
8 **Silberhumer GR**, Rahmel A, Karam V, Gonen M, Gyoeri G, Kern B, Adam R, Muehlbacher F, Rogiers X, Burroughs AK, Berlakovich GA. The difficulty in defining extended donor criteria for liver grafts: the Eurotransplant experience. *Transpl Int* 2013; **26**: 990-998 [PMID: 23931659 DOI: 10.1111/tri.12156]
9 **Ploeg RJ**, D'Alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, Sasaki T, Sollinger HW, Belzer FO, Kalayoglu M. Risk factors for primary dysfunction after liver transplantation--a multivariate analysis. *Transplantation* 1993; **55**: 807-813 [PMID: 8475556 DOI: 10.1097/00007890-199304000-00024]
10 **Feng S**, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, Greenstein SM, Merion RM. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783-790 [PMID: 16539636 DOI: 10.1111/j.1600-6143.2006.01242.x]
11 **Nemes B**, Gámán G, Polak WG, Gelley F, Hara T, Ono S, Baimakhanov Z, Piros L, Eguchi S. Extended-criteria donors in liver transplantation Part II: reviewing the impact of extended-criteria donors on the complications and outcomes of liver transplantation. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 841-859 [PMID: 26831547 DOI: 10.1586/17474124.2016.1149062]
12 **Boteon YL**, Afford SC, Mergental H. Pushing the Limits: Machine Preservation of the Liver as a Tool to Recondition High-Risk Grafts. *Curr Transplant Rep* 2018; **5**: 113-120 [PMID: 29774176 DOI: 10.1007/s40472-018-0188-7]
13 **Schlegel A**, Kron P, Graf R, Dutkowski P, Clavien PA. Warm vs. cold perfusion techniques to rescue rodent liver grafts. *J Hepatol* 2014; **61**: 1267-1275 [PMID: 25086285 DOI: 10.1016/j.jhep.2014.07.023]
14 **Selten J**, Schlegel A, de Jonge J, Dutkowski P. Hypo- and normothermic perfusion of the liver:

Which way to go? *Best Pract Res Clin Gastroenterol* 2017; **31**: 171-179 [PMID: 28624105 DOI: 10.1016/j.bpg.2017.04.001]
15 **Yuan X**, Theruvath AJ, Ge X, Floerchinger B, Jurisch A, García-Cardeña G, Tullius SG. Machine perfusion or cold storage in organ transplantation: indication, mechanisms, and future perspectives. *Transpl Int* 2010; **23**: 561-570 [PMID: 20074082 DOI: 10.1111/j.1432-2277.2009.01047.x]
16 **Nasralla D**, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, Chiocchia V, Dutton SJ, García-Valdecasas JC, Heaton N, Imber C, Jassem W, Jochmans I, Karani J, Knight SR, Kocabayoglu P, Malagò M, Mirza D, Morris PJ, Pallan A, Paul A, Pavel M, Perera MTPR, Pirenne J, Ravikumar R, Russell L, Upponi S, Watson CJE, Weissenbacher A, Ploeg RJ, Friend PJ; Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557**: 50-56 [PMID: 29670285 DOI: 10.1038/s41586-018-0047-9]
17 **He X**, Guo Z, Zhao Q, Ju W, Wang D, Wu L, Yang L, Ji F, Tang Y, Zhang Z, Huang S, Wang L, Zhu Z, Liu K, Zhu Y, Gao Y, Xiong W, Han M, Liao B, Chen M, Ma Y, Zhu X, Huang W, Cai C, Guan X, Li XC, Huang J. The first case of ischemia-free organ transplantation in humans: A proof of concept. *Am J Transplant* 2018; **18**: 737-744 [PMID: 29127685 DOI: 10.1111/ajt.14583]
18 **Boteon YL**, Boteon APCS, Attard J, Mergental H, Mirza DF, Bhogal RH, Afford SC. Ex situ machine perfusion as a tool to recondition steatotic donor livers: Troublesome features of fatty livers and the role of defatting therapies. A systematic review. *Am J Transplant* 2018; **18**: 2384-2399 [PMID: 29947472 DOI: 10.1111/ajt.14992]
19 **Miñambres E**, Suberviola B, Dominguez-Gil B, Rodrigo E, Ruiz-San Millan JC, Rodríguez-San Juan JC, Ballesteros MA. Improving the Outcomes of Organs Obtained From Controlled Donation After Circulatory Death Donors Using Abdominal Normothermic Regional Perfusion. *Am J Transplant* 2017; **17**: 2165-2172 [PMID: 28141909 DOI: 10.1111/ajt.14214]
20 **Oniscu GC**, Randle LV, Muiesan P, Butler AJ, Currie IS, Perera MT, Forsythe JL, Watson CJ. In situ normothermic regional perfusion for controlled donation after circulatory death--the United Kingdom experience. *Am J Transplant* 2014; **14**: 2846-2854 [PMID: 25283987 DOI: 10.1111/ajt.12927]
21 **García-Valdecasas JC**, Tabet J, Valero R, Taurá P, Rull R, García F, Montserrat E, González FX, Ordi J, Beltran J, López-Boado MA, Deulofeu R, Angás J, Cifuentes A, Visa J. Liver conditioning after cardiac arrest: the use of normothermic recirculation in an experimental animal model. *Transpl Int* 1998; **11**: 424-432 [PMID: 9870271 DOI: 10.1007/s001470050169]
22 **Schlegel A**, Muller X, Dutkowski P. Hypothermic Machine Preservation of the Liver: State of the Art. *Curr Transplant Rep* 2018; **5**: 93-102 [PMID: 29564206 DOI: 10.1007/s40472-018-0183-z]
23 **van Rijn R**, Karimian N, Matton APM, Burlage LC, Westerkamp AC, van den Berg AP, de Kleine RHJ, de Boer MT, Lisman T, Porte RJ. Dual hypothermic oxygenated machine perfusion in liver transplants donated after circulatory death. *Br J Surg* 2017; **104**: 907-917 [PMID: 28394402 DOI: 10.1002/bjs.10515]
24 **Karangwa SA**, Dutkowski P, Fontes P, Friend PJ, Guarrera JV, Markmann JF, Mergental H, Minor T, Quintini C, Selzner M, Uygun K, Watson CJ, Porte RJ. Machine Perfusion of Donor Livers for Transplantation: A Proposal for Standardized Nomenclature and Reporting Guidelines. *Am J Transplant* 2016; **16**: 2932-2942 [PMID: 27129409 DOI: 10.1111/ajt.13843]
25 **Berendsen TA**, Bruinsma BG, Lee J, D'Andrea V, Liu Q, Izamis ML, Uygun K, Yarmush ML. A simplified subnormothermic machine perfusion system restores ischemically damaged liver grafts in a rat model of orthotopic liver transplantation. *Transplant Res* 2012; **1**: 6 [PMID: 23369351 DOI: 10.1186/2047-1440-1-6]
26 **Fontes P**, Lopez R, van der Plaats A, Vodovotz Y, Minervini M, Scott V, Soltys K, Shiva S, Paranjpe S, Sadowsky D, Barclay D, Zamora R, Stolz D, Demetris A, Michalopoulos G, Marsh JW. Liver preservation with machine perfusion and a newly developed cell-free oxygen carrier solution under subnormothermic conditions. *Am J Transplant* 2015; **15**: 381-394 [PMID: 25612645 DOI: 10.1111/ajt.12991]
27 **Minor T**, Efferz P, Fox M, Wohlschlaeger J, Lüer B. Controlled oxygenated rewarming of cold stored liver grafts by thermally graduated machine perfusion prior to reperfusion. *Am J Transplant* 2013; **13**: 1450-1460 [PMID: 23617781 DOI: 10.1111/ajt.12235]
28 **Watson CJE**, Kosmoliaptsis V, Pley C, Randle L, Fear C, Crick K, Gimson AE, Allison M, Upponi S, Brais R, Jochmans I, Butler AJ. Observations on the ex situ perfusion of livers for transplantation. *Am J Transplant* 2018; **18**: 2005-2020 [PMID: 29419931 DOI: 10.1111/ajt.14687]
29 **Boteon YL**, Laing RW, Schlegel A, Wallace L, Smith A, Attard J, Bhogal RH, Neil DAH, Hübscher S, Perera MTPR, Mirza DF, Afford SC, Mergental H. Combined Hypothermic and Normothermic Machine Perfusion Improves Functional Recovery of Extended Criteria Donor Livers. *Liver Transpl* 2018; **24**: 1699-1715 [PMID: 30058119 DOI: 10.1002/lt.25315]
30 **Schlegel A**, Kron P, Graf R, Clavien PA, Dutkowski P. Hypothermic Oxygenated Perfusion (HOPE) downregulates the immune response in a rat model of liver transplantation. *Ann Surg* 2014; **260**: 931-937; discussion 937-938 [PMID: 25243553 DOI: 10.1097/SLA.0000000000000941]
31 **Jawad R**, D'souza M, Selenius LA, Lundgren MW, Danielsson O, Nowak G, Björnstedt M, Isaksson B. Morphological alterations and redox changes associated with hepatic warm ischemia-reperfusion injury. *World J Hepatol* 2017; **9**: 1261-1269 [PMID: 29290907 DOI: 10.4254/wjh.v9.i34.1261]

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