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Casting Light on **HO**st-cytomegaloviRUs interaction in **S**olid organ transplantation

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SPECIAL ISSUE EDITORIAL
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Current Challenges and Advances on Infectious Diseases in Solid Organ Transplantation

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Keywords: cytomegalovirus, multidrug resistant bacterial infection, pancreas allograft, oncogenic viruses, antifungals

Editorial on the Special Issue

Current Challenges and Advances on Infectious Diseases in Solid Organ Transplantation

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Infection remains one of the most common complications after organ transplantation. The epidemiology of infection in solid-organ transplant (SOT) recipients is shaped by the interplay of two key factors: the lifelong use of immunosuppressive drugs impairing cellular immunity, and the surgical procedure itself, along with the subsequent hospital stay [1]. SOT recipients are prone to develop a wide range of infections, caused by opportunistic pathogens like cytomegalovirus (CMV) and molds, to more common healthcare-associated infections, which may sometimes be caused by multidrug-resistant (MDR) organisms. Additionally, certain pathogens can be linked to oncogenic processes triggered by a loss of immune control.

Transplant infectious diseases cover therefore a broad spectrum of research areas, including viral immunology, infection control strategies for MDR organisms, and complications related to immunosuppression, among others. This diversity in managing infections in SOT recipients is highlighted in this Special Issue titled "*Current Challenges and Advances in Infectious Diseases in Solid Organ Transplantation*."

Serris et al. summarized the 2023 Transplantation and Infection group annual meeting. Topics discussed included antibiotic and non-antibiotic approaches to manage various infections in SOT recipients. Innovative strategies to protect the gut microbiome are still under research, including fecal transplantation and new molecules inactivating non-absorbed antibiotics in the gastrointestinal tract. New antibiotic and antifungal drugs and the evidence to support their use in SOT recipients were reviewed. Gaps in knowledge regarding management of asymptomatic bacteriuria after kidney transplantation (KT) were discussed, including recent evidence to support avoiding antibiotic treatment in the first 2 months following transplantation. Type and duration of therapy for pyelonephritis, as well as innovative approaches for therapy and prevention are also discussed (Serris et al.)

Matuschik et al. reported the results of 138 ABO-incompatible KT procedures performed at Freiburg Transplant Center from 2004 to 2020. This retrospective study compared the use of single-

use antigen-selective ABO columns (81 patients) versus reusable nonantigen-specific immunoglobulin adsorption columns (57 patients) and found that use of the latter was associated with 3-fold increased risk for severe and recurrent post-transplant viral and bacterial infections, mainly urosepsis. Rates of allograft rejection were significantly higher with antigen selective ABO columns (29% vs. 14%), though graft survival was similar. Two years mortality was significantly higher with non-antigen specific immunoadsorption (Matuschik et al.)

Walti et al. comprehensively reviewed the latest advancements in the management of refractory and/or resistant CMV infection (R/R CMV) and disease. As highlighted by the authors, R/R CMV constitutes a challenging complication associated to worse graft and patient outcomes, which is in part explained by the common occurrence of drug toxicities with the use of options available to date (i.e., foscarnet or cidofovir). The results of phase 2/3 clinical trials with maribavir and letermovir are critically discussed, as well as controversial questions regarding the risk of emerging resistance, the benefit expected from combination therapy or secondary prophylaxis, or the optimal donor source for CMV-specific T-cells for adoptive immunotherapy. Observational studies exploring the potential role of letermovir for the treatment of R/R CMV were also scrutinized. Finally, the review offers a valuable summary of authors' institutional guidelines and their personal view on this topic (Walti et al.)

The overall clinical picture of other herpesviruses relevant to the SOT population due to their oncogenic potential—Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV8)— was covered by (Atamna et al.). The authors provided a thorough, albeit concise, overview of the epidemiology, risk factors, diagnosis, and state-of-the-art therapeutic approaches for post-transplant HHV8 disorders (Kaposi´s sarcoma, multicentric Castleman disease, primary effusion lymphoma and inflammatory cytokine syndrome) and EBV-related post-transplant lymphoproliferative disease. Unmet needs in the management of these complications, such as the optimal screening strategy for HHV8 and EBV DNAemia or the pre-emptive use of antivirals or rituximab in case of persistent and/or high-level replication, were also discussed (Atamna et al.)

Namsiripongpun et al. reported a prospective study of 81 KT recipients in Thailand who were monitored with a non-specific interferon (IFN)-γ ELISpot assay at transplantation and at 1 month. The main outcome of interest was CMV infection. In multivariable models, low IFN-γ ELISpot response at 1 month was an independent predictor of CMV infection. Of the patients with low IFN-γ response, >60% developed CMV infection compared to 20% among patients with higher response. This study, together with previous published literature, supports the concept that the risk of later CMV infection can be predicted by also non-specific cellular immune responses (Namsiripongpun et al.)

The review by Bestard et al. gives a comprehensive overview of immunobiology of CMV in transplantation and reviews the current evidence for assessing CMV-specific cell-mediated immunity (CMV-CMI). The potential of CMV-CMI assays to predict the risk of infection has been well described, but until recently clinicians have lacked data and advice on how to implement these assays to aid decision-making in clinical practice. The review very elegantly highlights the literature on both observational and interventional trials and gives practical recommendations and future directions on how to optimize the clinical use of the CMV-CMI assays (Bestard et al.)

The review by Lombardi et al. provides a complete dissection of the antibiotics active against MDR Gram-negative bacteria approved over the last years, specifically ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, cefiderocol and eravacycline. Activity spectrum, toxicity profile, clinical use, and PK/PD properties including therapeutic drug monitoring in the setting of liver transplantation were reviewed for each agent. The authors underlined the need of studies on the safety and optimal employment of these drugs in liver transplant recipients.

SOT recipients are particularly vulnerable to MDR organisms, which significantly contribute to morbidity and mortality. Freire et al. addresses the gap in systematic reporting of MDR organism prevalence, especially across high-income (HIC) and low- and middle-income countries (LMIC), where diagnostic tools, screening practices, and drug availability vary. The review focuses on major MDR Gram-negative organisms like Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. It highlights the need for advanced diagnostics and access to new antibiotics to improve outcomes in SOT recipients. Standardization in MDR organism reporting and global epidemiological understanding remains a critical challenge.

Grasberger et al. performed a retrospective study in Finland aimed at assessing the total burden of infections in recipients of simultaneous pancreas-kidney transplantation (SPK) compared with kidney transplantation alone (KTA). The authors compared infection-related hospitalizations and bacteremias during 1- and 5-year follow-up after transplantation, among 162 SPK and 153 type 1 diabetics KTA patients. The inclusion criteria of donor and recipient were age <60 and BMI <30. During the first year, SPK patients had more infection-related hospitalizations (0.54 vs. 0.31 PPY, IRR 1.76, $p < 0.001$) and bacteremias (0.11 vs. 0.01 PPY, IRR 17.12, $p < 0.001$) compared to KTA patients. SPK was an independent risk factor for infection-related hospitalization and bacteremia during the first-year post-transplant, but not during the 5-year follow-up. Patient survival did not differ between groups, however, KTA patients had inferior kidney graft survival.

SOT recipients are at an elevated risk for invasive mold diseases (IMD). Isavuconazole, a novel broad-spectrum antifungal agent, has shown a favorable profile, with good tissue penetration, minimal drug interactions, and fewer adverse effects compared to other azoles like voriconazole and posaconazole. Silva et al. conducted an extensive literature review on isavuconazole use in IMD treatment for SOT recipients. The review included 145 SOT patients, mostly lung and kidney transplant recipients, treated with isavuconazole mainly for *Aspergillus* infections. The drug was well-tolerated, with manageable drug-drug interactions with immunosuppressive agents. The authors have concluded that isavuconazole presents as a viable alternative for IMD treatment in this population, warranting further prospective studies.

In conclusion, this Special Issue provides a comprehensive overview of the epidemiology, prevention, and treatment of a wide range of transplant infectious diseases. It emphasizes the importance of novel multidisciplinary management strategies to enhance allograft and patient outcomes.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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MEETING REPORT
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New Approaches to Manage Infections in Transplant Recipients: Report From the 2023 GTI (Infection and Transplantation Group) Annual Meeting

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INTRODUCTION

This year's GTI ("Groupe Transplantation and Infection") annual meeting was held in Paris, France in February 2023. This meeting focused on new approaches to manage infectious complications in solid organ and stem cell transplant recipients.

In this meeting report, we summarize the presentations and discussions from this annual meeting. Covered topics included new anti-infective agents and non-antibiotic approaches to manage infections due to multidrug-resistant Gram-negative bacteria, staphylococci, and fungal infections, as well as new approaches to manage symptomatic urinary tract infections and asymptomatic bacteriuria in kidney

transplant recipients. Innovative approaches are needed to manage infectious complications in transplant recipients, who are at high risk of difficult-to-treat infections and side effects associated with the use of anti-infective agents.

MANAGEMENT OF POST-TRANSPLANT BACTERIAL INFECTIONS

Multidrug Resistant Enterobacterales Infections in Solid Organ Transplantation: Current Situation and New Non-Antibiotic Approaches

Solid-organ transplantation (SOT) is the treatment of choice for patients diagnosed with end-stage organ disease, and the median survival of both recipients and grafts has significantly increased in the last years [1]. While the incidence of infections (including opportunistic ones such as cytomegalovirus [CMV]) is decreasing due to better prevention, the burden of "classical" infections linked to multidrug-resistant (MDR) bacteria especially related to Gram-negative bacilli (GNB) is increasing [2, 3]. Multidrug resistant Enterobacterales are involved in one-third of bacterial infections in SOT recipients [4]. Prior intestinal colonization with ESBL (extended spectrum beta-lactamase)-producing Enterobacterales is an essential prerequisite for the onset of infection among SOT recipients [5]. Furthermore, among patients with intestinal colonisation with MDR (multidrug resistance) Enterobacterales, prior exposure to anti-infectives appears to be a major risk factor for subsequent infection due to the colonizing strain [5]. This can be explained by an increase in intestinal density of resistant Gram-negative bacilli (commonly referred as relative fecal abundance) during antibiotic administration [6]. Antimicrobial stewardship (AMS) programs are designed to improve the quality of prescribing practices in terms of choice of antibiotic, dosage, duration, route of administration and de-escalation. Benoit Pilmis presented innovative AMS strategies aimed at limiting antibiotic-induced dysbiosis, decolonizing patients colonized by MDR Enterobacterales, and restoring a healthy microbiota [7]. The efficacy of oral colistin-neomycin in preventing multidrug-resistant Enterobacterales (MDR-E) infections in solid organ transplant (SOT) recipients have been evaluated previously in a multicentre, randomized, controlled, open-label, parallel-group clinical trial [8] but showed negative results in term of efficacy and tolerance (particularly for colistin).

Among these strategies, the exact benefits of fecal microbiota transplantation (FMT) remain unclear [9]. A multicenter randomized controlled trial (FeCeS study) evaluating the efficacy of FMT in decolonizing carriers of ESBL- or carbapenemase-producing Enterobacterales will provide an answer (NCT05035342). This indication of FMT in decolonizing patients has been evaluated in allo-hematopoietic stem cell transplant (allo-HSCT) recipients a systematic review has been recently published [10]. FMT was performed before or after HSCT but each time on a low number of patients. Decolonization was obtained in 40%–60% of cases. The majority of the included studies report FMT as a generally well tolerated procedure, with no serious adverse events. Interestingly, in the case series of Shouval et al. two patients developed bacteremia after the infusion, but targeted metagenomic sequencing demonstrated that the bacterial strains did not originate from the FMT inoculum [11].

Altogether, FMT seems an interesting option for decolonization, but the safety profile and efficacy of the procedure must be determined more strongly to better assess the role of FMT in allo-HSCT recipients.

One-promising way to protect the gut microbiota is to develop molecules to chelate or degrade the non-absorbed part of orally administered antibiotics and the fraction of oral and parenteral antibiotics excreted in the bile that reach the colon, induce dysbiosis and a decrease in richness and diversity of the microbiota. For example, ribaxamase (an orally administered beta-lactamase hydrolyzing β-lactams in the colon appears promising in Phase 2 studies although limited to β-lactam antibiotics) and DAV-132 which is a millimetric beads consisting of a core of a specific activated charcoal surrounded by a polymer coating that is insoluble during transit. The charcoal is activated in the ileum and adsorbs and thereby inactivates antibiotics in the caecum/colon [12–16]. For now, no investigation of this strategy exist in transplant recipients but its evaluation and implementation are of interest in the TOS patients, a population highly exposed to antibiotics.

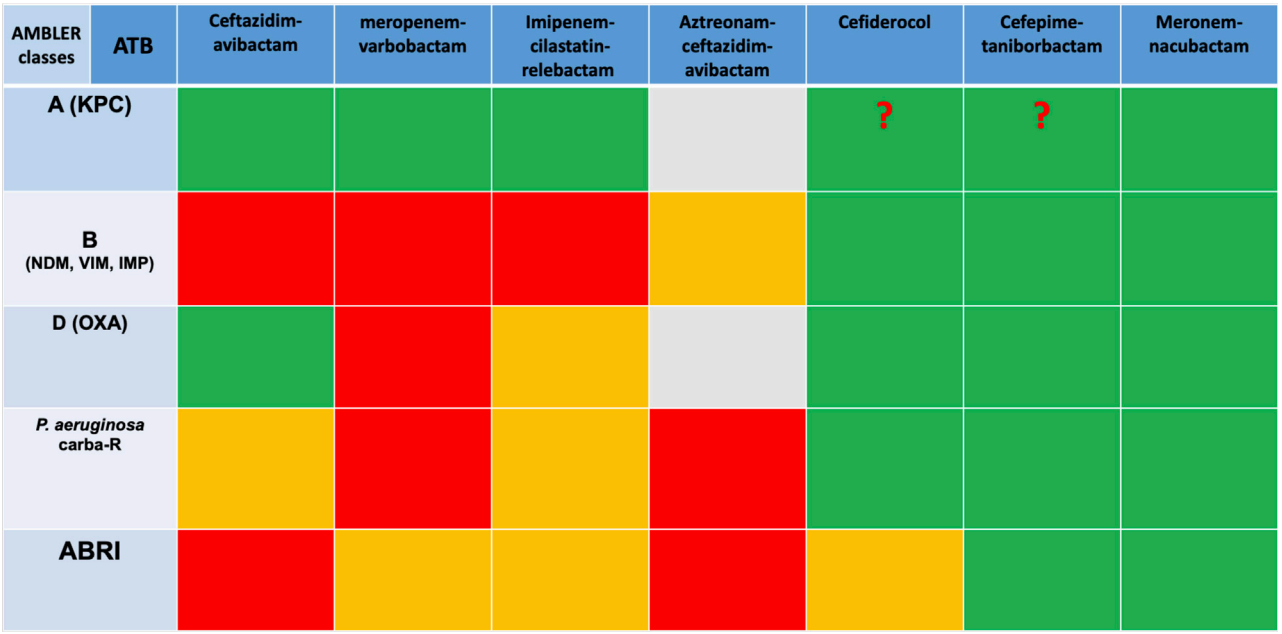
Multidrug Resistant Enterobacterales Infections in Solid Organ Transplantation: New Antibiotics

Antibiotic-resistant Gram-negative bacterial infections are the leading cause of death attributable to antibiotic resistance in Europe and worldwide. This is linked to the epidemic success of 3rd generation cephalosporins (3GC)- resistant Enterobacteriaceae. The widespread use of carbapenems to treat 3GC-resistant strains has led to the emergence of carbapenem-resistant isolates, in particular those secreting carbapenemases, with very limited therapeutic options. New molecules have recently been developed to combat carbapenem-resistant bacteria. Victoire de Lastours summarized the updated antimicrobial management of carbapenem-resistant bacteria related infection.

These include ceftazidime-avibactam, a combination of a 3GC with a new betalactamase inhibitor, avibactam. This combination is effective on strains carrying OXA 48 or KPC, but not metallobetalactamases. This molecule was granted authorization in Europe and the USA following 3 phase 3 trials in complicated intra-abdominal infections versus meropenem, as well as two trials in complicated urinary tract infections yielding non-inferiority. In a retrospective cohort study of 210 SOT recipients with carbapenemase-producing *Klebsiella pneumoniae* blood stream infections, ceftazidime-avibactam significantly increased the probability of 14 and 30 days clinical success, as compared to the best available therapy [17].

A second compound, meropenem-varbobactam, is also active against class A betalactamases (KPC) and cephalosporinases, but inactive against metallobetalactamases and oxacillinases, which limits its interest in some European coutries such as France,

TABLE 1 | Spectrum of new antibiotics regarding the type of resistance.



Abbreviations: ABRI, Acinetobacter *baumani mutli resistant; ATB, antibiotic; carba-R, carbapenem-resistant.*

TABLE 2 | Spectrum of activity, tissue diffusion and drug-drug interactions (DDIs) with immunosuppressive drugs of olorofim, ibrexafungerp and rezafungin.

Molecule	Spectrum of activity	Diffusion	DDIs with immunosuppressive drugs	Potential advantages
Olorofim	*Aspergillus* spp. *Scedosporium* spp. *Lomentospora prolificans Fusarium* spp. *Histoplasma capsulatum Blastomyces dermatitidis Coccidioides* spp.	• Good diffusion in kidney, liver, and lung • Low levels in CNS [54]	• Substrate of several CYP450 enzymes: anticipate dose reduction if given with a strong 3A4 inhibitor (or a moderate dual 3A4+2C9 inhibitor) • Weak inhibitor of CYP3A4: small reductions of tacrolimus and sirolimus might be needed (guided by standard monitoring)	Active against highly resistant molds
ibrexafungerp	*Candida* spp. including echinocandin resistant *C. glabrata* and *C. auris Aspergillus* spp. *Paecilomyces variotii Pneumocystis jirovecii*	• Good diffusion in liver, spleen, lungs, bone marrow, kidney, skin and uvea • Low levels in CNS [65]	• Substrate of CYP3A and P-glycoprotein: avoid coadministration of strong CYP3A inducers • Reversible inhibitor of CYP2C8 and CYP3A4 • interaction with tacrolimus: 1.4-fold increase in AUC; no change in tacrolimus Cmax [66]	• Active against resistant *Candida* species • First orally bioavailable inhibitor of [1(3)- β-D-glucan synthase]
Rezafungin	*Candida* spp. *Aspergillus* spp. *Pneumocystis jirovecii*	Improved drug penetration in liver and kidney abscesses (mouse model of intra-abdominal candidiasis) in comparison with micafungin [67]	Minimal inhibition of CYP450 enzymes [68]: Limited reduction (10%–19%) of the AUC or Cmax of tacrolimus, ciclosporine and mycophenolic acid (probably not clinically meaningful) [69]	• Long half-life allows once weekly dosing • Less hepatotoxicity • May prevent Pneumocystis pneumonia [61, 62]

where KPCs are rare. Non-inferiority has been demonstrated in several trials against optimized treatment. A third molecule, imipenem-relebactam, is also active against KPCs but not against oxacillinases or metallobetalactamases. Imipenem-relebactam is also effective against carbapenem-resistant strains of *Pseudomonas aeruginosa*, but not against carbapenem-resistant *Acinetobacter baumanii* (CRAB). The molecule has been approved in France only as a last resort for the treatment of patients with no other possible therapeutic alternative, and in particular if KPC-type carbapenemase are produced.

Altogether, several choices are now available to treat KPC and OXA-48 oxacillinases which are approved in France and Europe.

For carbapenem-resistant *P. aeruginosa*, ceftolozane-tazobactam is generally effective. Tolerance is generally good (as with beta-lactams), and these molecules are bactericidal. However, these molecules are not effective against metallobetalactamases nor against most CRAB, which poses major therapeutic problems. Its use was reported in a multicenter cohort study of 69 immunocompromised patients including 47 SOT, with multi-drug resistant *P. aeruginosa* infections, mostly respiratory and wound. Clinical cure was achieved in 68% and mortality was 19% [18].

A recently approved molecule, cefiderocol, is a siderophore cephalosporin which uses the bacterial iron entry machinery to achieve high concentrations inside the bacteria. It is unaffected by betalactamases, even metallobetalactamases, and acts as a Trojan horse. In pivotal trials, cefiderocol showed non-inferiority to high-dose meropenem in the treatment of gram-negative nosocomial pneumonia, except for *A. baumanii* infections, a result that remains unexplained. Cefiderocol has been marketed in Europe and the USA only as a last resort for infections caused by multi-resistant gram-negative bacteria, notably in cases of KPC and metallo-betalactamases.

This molecule therefore represents an important therapeutic hope, although it appears to have a relatively significant inoculum effect, which needs to be better studied. Finally, some cefiderocol-resistant strains have been described, combining several resistance mechanisms. To date, very few data are available in specific immunocompromised settings including solid organ transplantation [19], hematological malignancies [20, 21]. Most Cefiderocol prescriptions have primarily targeted multi-resistant severe *P. aeruginosa* infections, but its use has broadened to other difficult-to-treat non-fermentative gram negative bacteria, especially *S. maltophilia* for which its complex virulence and resistance profile drastically limit available antibiotics. Updated clinical and safety outcome data are needed in highly susceptible immunocompromised settings.

Another interesting combination in this context is ceftazidime-avibactam + aztreonam for strains carrying metallo-betalactamases. Several studies have demonstrated the efficacy of the avibactam + aztreonam combination, which is currently being developed by the manufacturer. An inoculum effect could also have an impact on the efficacy of this combination. This combination proved effective and safe in a serie of 4 SOT recipients with metallo-β-lactamase carbapenemase-producing Enterobacteriaceae [22].

Lastly, plazomicin, an aminoglycoside developed for the treatment of carbapenem-resistant Enterobacteriaceae infections, had shown interesting results in the United States, but was not developed in Europe due to its low commercial potential.

Treatment recommendations for carbapenem-resistant infections are summarized in the 2022 ESCMID guidelines [23]. Several new molecules are under development and could be of interest for the treatment of these infections, particularly those due to organisms producing a metallobetalactamase, such as cefepime-taniborbactam and meropenem-nacubactam. Studies are currently underway.

Finally, in the face of this type of infection, optimizing the use of available molecules is a crucial point, including rapid diagnosis of resistance, determination of MICs (minimal inhibitory concentration) for the different molecules and combinations available, and optimization of dosages with the use of high doses and prolonged infusions. Last but not least, multidisciplinary discussions between microbiologists and clinicians and the reduction of bacterial inoculum through drainage are essential. A summary of antibiotics efficiency regarding resistance mutation has been made in **Table 1**.

New Approaches to Manage Urinary Tract Infections in Kidney Transplant Recipients

The management of urinary tract infections (UTIs) in kidney transplant recipients represents a major opportunity for antimicrobial stewardship because kidney transplantation is the most common type of organ transplant worldwide, and because UTI is the most common infection in this population [3, 24]. Julien Coussement summarized the most recent evidence about the management of post-transplant symptomatic UTI and asymptomatic bacteriuria, and identified gaps of knowledge and clinical scenarios that remain understudied.

Asymptomatic bacteriuria, which is generally defined as significant bacteriuria (≥100.000 CFU/mL) without signs or symptoms of UTI (e.g., fever, chills, kidney pain, or symptoms of bladder inflammation), is relatively common after kidney transplantation [24].

Recent randomized trials have shown that the historical practice of screening for and treating asymptomatic bacteriuria is not beneficial in stable kidney transplant recipients [25–28]. A limited-size trial even suggested that asymptomatic bacteriuria might be left untreated in patients who are in the first 2 months post-transplant and have a ureteral stent [29]. Additional opportunities probably exist to improve the care of kidney transplant recipients with pyelonephritis. First, research is needed to determine the benefits and harms associated with the empiric use of very broad-spectrum antibiotics in kidney transplant recipients admitted for presumed pyelonephritis [24]. Second, a randomized trial is starting to determine whether 7 days of antibiotic therapy can be sufficient to treat non-severe episodes of pyelonephritis in kidney transplant recipients who are beyond the first month post-transplant and do not have a urinary catheter [30–32].

Besides, innovative non-antibiotic-based approaches are needed to better prevent symptomatic UTIs, which remain prevalent and detrimental after kidney transplantation. Julien Coussement discussed the potential benefits, harms and applicability of emerging approaches, including anti-adhesion therapies (which aim at preventing bacterial adhesion to host tissues, and therefore decreasing the risk of UTI) [33], intravesical instillation of a low-virulence organism (which aims at promoting bacterial interference) [34], and FMT (which aims at repopulating the gut with a "healthy" microbiome that could outcompete uropathogens) [35–38]. Vaccine candidates that are in development against extra-intestinal pathogenic *Escherichia coli* are also promising [39]. Many challenges, however, exist, including the fact that transplant recipients generally have an

impaired immune response to vaccines, and the fact that around half of the UTI episodes which occur after kidney transplantation are due to microorganisms other than *E. coli.*

New Antibiotics to Treat Infections Due to Gram-Positive Cocci

Aurélien Dinh reminded the drawbacks of vancomycin and daptomycin, before presenting new antibiotics targeting gram-positive cocci.

Vancomycin is a relatively old and difficult-to-manage glycopeptide. Several new antibiotics with activity against methicillin-resistant Staphyloc*occi* are now available.

Daptomycin is bactericidal and as effective as penicillin M against methicillin-susceptible *Staphylococcus aureus* and vancomycin for methicillin-resistant *S. aureus,* according to a randomized controlled trial (RCT) on bloodstream infections (BSI) [40]. Nevertheless, some treatment failures due to inoculum effect have been observed, and bacterial resistance is described, even among patients without previous exposure to this drug, which could be due to *in vivo* exposure to endogenous cationic peptides [41]. In liver transplant recipients, such resistance was indeed associated with prior daptomycin use and increased mortality [42]. In kidney transplant recipients, combinations of daptomycin and other antibiotics have also been suggested for resistant enterococcal infections [43, 44].

Dalbavancin is a new long acting glycolipopeptide, with a half-life of 14 days. MIC of dalbavancin against *S. aureus* and resistant coagulase-negative staphylococci are low. One retrospective cohort compared dalbavancin *versus* standard of care in patients with *S. aureus* bacteremia and found no significant difference [45]. Two RCTs are currently underway to better determine the effectiveness of dalbavancin in patients with *S. aureus* bacteremia [46, 47]. Dalbavancin is of particular interest for patients requiring prolonged antibiotic therapy, such as those with endocarditis or bone and joint infection (BJI) such as prosthetic joint infections. Several cohorts and literature reviews found dalbavancin to be safe, with nearly 80% cure rate in these indications and high level of patient satisfaction, mostly due to early discharge [48].

Ceftaroline and ceftobiprole are new generation cephalosporins with excellent activity against methicillin-resistant staphylococci according to bacterial killing curves [49]. Clinical efficacy during BJI and endocarditis are promising according to cohort studies [50, 51]. The ERADICATE trial comparing ceftobiprole *versus* daptomycin in *S. aureus* bacteremia showed non-inferiority [52].

So far, to our knowledge, no data exist regarding the use of dalvabancin, ceftaroline and ceftobiprole in SOT recipients.

Finally, oritavancin is a recently available lipopeptide, with a semi long-life activity (7 days) and important intra-cellular activity, which could be of interest for device-associated infection with biofilm [53].

These new antibiotics may allow new management and innovative approaches to treat patients with infections due to resistant Staphylococci.

MANAGEMENT OF FUNGAL INFECTIONS

Because of the toxicities of the available drugs and the emergence of resistance caused by an increased use of antifungal agents in the growing population at risk of invasive fungal diseases and in agriculture, there is a pressing need for more antifungal drug options. Recently, several new antifungal drugs have reached late-stage clinical development and obtained a temporary use authorization, as depicted by Alexandra Serris.

Olorofim is the only member of a novel class named orotomide. It inhibits fungal growth through inhibition of the fungal dihydroorotate dehydrogenase enzyme involved in pyrimidine synthesis. It has a good tissue distribution, notably in the kidney, liver, lung, and the brain (although at lower levels) [54]. It is metabolized by several CYP450 enzymes including CYP3A4 and is thus susceptible to strong CYP3A4 inhibitors and inducers. Olorofim exhibits activity *in vitro* against azole-resistant *Aspergillus, Scedosporium*, *Lomentospora*, *Rasamsonia*, dimorphic fungi (notably *Histoplasma*), dermatophytes, but has no activity against yeasts, *Mucorales* and *Alternaria alternata* [55, 56].

Olorofim is currently evaluated in two clinical studies: one open-label, single-arm study including patients with invasive fungal infections due to Lomentospora prolificans, Scedosporium spp., Aspergillus spp., and other resistant fungi with limited treatment options (ClinicalTrials.gov identifier: NCT03583164) and one phase III, randomized study to evaluate the efficacy and safety of olorofim versus liposomal amphotericin B in patients with invasive aspergillosis (ClinicalTrials.gov Identifier: NCT05101187). Published experience is currently limited to case reports (abstracts).

Ibrexafugerp is a first-in-class oral glucan synthase inhibitor, whose mechanism of action is close to the one of echinocandins (but with a different binding site). It is fungicidal against most wild-type, echinocandin or azole-resistant *Candida* spp., including *C. auris*, and fungistatic against *Aspergillus* spp [57]. Based on animal models, ibrexafungerp shows a high tissue penetration in the spleen, liver, lungs, kidney, vaginal tissue, and muscles, but not in the brain [58].

An interim analysis of the phase III FURI study evaluating the efficacy and safety of ibrexafungerp in patients with severe mucocutaneous candidiasis, invasive candidiasis, chronic or invasive aspergillosis reported complete or partial response in 58% of the patients [59]. Inclusion criteria were further expanded to include histoplasmosis, coccidioidomycosis and blastomycosis.

Rezafungin is the first member of second-generation echinocandins with enhanced pharmacokinetic/pharmacodynamic parameters, allowing for a weekly administration and potential less hepatic toxicity [60]. It has potent *in vitro* activity against most *Candida* spp., including *C. auris*, and common dermatophytes [58].

Moreover, rezafungin has shown promising results as prophylactic and curative treatment of pneumocystis *in vivo* by eradicating both the cyst and trophic forms of the fungus [61, 62]. A case report of the successful eradication of a refractory intra-abdominal candidiasis with rezafungin in a liver transplant recipient was published in 2022 [63] and rezafungin was recently

found non-inferior to caspofungine in a Phase 3 trial (ReSTORE) for the treatment of candidemia/invasive candidiasis [64].

These antifungal treatments offer significant improvement in terms of spectrum of activity, tolerability, drug interactions and/or route of administration. Further clinical studies will be needed to evaluate their optimal place in the therapeutic arsenal in the solid organ transplant recipient population, taking into account the emergence of drug-resistant fungi and the problem of drug-drug interactions with immunosuppressants. **Table 2** summarize the Spectrum of activity, tissue diffusion and drug-drug interactions (DDIs) with immunosuppressive drugs of olorofim, ibrexafungerp and rezafungin.

CONCLUSION

During the well-attended "**Infection and Transplantation Group**" day, the major advances in the field of **new anti-infective therapies in transplantation** were presented and discussed. New direct and indirect anti-infective approaches in transplantation are devoted to several improvements:

- decrease antibiotics pressure in our high risk multidrug resistant bacteria population with a better use of already known antibiotics and new original non-antibiotic approaches that have promising usages.
- improve efficacy of bacterial and fungal treatment with antibiotics or antifungal therapy that have a good inoculum effect and a good broadcast
- improve the tolerance of antimicrobial drugs in our polymedicated population with high risk of drugs interactions.

Altogether, those new approaches are likely to feature alternative anti-infective therapies that promise to change patient management.

AUTHOR CONTRIBUTIONS

AlS, JC, BP, VD, AD, and HK wrote the manuscript. AD, AS, FA, OL, EM, NK, EF, DL, JD, FC, AL, and HK revised the manuscript. AS, FA, OL, EM, NK, EF, DL, JD, FC, AL, and HK conceived the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Non-antigen-specific Immunoadsorption Is a Risk Factor for Severe Postoperative Infections in ABO-Incompatible Kidney Transplant Recipients

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ABO-incompatible (ABOi) living kidney transplantation (KTx) is an established procedure to address the demand for kidney transplants with outcomes comparable to ABO-compatible KTx. Desensitization involves the use of immunoadsorption (IA) to eliminate preformed antibodies against the allograft. This monocentric retrospective study compares single-use antigen-selective Glycosorb® ABO columns to reusable non-antigen-specific Immunosorba® immunoglobulin adsorption columns regarding postoperative infectious complications and outcome. It includes all 138 ABOi KTx performed at Freiburg Transplant Center from 2004–2020. We compare 81 patients desensitized using antigen-specific columns (sIA) to 57 patients who received IA using non-antigen-specific columns (nsIA). We describe distribution of infections, mortality and allograft survival in both groups and use Cox proportional hazards regression to test for the association of IA type with severe infections. Desensitization with nsIA tripled the risk of severe postoperative infections (adjusted HR 3.08, 95% CI: 1.3–8.1) compared to sIA. nsIA was associated with significantly more recurring (21.4% vs. 6.2%) and severe infections (28.6% vs. 8.6%), mostly in the form of urosepsis. A significantly higher proportion of patients with sIA suffered from allograft rejection (29.6% vs. 14.0%). However, allograft survival was comparable. nsIA is associated with a two-fold risk of developing a severe postoperative infection after ABOi KTx.

Keywords: ABO-incompatible kidney transplantation, complications, immunoadsorption, infections, mortality

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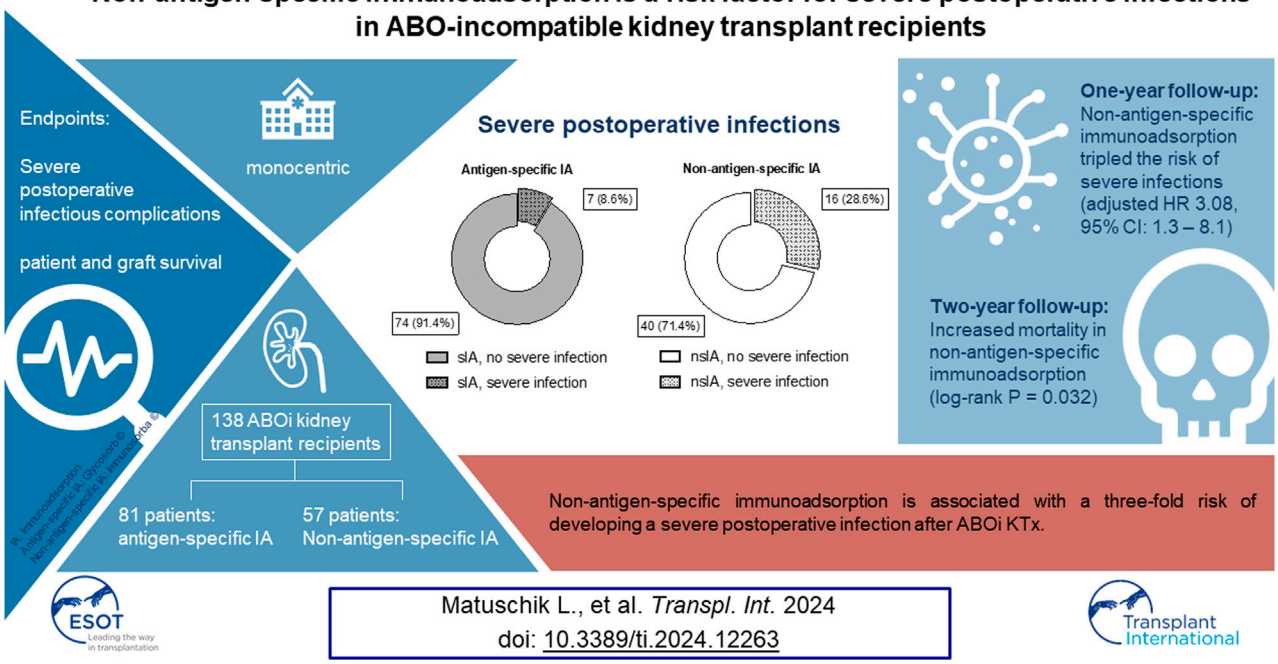


GRAPHICAL ABSTRACT

INTRODUCTION

ABO-incompatible (ABOi) kidney transplantation (KTx) has become an established procedure to meet the demand for kidney transplants in patients with end-stage renal disease [1–3]. To prevent hyperacute or acute antibody-mediated allograft rejections due to pre-existing antibodies in the recipient, different ABOi protocols have evolved over the past years. These protocols have led to patient and graft survival rates comparable to conventional ABO-compatible (ABOc) transplantations [4, 5]. In accordance with Tydén's initial desensitization protocol, our institution's protocol has now been used for nearly 20 years [6]. It entails anti-CD20 treatment with Rituximab (375 mg/m^2), serial immunoadsorption (IA) to eliminate preformed allograft antibodies and initiation of immunosuppressive maintenance therapy 9 days before the scheduled transplantation [1, 6]. From April 2004 until November 2011, antigen-specific Glycosorb® ABO columns (sIA) were used to perform IA. These single-use columns contain the specific terminal carbohydrates of type A or B antigens as ligands linked to a sepharose matrix to eliminate donor-specific anti-A or anti-B IgM and IgG [7, 8]. From December 2011 until now, we have used reusable non-specific Immunosorba® immunoglobulin adsorption columns (nsIA). They use staphylococcal antigen A, covalently linked to a sepharose matrix as the stationary phase of chromatography. Therefore, predominantly IgG1, IgG2 and IgG4, but also, to a lesser extent, IgA and IgM can be eliminated [9]. Several clinical studies found significantly higher rates of severe infections and infection-related mortality in ABOi transplanted patients compared to ABOc controls [10–12]. Only a small study investigated endpoint differences associated with IA modality in ABOi which showed no difference in infectious complications [13].

Based on our clinical experience, we suspected an association of nsIA with severe postoperative infectious complications.

To investigate this, we meticulously describe distribution of clinical covariates and infectious complications during the first postoperative year in nsIA and sIA KTx recipients. Secondly, we test whether nsIA is an independent risk factor for postoperative infections. Finally, we investigate whether nsIA is an independent predictor of recipient and graft survival in ABOi KTx.

PATIENTS AND METHODS

Patients and Study Design

From 1 April 2004 until 16 June 2020 138 patients underwent ABOi living donor KTx in our Transplant Center. Mean patient follow-up is 7.4 years (2,703 days). This investigation is a monocentric retrospective analysis. The protocol was approved by our local IRB and registered in the German Clinical Trials Register (protocol number 296/20; registration number: DRKS00022385). All patients of the Freiburg living donor kidney program gave written informed consent for collecting and storing data in our living donor transplant registry.

The donor was examined during a 3-day inpatient stay. Statutory approval was given by the transplantation ethics

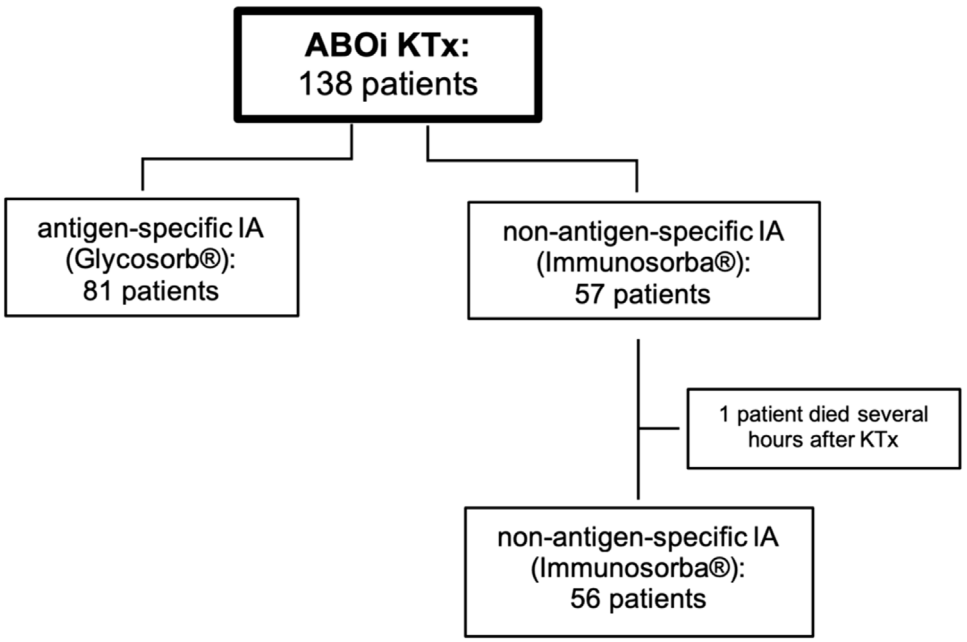


FIGURE 1 | Study profile. 138 patients received ABO-incompatible living kidney transplantation after desensitization using different immunoadsorption columns. ABOi, ABO-incompatible; IA, immunoadsorption; KTx, kidney transplantation.

committee of the District Medical Association Südbaden. The surgical procedure, graft preparation and recipient follow-up were performed as described before [14]. For the whole study period from 2004 to 2019, we used the ureteral stent OptiFlex 6 F 22 cm (OptiMed GmbH, Ettlingen, Germany). During the first two postoperative weeks, all recipients were treated on our transplant intermediate care ward.

Pre-transplant data were collected from the recipients' local nephrologists and clinical data from clinical records. Clinical data were documented in the patients' EMR during the whole study period. Follow-up data were documented in the EMR as well, as our nephrological transplant outpatient clinic uses the same hospital-wide electronic system. Delayed graft function was defined as the need of ≥1 dialysis treatments during the first 7 postoperative days. Graft loss was defined as the need to resume dialysis permanently caused by irreversible graft failure. Acute reversible graft failure was not included in statistics. The data of one patient, who died several hours after the transplantation due to myocardial infarction, are included in survival analysis, but not in the analysis of infections.

Immunosuppression Regimes, Desensitization Protocol

Single-dose Rituximab (375 mg/m^2 body surface; MabThera®, Roche Pharma AG, Grenzach-Wyhlen, Germany or Truxima®, Millmount Healthcare Ltd., Stamullen, Ireland) was administered approximately 30 days before the scheduled transplantation. Triple maintenance immunosuppression therapy was started 9 days before transplantation with the calcineurin-inhibitor tacrolimus (Prograf®, Astellas Seiyaku K.K., Tokyo, Japan; initial target trough level 12–15 ng/mL), mycophenolic acid (CellCept®, Roche Pharma AG, Grenzach-Wyhlen, Germany; 2,000 mg daily) and prednisone (30 mg daily). In case of tacrolimus intolerance (3 patients), the regimen was switched to cyclosporine (Sandimmun Optoral®, Novartis AG, Switzerland).

Additionally, induction therapy with 20 mg Basiliximab (Simulect®, Novartis AG, Basel, Switzerland) was administered on the day of transplantation and on day 4 after transplantation. In two patients, hypersensitivity against Basiliximab was detected; these patients received thymoglobulin (Sanofi-Aventis, Paris, France). IA was started 8 days before the scheduled transplantation date and performed on commercially available apheresis devices (Octo Nova™, Diamed Medizintechnik, Cologne, Germany) with hollow-fiber plasma separators (P2™, Fresenius Medical Care, Bad Homburg, Germany or Microplas MPS 07™, Bellco/Medtronic, Dublin, Ireland). The study profile is depicted in **Figure 1**. From April 2004 until November 2011, sIA was performed in 81 patients using antigen-specific Glycosorb® ABO columns (Glycorex, Lund, Sweden). These single-use columns contain the specific terminal carbohydrates for A or B blood group antigens as ligands linked to a sepharose matrix to eliminate the specific anti-A or anti-B isoagglutinins. From December 2011 until June 2020, reusable non-antigen-specific Immunosorba® immunoglobulin adsorption columns (Fresenius Medical Care, Bad Homburg, Germany) were used in 57 patients. These columns use staphylococcal antigen A, covalently linked to a sepharose matrix, as the stationary phase of chromatography. Immunoadsorption was performed

every other day as described before [15], until the target titers of isoagglutinins (IgG and IgM) against donor erythrocytes were ≤1: 4 on the day of surgery. If this target titer could not be reached until the scheduled date of KTx, IA was performed preoperatively on the day of surgery. In this case, the first titer measured after transplantation is used for statistics. Plasmapheresis (PPh) was initiated when isoagglutinin target titer levels could not be achieved by the preceding immunoadsorptions.

After transplantation, monitoring of isoagglutinin titers was performed daily during the first 7 days and every other day until the 14th postoperative day. If titers exceeded 1:8 IgM/IgG in the first week and 1:16 IgM/IgG in the second week post transplantation, immunoadsorption was scheduled on the same day.

IgG/IgM isohaemagglutinin titers were measured by our Medical Center's Department of Transfusion Medicine. The first anti-donor isohaemagglutinin titers were quantified by a conventional tube centrifugation haemagglutination test (described by Winters et al. [16]). However, in mid-2007, i.e., after the first 20–30 ABOi KTx were performed in our center, a gel centrifugation haemagglutinin test with donor erythrocytes, able to distinguish between IgG and IgM isohaemagglutinins, was established (using the Diamed-Coombs-Anti-IgG® and Diamed-ID-NaCl® systems; DiaMed Diagnostika, Germany (current names: Coombs Anti-IgG and NaCl, BIO-RAD, Germany)). A detailed description of the method is provided by Wilpert et al. [15]. For quality control, the previous sample or pooled plasma of ten random donors are tested simultaneously. Antigen density proved to be stable, however, a direct correlation to renal tissue antigen density cannot be drawn.

Maintenance immunosuppression was administered as described before and not altered during the observation period [1]. All patients received anti-infective prophylaxis comprising valganciclovir for 100 days in CMV positive recipients and for 200 days in a high-risk constellation with a CMV seropositive donor, but negative recipient. Trimethoprim/sulfamethoxazole was administered for 6 months post transplantation and fluconazole prophylaxis until postoperative day 28.

Infections

Risk of severe infectious complications during the first year after KTx was the primary endpoint of this retrospective study. In line with several other clinical studies [10, 12, 17], we distinguished between non-severe and severe infections in order to enhance the discriminatory power between uncomplicated postoperative developments and clinically relevant adverse events. Severe infections required the detection of pathogens in the blood stream or the state of sepsis according to the Third International Consensus Definitions for Sepsis and Septic Shock [18]. Every case of severe infection was objectified by the presence of organ dysfunction according to a SOFA (Sequential (Sepsis-related) Organ Failure Assessment) score ≥2 [18]. All cases of severe infections were treated within the University Medical Center in Freiburg. For all 138 patients, in-house and outpatient microbial findings (from the local nephrologists) were meticulously checked to determine infection severity in a valid way. We differentiated between bacteriuria, which included all urinary samples with detected pathogens, and urinary tract infections (UTIs) with a pathogen amount ≥ 10^5/mL urine. Urine cultures were collected solely when an infection was suspected, i.e., when patients had symptoms such as dysuria, a urine test strip showing leukocyturia or nitrite-positivity, or the blood count showed elevated inflammatory values. Antibiotic prophylaxis to prevent UTI was not used in our center. Standard antibiotic treatment of UTIs had to be changed in 2019 following a "Rote Hand-Brief" of the European Medicines Agency and the German Institute for Drugs and Medical Devices, replacing norfloxacin with amoxicillin/clavulanic acid as standard antibiotic due to its potentially harmful side effects, especially in combination with corticosteroids. After obtaining the results of microbial urine culture, the antibiotic regimen was altered according to microbial resistance if necessary. Standard perioperative antibiotic prophylaxis comprised cefazoline and metronidazole. Recurring infections were defined as ≥ 2 infections (not necessarily of the same pathogen) during the first year after transplantation requiring therapy and/or hospitalization. Multi-drug resistance was defined according to the International Expert Proposal for Interim Standard Definitions for Acquired Resistance as "acquired non-susceptibility to at least one agent in three or more antimicrobial categories" [19]. Patients were considered CMV- or BKV-positive with virus replications over 1,000 IU/mL (serum) respectively. BKV nephropathy was defined as histologically proven BK virus infection. CMV was monitored once weekly via PCR during the initial hospitalization period after KTx. Afterwards, controls were made after 4, 8 and 12 weeks and after 3, 6, 9 and 12 months. From the second year after KTx, CMV was monitored based on clinical symptoms. Treatment of CMV infection included high-dose valganciclovir. Treatment was initiated in patients with virus replications over 1000 IU/mL and continued until replication rate was not detectable any more for two consecutive weeks. In cases of valganciclovir resistance, foscavir (and recently letermovir) was used. BKV PCR was performed after 3, 6, 9 and 12 months. When serum virus replications exceeded 1,000 IU/mL, a biopsy to rule out BKV nephropathy was conducted. If positive, immunosuppression was reduced, beginning by reducing the mycophenolate dose. Further adjustments of the immunosuppressive therapy are made stepwise, depending on the individual risk of rejection and BKV replication.

Statistical Analysis

Results were defined as statistically significant when $p < 0.05$, all p-values being two-sided. All data were considered non-normal-distributed.

Severe postoperative infections were determined as primary endpoint. Categorical data are displayed as absolute and relative frequencies; a two-tailed Fisher's Exact test was performed for comparison. Continuous data are expressed as median and 95% confidence interval (CI); for analysis, Mann-Whitney-U test was used. The cumulative incidence of postoperative infections was assessed by a competing risk analysis using the Aalen-Johansen estimate via the "survfit" function in R [R version 4.1.2 (2021-11-

TABLE 1 | Baseline and extended characteristics of donors and recipient groups receiving either antigen-specific or non-antigen specific immunoadsorption before ABO-incompatible kidney transplantation.

	Antigen-specific IA (81 patients)	Non-antigen specific IA (57 patients)
Recipients' Characteristics		
Female sex, recipient (*n (%)*)	34 (42)	24 (42.1)
Age at transplantation, recipient (*years*)	46 (42, 49)	51 (45, 53)
BMI, recipient (kg/m^2)	24.3 (22.9, 25.5)	24.2 (23.3, 26.3)
ASA category, recipient (median (interquartile range))	3 (2, 3)	3 (3, 3)
Dialysis before transplantation (*n (%)*)	67 (82.72)	41 (71.93)
- Pre-emptive transplantation (*n (%)*)	14 (17.28)	16 (28.07)
Duration of dialysis before transplantation (*months*)	25 (17, 35)	17 (12, 27)
No. of HLA mismatches A + B + DR	4 (3, 4)	4 (3, 4)
PRA level (≥5%) (*n (%)*)	16 (19.75)	3 (5.26)
- Maximum PRA level	96%	66%
Donors' Characteristics		
Female sex, donor (*n (%)*)	51 (62.96)	31 (54.39)
Age at transplantation, donor (*years*)	50 (48, 52)	53 (50, 55)
Genetic relationship (haploidentical parents or siblings) (*n (%)*)	27 (33.33)	17 (29.83)
Surgical Data		
Duration of surgery (*min*)	168 (150, 180)	146 (127, 157)
Ischemia time, total (*min*)	183 (172, 190)	172 (163, 185)
- Cold ischemia time	147 (136, 158)	142 (137, 157)
- Warm ischemia time	30 (29, 33)	25 (24, 28)
Duration of hospitalization (*days*)	19 (18, 21)	19 (18, 23)
Immunological Data		
Total no. of IA	5 (5, 6)	5 (4, 5)
- No. of preoperative IA	5 (5, 6)	4 (4, 5)
- IA on the day of surgery (*n (%)*)	53 (65.43)	13 (22.81)
No. of patients undergoing PPh (*n (%)*)	24 (29.6)	45 (78.95)
- Total no. of PPh when needed	2.5 (2, 3)	2 (2, 3)
- No. of preoperative PPh when needed	2.5 (2, 3)	2 (2, 2)
- PPh on the day of surgery (*n (%)*)	2 (2.47)	7 (12.28)
High IgM/IgG titer (≥1:256) before Rituximab (*n (%)*)	22 (27.85)	14 (24.56)
- Total no. of IA	7 (5, 9)	5 (4, 6)
- No. of patients undergoing PPh (*n (%)*)	10 (45.46)	14 (100)
- Total no. of PPh when needed	3 (1, 5)	2 (2, 5)
- Total no. of IA + PPh	9.5 (8, 17)	8.5 (7, 13)
Total no. of IA + PPh (all patients)	6 (5, 8)	6 (6, 7)
Infectious Complications		
Any infection (*n (%)*)	59 (72.8)	40 (71.4)
- Days from KTx to first infection	11 (9, 20)	9 (7, 12)
Recurring infections (*n (%)*)	5 (6.17)	12 (21.43)
Severe infection (*n (%)*)	7 (8.6)	16 (28.6)
- Days from KTx to first sepsis	61 (5, 239)	56 (22, 126)
- Septic shock (*n (%)*)	2 (28.6)	5 (31.3)
Bacterial and Opportunistic Infections		
Blood culture pathogen detection (*n (%)*)	7 (8.6)	16 (28.6)
Urinary tract infections (*n (%)*)	38 (46.9)	24 (42.9)
- Multidrug-resistant bacteria (*n (%)*)	8 (21.1)	8 (33.3)
- Urosepsis (*n (%)*)	4 (10.5)	13 (54.2)
- Duration of ureteral stenting (*days*)	14 (13, 14)	20 (13, 40)
Viral Infections		
BKV		
- BK viremia (*n (%)*)	10 (12.4)	16 (287)
- Highest BK virus replication no. (*copies/mL*)	124,340 (14,100, 1,341,500)	138,864 (30,000, 86,300)
- Days from KTx to first BKV positivity	161.5 (85, 289)	100 (63, 180)

(Continued on following page)

TABLE 1 | (*Continued*) Baseline and extended characteristics of donors and recipient groups receiving either antigen-specific or non-antigen specific immunoadsorption before ABO-incompatible kidney transplantation.

	Antigen-specific IA (81 patients)	Non-antigen specific IA (57 patients)
- Duration of BK viremia (*days*)	163 (93, 355)	283 (216, 567)
- BK virus nephropathy (in BKV + patients) (*n (%)*)	4 (40)	4 (26.67)
CMV		
- CMV status of donor positive (*n (%)*)	46 (56.8)	27 (47.4)
- CMV status of recipient negative (*n (%)*)	36 (44.4)	28 (49.1)
- Risk constellation (D +/R -) (*n (%)*)	16 (19.8)	9 (15.8)
- CMV viremia (*n (%)*)	4 (4.9)	4 (7.0)
- Highest CMV replication no. (*copies/mL*)	3,895 (3,200, 5,250)	12,000 (2,000, 732,000)
- Days from KTx to first CMV positivity	34.5 (13, 234)	179.5 (118, 570)
- Duration of CMV viremia	18 (6, 606)	60.5 (13, 572)

Median values are provided (95% CI, of median) unless indicated otherwise. American Society of Anesthesiologists (ASA) category is shown in median (interquartile range). BKV: BK, virus; CMV: cytomegalovirus; D: donor; IA: immunoadsorption; IA: immunoadsorption; IgG: immunoglobulin G; IgM, immunoglobulin M; KTx: kidney transplantation; PPh: plasmapheresis; R: recipient. Patients were considered CMV- or BKV-positive with virus replications over 1000 IU/mL (serum) respectively.

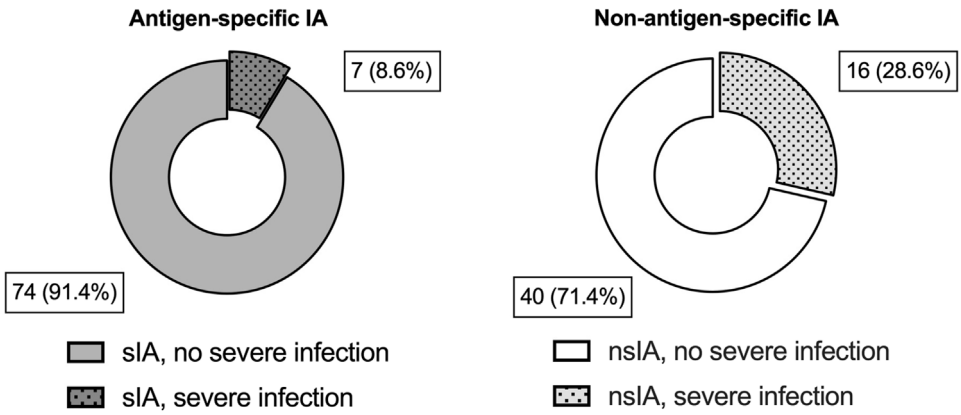


FIGURE 2 | Severe infectious complications during the first year after ABO-incompatible kidney transplantation. Shown are absolute numbers and percentages for each IA group for severe infectious complications during the first year after ABOi KTx. Grey blocks indicate patients desensitized with antigen-specific IA (sIA); white blocks represent patients receiving non-antigen-specific IA (nsIA). The incidence of severe infections was compared using a two-tailed Fisher's exact test (sIA vs. nsIA: 7 (8.6%) vs. 16 (28.6%), $p = 0.004$).

01) -- "Bird Hippie"], Gray's test was added to test for a difference between groups over the entire follow-up period. To set the focus on the time of onset of infections, only the first episode of a non-severe and the first episode of a severe infection per patient were taken into account. Multivariable Cox proportional hazards regression analysis was performed to examine the association of IA modality and severe postoperative infections. "Severe infection" was modelled as a binary categorical outcome. "Severe infections" were distinguished from "non-severe infections" as defined above (bacteremia or SOFA score ≥2). The proportional hazard assumption was tested by visualizing Scaled Schoenfeld residuals vs. time (**Supplementary Figure S1**).

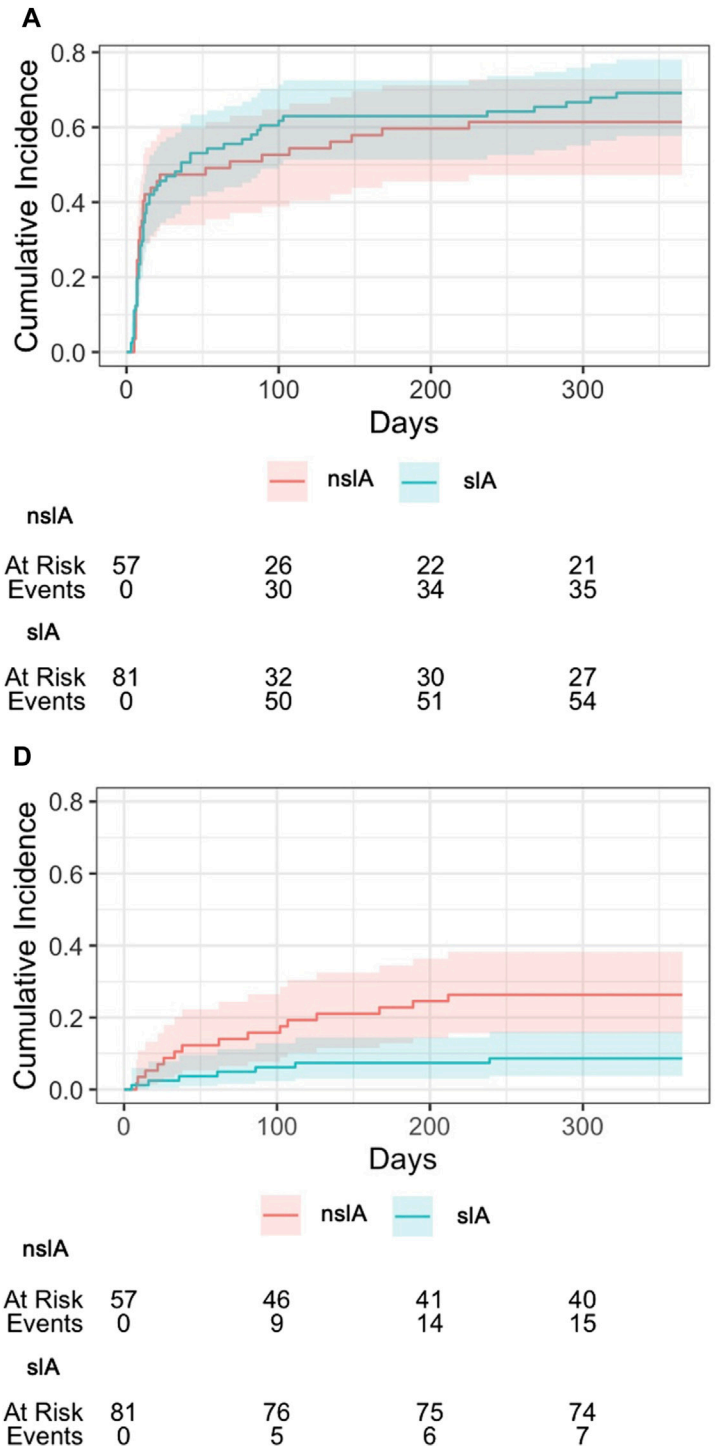
Patient and graft survival were investigated as secondary endpoints. To be able to include all 138 patients into this analysis, we set the cut-off at 2 years post transplantation. Cox proportional hazards regression analysis was performed to identify risk factors associated with graft loss and mortality during the first 2 years after ABOi KTx. Acute rejection episodes were not included in the multivariable models. We aimed at creating a regression model with adjustment for, according to our experience, clinically relevant and biologically plausible confounders. To validate the regression model used, Goodness-of-fit was examined via Partial likelihood ratio test, Wald test and Score test. Multicollinearity was evaluated using variance inflation factors (**Supplementary Table S1**).

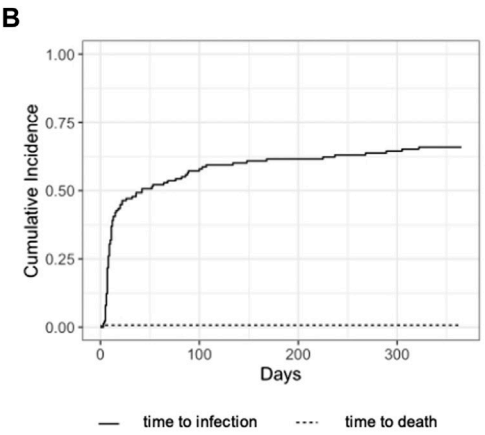
GraphPad Prism version 9.3 (GraphPad Software, San Diego, CA, United States) and R version 4.1.2 (2021-11-01) -- "Bird Hippie were used to perform all statistical analyses and to visualize data.

RESULTS

Baseline and Extended Characteristics

Postoperative infectious complications occurred in 99 cases during the first year after transplantation (72.2%). 23 patients (16.7%) developed a severe infection. Based on clinical experience, an increasing incidence rate of severe postoperative infectious complications was noted over the years.

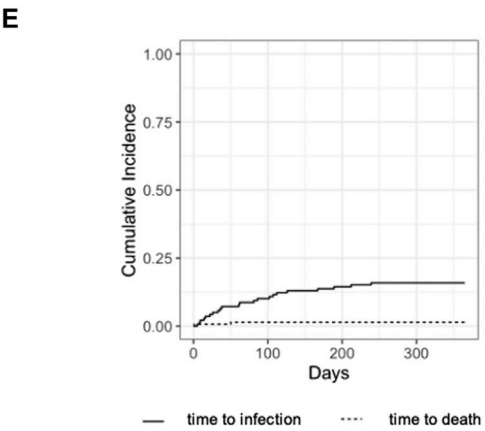




C

Characteristic	1-year cuminc	p-value[1]
IA.modality		0.5
nsIA	61% (47%, 73%)	
sIA	69% (58%, 78%)	

[1] Gray's Test



F

Characteristic	1-year cuminc	p-value[1]
IA.modality		0.005
nsIA	26% (16%, 38%)	
sIA	8.6% (3.8%, 16%)	

[1] Gray's Test

FIGURE 3 | Cumulative incidence of infectious complications after ABO-incompatible kidney transplantation. **(A)** Time period until the occurrence of the first infection after transplantation according to IA modality. nsIA: non-antigen-specific immunoadsorption; sIA: antigen-specific immunoadsorption, **(B)** Cumulative incidence of any infectious complication after KTx for the whole cohort. **(C)** Estimation of 1-year cumulative incidence of any post-transplant infection. "cuminc": cumulative incidence. **(D)** Time period until the occurrence of the first severe infection after KTx according to IA modality. nsIA: non-antigen-specific immunoadsorption; sIA, antigen-specific immunoadsorption, **(E)** Cumulative incidence of severe infectious complications after KTx for the whole cohort. **(F)** Estimation of 1-year cumulative incidence of severe post-transplant infections. A severe infection required the detection of pathogens in the blood stream or a SOFA score ≥2. To estimate the cumulative cause-specific infection-free survival, the Aalen-Johansen estimate was used; Gray's test was then used to test for a difference between cause-specific survival functions.

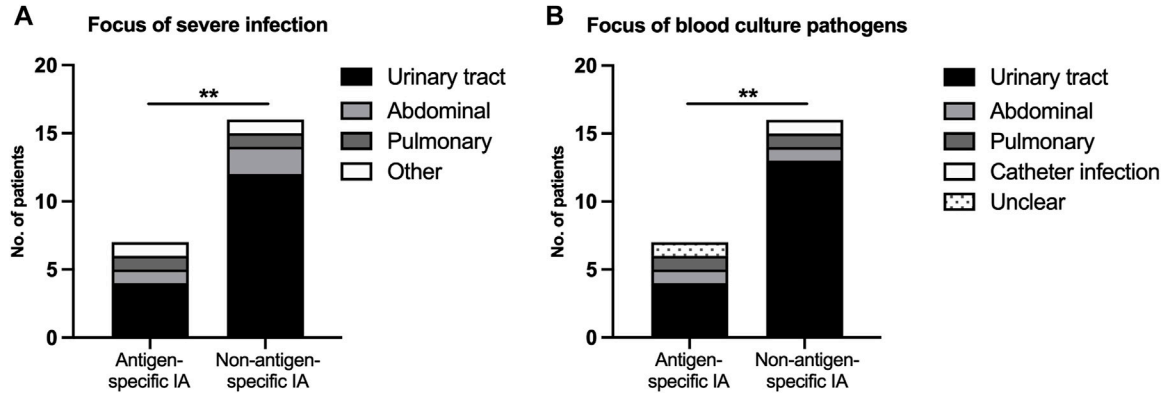


FIGURE 4 | Severe infectious complications after ABO-incompatible kidney transplantation. **(A)** Focus of severe infection, **(B)** Focus of blood culture pathogens. A severe infection was defined as the detection of pathogens in the blood stream or a SOFA score ≥2. *p*-values are estimated with a two-tailed Fisher's exact test. *Denotes statistical significance between antigen-specific IA and non-antigen-specific IA (**$p < 0.01$).

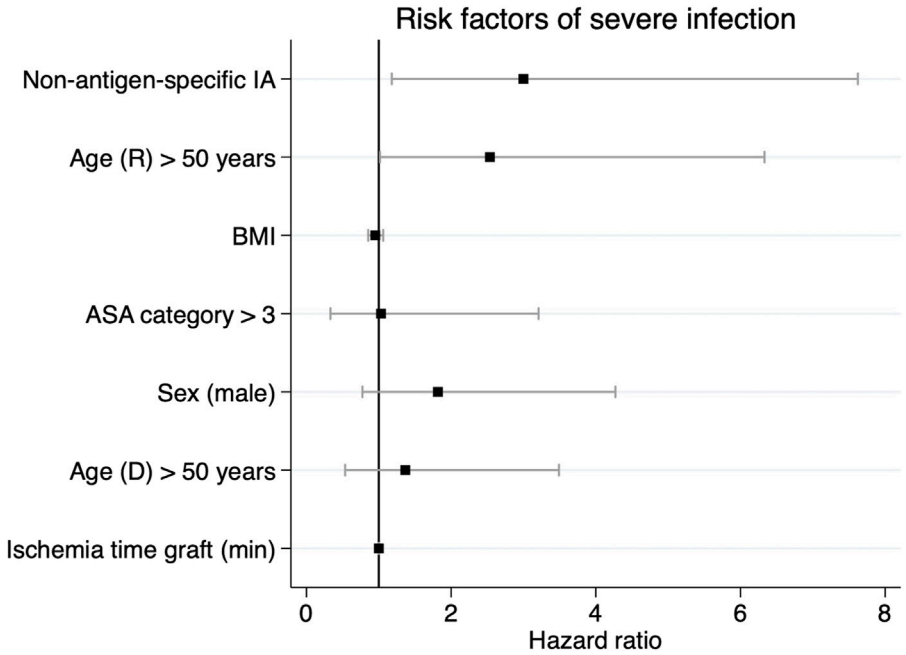


FIGURE 5 | Regression coefficient plot visualizing the relative hazard of postoperative severe infections during the first year after ABO-incompatible kidney transplantation. Provided are parameter estimates with 95% confidence limits. IA, ASA category, age >50 years and recipient sex were included as categorical variables. ASA, American Association of Anesthesiologists; IA, immunoadsorption.

Our cohort was split in two consecutive groups due to a switch in immunoadsorption column, the early group receiving sIA and the late group receiving nsIA (years 2004–2011 and 2011–2020). First, we investigated potential confounding demographic and clinical factors associated with these time windows.

Both IA groups were comparable concerning relevant donor and recipient characteristics, except for a significantly higher ASA category of nsIA patients (**Table 1**, for thorough analysis see **Supplementary Tables S3, S4**). Before desensitization, both groups had similar median isoagglutinin titers (1:16 (IgM), 1:64 (IgG), **Supplementary Table S3**, **Supplementary Figure S2**). In order to reach the target antibody titer of ≤1:4 before KTx, significantly more nsIA patients had to receive preoperative PPh (79% vs. 25%, **Table 1**. For a more detailed description of titer courses and IA treatments see **Supplementary Table S3** and **Supplementary Figure S2**).

Infectious Complications

Postoperative infections occurred frequently in both IA groups with a slightly higher incidence in sIA (**Table 1**). The crude risk

TABLE 2 | Characteristics of patients with and without severe infectious complications during the first year after ABO-incompatible kidney transplantation.

	Severe postoperative infection (23 patients, 16.7%)	No severe postoperative infection (114 patients, 82.6%)
Recipients' Characteristics		
Female sex, recipient (*n (%)*)	13 (56.5)	44 (38.6)
Age at transplantation, recipient (*years*)	55 (45, 59)	47 (44, 49)
BMI, recipient (kg/m^2)	24.9 (20.2, 26.7)	24.3 (23.3, 25.5)
ASA category, recipient	3 (3, 3)	3 (3, 3)
Dialysis before transplantation (*n (%)*)	15 (65.2)	93 (81.6)
Duration of dialysis before transplantation (*months*)	10 (0, 27)	15.5 (10, 20)
No. of HLA mismatches A + B + DR	4 (3, 5)	4 (3, 4)
- A mismatch	1 (1, 2)	1 (1, 1)
- B mismatch	2 (1, 2)	1 (1, 2)
- DR mismatch	1 (1, 1)	1 (1, 1)
PRA level (≥5%) (*n (%)*)	4 (17.4)	15 (13.2)
Surgical data		
Duration of surgery (*min*)	148 (118, 157)	158.5 (146, 172)
Ischemia time, total (*min*)	166 (156, 193)	177.5 (172, 187)
- Cold ischemia time	140 (135, 161)	145.5 (138, 156)
- Warm ischemia time	25 (22, 30)	39.5 (27, 31)
Duration of hospitalization (*days*)	23 (17, 29)	19 (18, 20)
Immunological Data		
Non-antigen-specific immunoadsorption (*n (%)*)	16 (69.6)	40 (35.1)
Patients with high IgM/IgG titer (≥1:256) before Rituximab (*n (%)*)	5 (21.7)	31 (27.2)
Total no. of IA	5 (4, 6)	5 (5, 5)
No. of patients undergoing PPh (*n (%)*)	15 (65.2)	53 (46.5)
Total no. of IA + PPh (all patients)	6 (6, 7)	6 (5, 7)
Subgroups based on desensitization (*n (%)*)		
- Patients that only received sIA (57 of 81 pat.)	2 (3.5)	55 (96.5)
- Patients that only received nsIA (12 of 57 pat.)	3 (25)	9 (75)
- Patients with sIA + PPh (24 of 81 pat.)	2 (8.3)	22 (91.7)
- Patients with nsIA + PPh (45 of 57 pat.)	13 (28.9)	32 (71.1)

Median values are provided (95% CI, of median) unless indicated otherwise. ASA, american society of anesthesiologists; BMI, body mass index; HLA, human leukocyte antigen; IA, immunoadsorption; IgG, immunoglobulin G; IgM, immunoglobulin M; PPh, plasmapheresis; PRA, panel-reactive antibody.

for severe infections and septic shock was higher in nsIA (28.6% vs. 8.6%; 21.7% vs. 12.5%, **Table 1**; **Figure 2**).

These findings are congruent with a competing risk analysis comparing the cumulative incidence of non-severe vs. severe infections in sIA and nsIA (**Figure 3**). In both groups, esp. uncomplicated urinary tract infections (UTIs), were common during the first 3 months after KTx, affecting over 50% of all patients (**Figure 3A**). In the sIA group, 91.5% of the depicted first episode of a postoperative non-severe infection were UTIs, with only 5 cases of other foci (3 x pulmonary, 1 BKV nephropathy and 1 case with unclear focus). Similarly, 90% of the first non-severe infections in the nsIA group were UTIs, with only two further cases of pneumonia, 1 catheter sepsis and 1 BKV nephropathy.

By contrast, the median onset of the first severe infection after KTx was after 2–3 months (**Table 1**; **Figure 3D**). Within the first year after KTx, the incidence of severe infections was significantly higher in nsIA compared to sIA (**Figure 3F**). Recurring infections were significantly more frequent in nsIA (21.4% vs. 6.2%, **Table 1**).

In accordance with a higher risk of severe infections, bacteremia was more common in nsIA (28.6% vs. 8.6%, **Table 1**), the predominant focus in both groups being the urinary tract (**Figure 4**, **Supplementary Table S2**). The time of onset for UTIs (40 days vs. 41 days post-transplant) as well as the proportion of patients suffering from an uncomplicated UTI (sIA: 46.9% vs. nsIA: 42.9%) was similar between the IA groups. Urosepticemias, however, made up to 54.2% of all UTIs in nsIA, compared to 10.5% in sIA (**Table 1**). The spectrum of detected pathogens included slightly more multi-drug resistant bacteria in nsIA (**Table 1**; **Figure 5**; for antibiotic susceptibility profiles of MDR pathogens see **Supplementary Table S5**). Concerning severe infections, the predominant pathogen in both groups was *Escherichia coli*, with a higher percentage of *Escherichia coli with extended-spectrum beta-lactamases* (ESBLs) in the sIA group (35% vs. 20%). Whereas *Enterococcus faecalis* was the second most detected pathogen causing UTIs of patients receiving sIA, it was *Klebsiella species* in the nsIA group (**Supplementary Figure S3**).

Septic shock occurred in 2 cases, i.e., 28.6% of severe infections, in the sIA group. One patient developed *C. difficile*-associated colitis, in the second patient, the focus remained unclear. In the nsIA group, five patients suffered from septic shock, equivalent to 31.3% of severe infections in this group. The underlying causes were two cases of urosepsis with multi-organ

TABLE 3 | Relative hazard of postoperative severe infections during the first year after ABOi KTx by risk factors.

Predictor variable	HR	95% CI	*p*-value
Non-antigen-specific IA	3.083	1.3–8.1	0.015
Age (R) > 50 years	2.534	1.0–6.6	0.045
BMI	0.954	0.8–1.1	0.410
ASA category >3	0.805	0.1–3.0	0.727
Sex (male)	1.797	0.8–4.4	0.210
Age (D) > 50 years	1.386	0.6–3.7	0.215
Ischemia time graft (min)	1.000	0.99–1.0	0.931

IA, ASA, category, age >50 years and recipient sex were included as categorical variables. Goodness-of-fit tests and VIFs, are provided as ***Supplementary Material*** *(****Supplementary Table S1****). ASA, american association of anesthesiologists; CI, confidence interval; D, donor; HR, hazard ratio; IA, immunoadsorption; R, recipient.*

TABLE 4 | Relative hazard of graft loss during the first 2 years after transplantation by risk factors.

Predictor variable	HR	95% CI	*p*-value
Non-antigen-specific IA	2.790	0.75–12.41	0.137
Age (R) > 50 years	5.142	1.22–32.56	0.042
BMI	1.113	0.96–1.29	0.150
ASA category >3	0.290	0.01–3.27	0.391
Sex (female)	6.382	1.59–38.26	0.018
Age (D) > 50 years	1.292	0.30–7.64	0.746
Ischemia time graft (min)	1.006	1.00–1.01	0.007

IA, ASA, category, recipient sex and age >50 years were included as categorical variables. ASA, american association of anesthesiologists; BMI, body mass index; CI, confidence interval; D, donor; HR, hazard ratio; IA, immunoadsorption; R, recipient.

failure (*K. pneumoniae, E. coli*), one abdominal sepsis due to caecal ischemia with consecutive perforation (*E. faecium VRE*), an abdominal wall phlegmon with development of an abscess (*E. coli*) and a *parainfluenza-2* viral pneumonia.

As the main increase of severe infections in the nsIA group was due to urosepsis, other UTI-associated factors were analyzed: whereas the manufacturer and product of the ureteral stents did not change, the duration of stenting was significantly longer in the nsIA group (20 (13, 40) days vs. 14 (13, 14) days in the sIA group, **Table 1**). Additionally, when comparing only patients that needed additional PPh to their IA treatment, we found significantly more cases of urosepsis within the nsIA + PPh group (11 cases) than within the sIA + PPh group (only one case).

BK viremia was detected significantly more often in nsIA (28.6% vs. 12.4%, **Table 1**) and duration of viremia was significantly longer (283 vs. 163 days, **Table 1**). Unadjusted comparison of onset of BK viremia, highest BKV replication numbers and BKV nephropathy were comparable (**Table 1**). No differences regarding CMV infections were detected (**Table 1**).

To further investigate the suspected association of nsIA and severe postoperative infections, firstly, we performed a more thorough analysis of the 23 patients (16.7%) that developed a severe infection (**Table 2**). In the first group, average age was higher, length of hospitalization was longer and the proportion of female recipients was higher. There was no difference regarding BMI, ASA category, the number of mismatches, duration of surgery and ischemia time. 69.6% of patients with severe infections received nsIA. To take PPh as immunomodulating factor into account, we performed several subgroup analyses, e.g., of patients who exclusively received IA, but no PPh. Of 57 patients (70.4%) in the sIA group, 2 (3.5%) suffered from a severe infection. Only 12 patients (21.1%) in the nsIA group did not require PPh. However, 3 (25%) developed a severe infection. In this small, crude subgroup analysis, nsIA is associated with a higher risk of severe infections (**Table 2**).

Secondly, we aimed to identify independent risk factors of severe infectious complications after ABOi KTx using a multivariable Cox regression analysis. Clinically relevant confounders such as age, ASA category, sex and ischemia time were included in the model. NsIA was independently associated with a 3.08 HR with severe infections (95% CI: 1.3–8.1, **Table 3**; **Figure 5**). Moreover, recipient age >50 years was associated with severe infections (HR 2.53, 95% CI: 1.0–6.0, **Table 3**; **Figure 5**).

Graft Function and Patient Survival

After identifying nsIA as an independent risk of severe infections, we aimed at analyzing its potential impact on graft function and patient survival.

Graft function was equal in both IA groups, and delayed graft function, creatinine levels at discharge and at last follow-up were comparable (**Supplementary Table S6**). A significantly higher number of sIA patients developed any type of graft rejection (29.6% vs. 14.0%) requiring significantly more graft biopsies (**Supplementary Table S6**; for a detailed description of rejection episodes and their individual treatment see **Supplementary Table S7**).

During a follow-up period of 2 years, five cases of graft loss were recorded in total (**Supplementary Table S6**). In sIA, two (66.7%) graft losses occurred due to chronic rejection, while thrombosis was the cause of the third graft loss. By contrast, both graft losses in nsIA were caused by urosepsis, in one case accompanied by coagulopathy and hemorrhagic shock (**Supplementary Table S6**; for description of individual etiologic factors of graft failures see **Supplementary Table S8**).

To determine independent risk factors associated with graft loss during the first 2 years after KTx, a Cox multivariable regression analysis was conducted (**Table 4**). IA modality was no independent risk for graft loss (**Table 4**); however, it was independently associated with recipient age >50 years (HR 5.14, 95% CI: 1.2–32.6), female sex (HR 6.38, 95% CI: 1.6–38.3) and warm ischemia time (HR 1.006 per minute, 95% CI: 1.00–1.01).

Despite a similar number of deaths during the whole follow-up period (mean: 7.4 years) and a low overall mortality rate, a higher number of nsIA patients died during the first 2 years (8.8% vs. 1.2%, **Supplementary Table S6**; log-rank $p = 0.032$; **Figure 6**). In sIA, three patients died from sepsis-related multi-organ failure–only one of them during the first 2 years after KTx–one patient died due to metastatic squamous cell carcinoma, and the cause of one death remains unknown. In nsIA, all recorded deaths occurred during the first 2 years after KTx: two patients died from septic multi-organ failure, two patients due to cardiogenic shock and one patient due to metastatic lung carcinoma (see **Supplementary Table S9** for causes of death with functioning graft).

To identify mortality-associated risk factors, a Cox proportional hazards regression analysis was implemented.

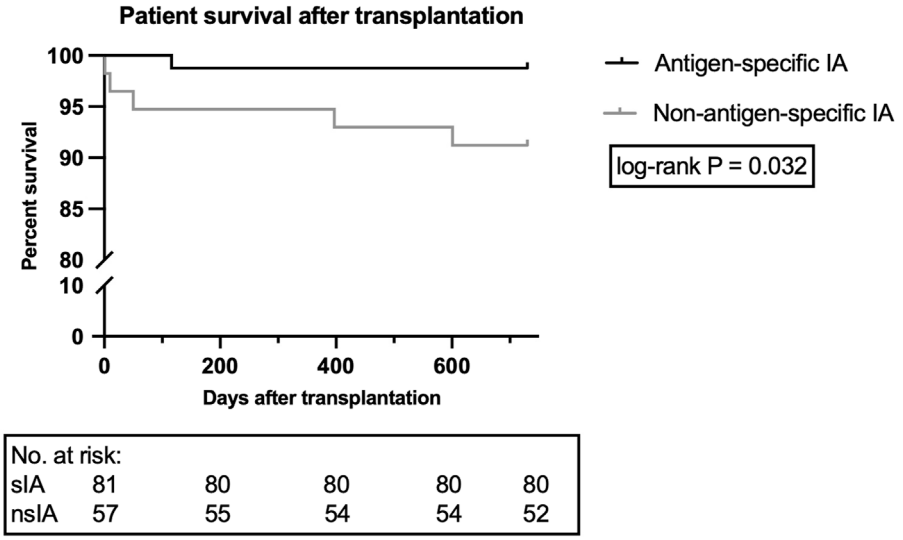


FIGURE 6 | Patient survival during the first 2 years after ABOi kidney transplantation. Data are shown for 81 patients receiving sIA and 57 patients receiving nsIA. To display the time period until the occurrence of patient death during the first 2 years after kidney transplantation via Kaplan-Meier graph, a log-rank test was utilized. nsIA, non-antigen-specific immunoadsorption; sIA, antigen-specific immunoadsorption.

TABLE 5 | Relative hazard of patient death during the first 2 years after transplantation by risk factors.

	Univariable			Multivariable		
Predictor variable	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Non-antigen-specific IA	7.359	1.2–140.9	0.069	6.203	0.91–131.0	0.110
Age (R) > 50 years	7.511	1.2–143.8	0.066	7.954	1.09–169.9	0.077
BMI	1.043	0.8–1.2	0.659	1.006	0.82–1.22	0.951
ASA category >3	2.466	0.1–15.3	0.410	1.629	0.06–15.63	0.712
Sex (female)	2.973	0.6–21.4	0.208	3.645	0.67–28.53	0.152
Age (D) > 50 years	1.671	0.3–12.1	0.553	0.701	0.11–5.80	0.713
Ischemia time graft (min)	0.999	0.98–1.01	0.920	1.003	0.98–1.01	0.595

Univariable and multiple Cox proportional hazards regression. IA, ASA, category, recipient sex and age >50 years were included as categorical variables. ASA, american association of anesthesiologists; BMI, body mass index; CI, confidence interval; D, donor; HR, hazard ratio; IA, immunoadsorption; R, recipient.

Univariable analysis revealed an increased mortality risk for nsIA patients (HR: 7.4, 95% CI: 1.2–140.9) as well as for recipients >50 years (HR: 7.5, 95% CI: 1.2–143.8, **Table 5**).

After adjusting for age, BMI, ASA category, sex and ischemia time, only recipient age >50 years was independently associated with two-year mortality (HR: 7.95, 95% CI: 1.09–169.9, **Table 5**).

DISCUSSION

Based on our clinical experience, we had hypothesized nsIA to be associated with severe postoperative infectious complications. Indeed, in this cohort, IA modality was independently associated with risk of severe infections and an increased two-year mortality.

ABOi KTx has become a well-established method to expand the living donor pool with patient and graft survival similar to ABOc KTx. However, it is associated with higher postoperative infectious complication risk [4, 10, 11, 17, 20]. Intensified immunosuppression protocols contribute to impaired pathogen defense. Immunoadsorption is among the established methods to reduce the recipient's level of preformed anti-A/B isoagglutinins against the allograft [21]. Existing protocols differ regarding the selectivity of antibody removal: antigen-specific immunoadsorption was implemented in 2003, soon to be followed by non-antigen-specific IA protocols [6, 22].

So far, the impact of different IA protocols concerning overall patient survival and graft function was mostly compared to ABOc cohorts [3, 4, 10, 15]. Studies from London and Heidelberg found a significant rise in death rates in ABOi due to infectious complications during the early posttransplantation period [4, 17, 23]. They reported mainly opportunistic and viral infections, indicating an increased immunosuppressive burden in ABOi compared to ABOc KTx [17, 24]. In contrast to this, we did not find increased infection rates in ABOi patients compared to ABOc in our center [1].

In 2012, we transitioned from sIA (modified Swedish protocol) [1, 15] to nsIA due to the substantial economic burden of blood group-specific single use columns (~5 IA/patient). Morath et al. and others had not found any differences in graft function and patient survival using nsIA [22, 25]. Thölking et al. compared the same IA columns as used at our Transplantation Center, namely, the antigen-specific Glycosorb® column to the non-antigen-specific Immunosorba® column [13]. An association of postoperative bacterial and viral infections with IA modality was not found [13, 22]. In our substantially bigger cohort, nsIA is independently associated with a two-fold risk of severe postoperative infections, mainly occurring during the first 6 months postoperatively. This is similar to the multi-center analysis conducted by Opelz et al., who found an increase in infections during the first year after ABOi KTx [4]. The risk of early postoperative infections may be associated with Rituximab administration 30 days prior to the scheduled KTx (Swedish protocol) [26]. Rituximab associated B-cell depletion was found to last for almost half a year [27]. During this time, an additional hypogammaglobulinemia was observed, hence enhancing the risk of infections [28]. This risk predisposition appears to be significantly increased in nsIA patients.

The main increase of severe infections in the nsIA group was due to urosepsis. The urosepsis rate of our nsIA group, however, is similar to published data from other centers that desensitized their KTx recipients by non-antigen-specific immunoadsorption [10]. Potential factors other than IA, which could be associated with the development of postoperative urosepsis in the nsIA group, are the longer duration of ureteral stenting and additionally, the need for PPh on top of IA treatment.

The risk of BKV positivity was significantly higher and the duration of BK viremia significantly longer in nsIA. Data on the duration of BK viremia after semi-selective IA are scarce. Significantly higher incidences of BKV nephropathy in ABOi recipients desensitized by sIA or PPh were found in two studies from the United Kingdom and United States in comparison to ABOc recipients and HLA-incompatible patients, respectively [29, 30]. Speer et al. found a higher risk of BKV positivity specifically in "high-titer" compared to "low-titer" patients within their ABOi cohort [10]. In line with other groups with comparable immunosuppressive regimens and desensitization protocols, we did not find any differences concerning CMV positivity [10, 13, 22].

Although the overall mortality rate was low, retrospective analysis found an increased mortality during the first 2 years after KTx in nsIA patients. This finding has not been reported previously [13, 22]. Most recent studies compare ABOc to ABOi patients and show conflicting results. Whereas Genberg et al. did not report any differences in patient survival, others found a significant rise in death rates due to infectious complications during the early post-transplant period in ABOi patients [3, 4, 17, 23]. In line with our retrospective analysis, univariable Cox proportional hazard regression revealed an elevated mortality risk during the first 2 years post-transplantation in nsIA compared to sIA. However, after adjusting for clinical confounders, the Cox regression model did not show an independent effect of the IA column on mortality. Mortality was <5% during the first 2 years post transplantation in our cohort. The low number of adverse events, as well as the large confidence interval, indicate a lack of statistical power. Our data, combined with our clinical experience, strongly suggest that there is a relevant difference in risk of mortality. However, pooled analysis of larger data is necessary to make a valid inference.

The risk of severe infections in our cohort is higher than in other studies. This may be due to a stricter preoperative desensitization protocol. We aimed at preoperative IgM and IgG isoagglutinin target titers ≤1:4, whereas the Stockholm protocol accepts ≤1:8 and other studies used ≤1:16 as cut-off pre-transplantation. A titer of >1:16 has been associated with an elevated risk of antibody mediated rejections [10, 13, 22, 26, 31]. Interestingly, there is increasing evidence of successful ABOi KTx without preoperative anti-blood group antibody removal in patients with low initial titers, even in pediatric patients, with comparable outcomes as following ABOc KTx [17, 32, 33].

The total number of preoperative IA and PPh treatments did not differ between the two groups and was similar to Thölking et al. [13]. Significantly more nsIA patients had to receive preoperative PPh, mostly due to limited adsorption of IgM isoagglutinin by IA [34]. This may augment the predisposition to postoperative infections due to the non-selective depletion of antibodies by apheresis [35, 36]. Therefore, postoperative IA treatments were scheduled if titers exceeded 1:8 during the first 7 days and 1:16 during the following week. This displays a stricter strategy than performed by other groups and resulted in lower rates of allograft rejections compared to their cohorts [10, 22].

Although currently 80% of our ABOi patients need preoperative PPh, we prefer non-antigen-specific IA with intercurrent PPh when needed compared to a desensitization protocol solely based on PPh. PPh is accompanied by an alteration of coagulation (when exchanged with human albumin), which may lead to more frequent postoperative bleeds. Alternatively, exchanging the patient's plasma volume with fresh frozen plasma (FFP), is associated with exposure to unwanted allogenic components of FFPs as well as the transfusion-related risk of infection [37].

Immunoadsorption, on the contrary, allows the elimination of isoagglutinins and only slightly changes the concentration of coagulation factors and other immunoglobulins.

Although this analysis currently represents the largest patient collective comparing sIA to nsIA, its limitations include the observational monocentric approach and a cohort consisting mainly of patients of European origin. Data were collected retrospectively over a large time frame (16 years) and not contemporaneously, which makes biases inherent. Due to our team's increasing clinical experience and protocol standardization, the group that received nsIA comprised significantly more patients suffering from pre-existing medical conditions (higher ASA category). This may confound the association between IA modality and infectious complications. In this respect, a prospective randomized and at least one-side-blinded comparison of IA columns should be conducted. Especially regarding survival analysis, larger patient cohorts are needed to reduce the risk of inconclusive results.

This is the first study to show that nsIA in ABOi KTx is an independent risk for severe postoperative infectious complications. sIA correlates with increased rejection rates, however, with a similar long-term graft survival.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of the University of Freiburg and registered in the German Clinical Trials Register: protocol number 296/20; registration number: DRKS00022385. The study was conducted in accordance with the local legislation and institutional requirements. All patients of the Freiburg living donor kidney program gave written informed consent for collecting and storing data in our living donor transplant registry in accordance with the national legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: BJ and JS. Data collection: LM and KL. Data analysis: LM and GS. Project administration: BJ. Visualization: LM and GS. Writing—original draft: LM. Writing—review and editing: BJ, JS, GS, YT, PH, GW, and SF-F. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12263/full#supplementary-material

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REVIEW
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New Treatment Options for Refractory/Resistant CMV Infection

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Despite advances in monitoring and treatment, cytomegalovirus (CMV) infections remain one of the most common complications after solid organ transplantation (SOT). CMV infection may fail to respond to standard first- and second-line antiviral therapies with or without the presence of antiviral resistance to these therapies. This failure to respond after 14 days of appropriate treatment is referred to as "resistant/refractory CMV." Limited data on refractory CMV without antiviral resistance are available. Reported rates of resistant CMV are up to 18% in SOT recipients treated for CMV. Therapeutic options for treating these infections are limited due to the toxicity of the agent used or transplant-related complications. This is often the challenge with conventional agents such as ganciclovir, foscarnet and cidofovir. Recent introduction of new CMV agents including maribavir and letermovir as well as the use of adoptive T cell therapy may improve the outcome of these difficult-to-treat infections in SOT recipients. In this expert review, we focus on new treatment options for resistant/refractory CMV infection and disease in SOT recipients, with an emphasis on maribavir, letermovir, and adoptive T cell therapy.

Keywords: cytomegalovirus, antiviral resistance, antiviral therapy, letermovir, maribavir, virus-specific adoptive T cell therapy

INTRODUCTION

Following primary infection, cytomegalovirus (CMV) establishes lifelong latency in the human body. Seropositivity in adults ranges from 40% to 90% [1, 2]. After solid organ transplantation (SOT), reactivation of CMV is facilitated by drug-induced immunosuppression which is required to prevent and treat transplant rejection [1]. CMV remains one of the most common opportunistic infections in SOT and CMV disease affects overall around 5%–15% of patients despite preventive strategies [3–7]. Up to one-third of patients experience recurrent CMV [8], termed as repeated CMV after an interval without evidence of virus. For study purposes, "CMV infection" is defined as evidence of virus antigens or nucleic acid in any body specimen [9]. "CMV disease" is defined as additional presence of virus attributable signs or symptoms and includes CMV end-organ diseases and the "CMV syndrome"; The later is defined by detection of CMV in the blood together with at least two clinical findings including fever, malaise, leuko-, neutro- or thrombocytopenia, atypical lymphocytes or elevated liver enzymes [9].

The first line antiviral drug for CMV prevention and treatment is intravenous ganciclovir or its oral prodrug valganciclovir [10, 11]. This guanine analog requires phosphorylation by a viral kinase (UL97) for activation and inhibits the viral DNA polymerase (UL54) [1]. Neutropenia is a major toxicity occurring in 18%–47% [12]. Foscarnet and cidofovir are second-line treatments which also

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TABLE 1 | Advantages and limitations of new treatment options for refractory/resistant CMV in SOT.

	Mode of action	Advantages	Limitations
Maribavir	- Inhibition of viral UL97 kinase	- Well tolerated - Oral formulation - Efficacy demonstrated in a Phase 3 randomized controlled trial - Regulatory approval for this indication	- Dysgeusia in one-third of patients - No intravenous formulation - Reduced efficacy with high viral loads and in refractory CMV without resistance - Poor penetration to CNS/retina - Drug-drug interactions - Recurrences after successful treatment - Resistances
Letermovir	- Inhibition of viral terminase complex	- Well tolerated - Oral and intravenous formulation - Combination therapy with ganciclovir possible - Possible option as secondary prophylaxis	- No randomized controlled trials - Approved only for prophylaxis - Reduced efficacy with high viral loads - Relevant interaction with cyclosporine, sirolimus, tacrolimus - Recurrences after successful treatment - Resistances
CMV-specific adoptive T cell therapy	- Autologous or allogeneic *ex vivo* selected (and expanded) CMV-specific T cells to restore CMV-specific T cell immunity	- Mechanistic approach to restore immunity - Reported to be safe - Alternative in drug resistant CMV - Multi-virus specific commercial products under development	- No randomized controlled trials - Safety/efficacy await confirmation in Phase 3 trials - Complex donor selection - Not widespread available - Time/cost intensive laboratory protocols - Expansion and function limited by immunosuppressive drugs

target the viral polymerase but their use is often limited by severe toxicities including nephrotoxicity in 14%–78% [8, 13–15]. Despite these well-established anti-CMV therapies, refractory and/or resistant (R/R) CMV provide a major challenge to clinicians [16].

CMV infection is clinically referred to as "refractory" if the viral load in the blood increases (>1 $\log_{10}$ compared to the maximum viral load in the first week) or persists after at least 2 weeks of appropriately dosed antiviral therapy [17]. Similarly, "refractory disease" is suspected if clinical signs or symptoms worsen or do not improve after 2 weeks of appropriate treatment [17]. A reduction in immunosuppression, an increase in the dose of ganciclovir, the addition of or a switch to second-line therapy, and resistance testing are then recommended [10, 11, 18]. In around one-third to half of refractory CMV cases, no drug-resistance can be detected [8, 13, 19]; suboptimal treatment responses may result from insufficient drug levels at site of infection.

"Resistant CMV" is defined as reduced susceptibility to one or more anti-CMV agents caused by viral gene mutation(s) [17]. In clinical practice, genotypic methods are used for diagnostics. Ganciclovir-resistant CMV occurs in around 1%–3% of SOT or 6%–18% of SOT recipients treated for CMV [4, 13, 18, 20–26], respectively, but may be more frequent in CMV seronegative recipients of organs from seropositive donors (D+/R− serostatus) [21, 25] and after lung transplantation [20]. Mutations in the UL97 gene are most frequent [1, 23]. UL54 mutations usually emerge upon extended pre-treatment and can confer cross-resistance with cidofovir and foscarnet [1]. Within the same gene, mutations in different codons are associated with varying levels of resistance [1]. Risk factors for drug-resistant CMV include D+/R− serostatus, lung transplant, high viral-loads, ongoing viral replication, prolonged antiviral exposure, subtherapeutic antiviral levels [4, 13], profound immunosuppression, and recurrent CMV infection [10, 18, 21, 23].

R/R CMV is further associated with complicated clinical courses including drug-toxicities, longer hospitalizations, and poor outcomes [17, 18, 27]; in a study of SOT recipients who were treated with foscarnet for ganciclovir-resistant or refractory CMV (n = 39; 0.66% of all SOT), 33% did not clear virus, 21% had recurrent CMV, and >50% had nephrotoxicities [13]. In lung and kidney transplants, R/R CMV was associated with increased frequencies of transplant dysfunction [18, 28]. Mortality seems also higher in resistant compared to non-resistant CMV in SOT; in a study that compared 39 ganciclovir-resistant cases with 109 ganciclovir-sensitive controls, mortality was 11% vs. 1% at 3 months, and 16% vs. 6% at 1 year after CMV diagnosis [18]. In summary, R/R CMV remains a major challenge and new effective and safe treatment options are needed.

In this review, we summarize and discuss the latest findings on maribavir, letermovir, and CMV-specific adoptive T cell therapies as treatment options for R/R CMV after SOT (summary in

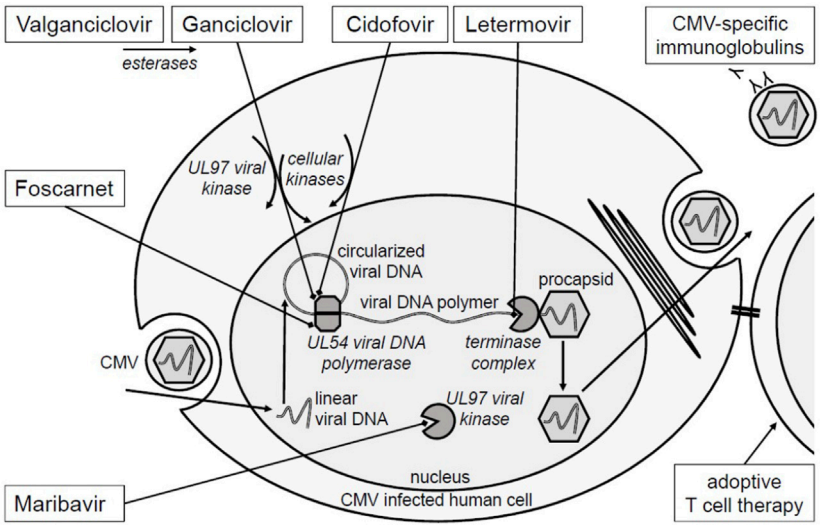

FIGURE 1 | Mechanism of action of anti-CMV therapies. Ganciclovir and cidofovir are analogs of the phosphorylated nucleosides deoxyguanosine and deoxycytidine. Valganciclovir is an oral prodrug of ganciclovir. Ganciclovir requires phosphorylation by the *viral protein kinase* (UL97) for activation. Both, ganciclovir and cidofovir require phosphorylation by host *cellular phosphokinases* for activation**.** Both drugs competitively inhibit the *viral DNA polymerase* (UL54) at the desoxynucleotide triphosphate binding site. In contrast, foscarnet is an analog of pyrophosphate and inhibits UL54 at the pyrophosphate binding site. Maribavir has another target; by inhibition of the *viral protein kinase* (UL97), it inhibits phosphorylation of viral and host cellular proteins and consequently viral replication. Letermovir inhibits binding of the newly produced viral DNA polymers to the *viral terminase complex* [29, 30]. In this way it inhibits DNA cleaving and packaging into the viral procapsid. Mutations at the drug binding sites or in the activating viral kinases confer to resistances. CMV-specific adoptive T cells recognize CMV-infected cells via T cell receptor. Enzymes are displayed in italics.

Table 1). Mode of action of established and new antivirals are shown in **Figure 1**.

NEW TREATMENT OPTIONS FOR R/R CMV

Maribavir

History of the Drug Up Through the Phase 2 R/R Trial

Maribavir is an oral benzimidazole riboside antiviral which has been in development for many years, but only recently became available as therapy for R/R CMV. It inhibits viral UL97 kinase and thus interferes with multiple pathways including nuclear egress of CMV viral capsids. It has no significant renal, hematologic, or hepatic toxicity; its most common adverse effect is dysgeusia. Early trials for prophylaxis in stem cell transplant [31] and liver transplant recipients [32] failed to show efficacy, likely because the dose selected, 100 mg twice daily, was too low [33]. However, a case series of six patients with R/R CMV treated with compassionate use maribavir at doses of 400–800 mg twice daily showed striking responses in several patients [34]. This, and the toxicity of other agents available for R/R CMV, spurred the performance of a Phase 2 trial of 3 dosing regimens for maribavir (400, 800, and 1,200 mg twice daily) among SOT and HSCT recipients [19]. This study demonstrated clearance of CMV DNAemia at 6 weeks of therapy in 70%, 63%, and 68%, respectively, in this highly treatment-experienced population [19].

Phase 3 Trials

Subsequently, a multicenter Phase 3 trial of maribavir versus investigator-assigned therapy (IAT) was performed involving 352 SOT and HSCT recipients in a 2:1 randomization [8]. IAT, which could be ganciclovir, valganciclovir, foscarnet, cidofovir, or a combination of these, was chosen as the comparator because of patients' varied treatment histories. The primary endpoint, confirmed CMV-DNA clearance at the end of week 8, was achieved by 55.7% in the maribavir arm vs. 23.9% in the IAT arm ($p > 0.001$). The key secondary endpoint, a composite of CMV-DNA clearance and symptom control at the end of week 8 maintained through week 16, was achieved by 18.7% vs. 10.3% ($p = 0.01$). Dysgeusia was the most frequent adverse effect in the maribavir group (37.2%); the maribavir group also had significantly less neutropenia than the val/ganciclovir group and less acute kidney injury than the foscarnet group [8]. These results led to the approval of maribavir by the US FDA in 2021 for treatment of post-transplant CMV infection/disease in patients age 12 and older, that is refractory (with or without genotypic resistance) to treatment with ganciclovir, valganciclovir, cidofovir or foscarnet, with a similar authorization by the EMA in 2022. A second Phase 3 randomized double-blinded trial (the AURORA trial, NCT02927067) compared maribavir to valganciclovir for treatment of asymptomatic CMV DNAemia in stem cell transplant recipients. At the time of this writing, full results have not yet been published, but topline results were announced by the study

sponsor (Takeda) in December 2022. At week 8, which was the end of study treatment, 69.6% of patients treated with maribavir achieved CMV clearance vs. 77.4% for valganciclovir; this did not meet non-inferiority based on a prespecified margin of 7%. At week 16, 52.7% of patients treated with maribavir achieved maintenance of viremia clearance and symptom control vs. 48.5% for valganciclovir. Similar post-treatment maintenance effect was observed at week 12 (59.3% vs. 57.3%) and week 20 (43.2% vs. 42.3%) time points. Maribavir's safety profile was confirmed, particularly with regards to neutropenia (21.2% vs. 63.5% for valganciclovir). Despite not meeting the prespecified noninferiority margin, this study demonstrated that maribavir has potential utility for treatment of non-refractory CMV DNAemia, with a lower risk of hematologic toxicity than valganciclovir.

Questions About Optimal Use

While the approval of maribavir for R/R CMV was long-awaited, questions about optimal use remain. In the Phase 3 R/R CMV trial, subgroup analyses showed that the proportion achieving the primary endpoint was higher when maribavir was initiated at a viral load of <9100 IU/mL than at higher viral loads (62.1% vs. 43.9%), and was higher with documented genotypic resistance vs. refractory CMV without resistance (62.8% vs. 43.8%) [8]. Some experts have proposed that R/R CMV with high viral load might most effectively be treated with an agent such as foscarnet initially, then switch over to maribavir at a lower viral load, to minimize foscarnet toxicity and to maximize the efficacy of maribavir [35]. Another issue, as with all therapies for R/R CMV, is the risk for recurrences. While maribavir achieved the key secondary endpoint significantly more often than IAT, the numbers in both groups were relatively low (who maintained CMV clearance and symptom control out to week 16 after completion of therapy at week [8]). Of note, the Phase 3 R/R maribavir trial [8] did not permit secondary prophylaxis after the defined 8 weeks treatment period, whereas the Phase 2 R/R maribavir study had allowed continuation of maribavir out to 24 weeks [19]. Whether secondary prophylaxis would be of benefit (in terms of decreasing recurrences after CMV DNAemia clearance), and whether that would be offset by potential increases in maribavir resistance, has yet to be studied, but will be important to assess. Although the evidence supporting the use of secondary prophylaxis is mostly lacking, many centers use secondary prophylaxis, and current guidelines recommend considering secondary prophylaxis in high-risk scenarios [10]. Combination therapy with maribavir is also a promising frontier that is yet to be explored. Chou et al. demonstrated that the maribavir/ganciclovir combination is antagonistic, and additive for maribavir + foscarnet or cidofovir or letermovir, but synergistic for maribavir + rapamycin (sirolimus) [36]. The use of an mTOR inhibitor-based immunosuppressive regimen is another strategy in prevention or management of R/R CMV particularly in organ transplant recipients [37]. The maribavir + mTOR inhibitor combination deserves further study.

Resistance

Perhaps the most important questions regarding its future utility relate to the risk for development of resistance to maribavir. An impressive body of work by Chou has addressed this issue for nearly 20 years, now utilizing updated sequencing technology [38]. Chou et al. analyzed resistance mutations from the Phase 2 maribavir trials, and found known UL97 maribavir resistance mutations after 46–166 days of maribavir therapy (T409M or H411Y) in 17 of 23 who had had CMV recurrences while on maribavir [39]. Moreover, they identified the mutation UL97 C480F in six patients, which confers high-level maribavir resistance and low-level ganciclovir resistance [39]. A recent real-world case series described maribavir resistance in 4 of 13 patients treated for R/R CMV (with H411Y in 2, T409M in 1, and C480F in 1) [40]. Another report described two patients refractory to maribavir, one with H411Y and one without known maribavir resistance mutations [41].

Conclusion

Maribavir has far less toxicity than other agents for R/R CMV, and is a major advance in treatment of this entity. However, we still have much to learn about optimizing its use and preventing recurrences and resistance.

Letermovir

Background and Mechanism of Action

Letermovir is a 3,4-dihydroquinazoline derivative and is an inhibitor of the viral terminase complex, mainly at the pUL56 subunit. Terminase inhibition leads to compromised viral replication by inhibiting the cleavage of genome particles to units of proper length and accumulation of immature viral DNA [29]. Based on the mechanism of action, letermovir is selectively active only against CMV, and mechanism-derived adverse effects are unlikely. Letermovir was approved in 2017 for prophylactic use in adult CMV-seropositive allogeneic hematopoietic stem cell transplant (HCT) recipients, where it has shown good efficacy in the placebo-controlled phase III trial [42] and as of 6 June 2023, the US FDA approved letermovir for the new indication of CMV prophylaxis in D+/R− kidney transplant recipients, based on the results of the Phase 3 trial [43]. No statistically significant differences were seen in the frequency or severity of any adverse events between letermovir and placebo, although gastrointestinal adverse events (such as nausea) were slightly more common in the letermovir group. It is available in both peroral (PO) and intravenous (IV) formulations. The standard dose is 480 mg daily (IV/PO) when used as prophylaxis. However, due to interaction via the hepatic drug transporter organic-anion-transporting polypeptide (OATP), cyclosporine increases bioavailability of letermovir, and dose reduction to 240 mg daily is recommended [43].

Letermovir Prophylaxis Among SOT Recipients

In the phase 3 trial, 601 CMV D+/R− adult kidney transplant recipients were randomized to receive prophylaxis with either valganciclovir or letermovir 480 mg once daily (240 mg if used with cyclosporine) until week 28 after transplantation. Primary efficacy endpoint of the study was met, as letermovir was non-

TABLE 2 | Studies or case series reporting the use of letermovir (LTV) for treatment of refractory/resistant CMV infection, or after failure to tolerate first-line treatment.

Author/journal/ year	Type of SOT and number of patients	Reason for LTV treatment	Dose of LTV	Outcomes
Linder et al. [46] Transplant Infect Dis 2021	27 SOT (13 lung, 6 kidney, 2 heart, 1 liver, 5 other) In addition, 21 HCT included	Intolerance to other antivirals (77%), resistance concerns (33%)	480 mg OD: 87% 720 mg OD: 13% (titrated up to 960 mg in two patients) Oral: 89% Intravenous: 11%	Good virologic outcomes if viral load <1,000 IU/mL at starting LTV; if > 1,000 IU/mL at starting, only approx. 40% reached DNAemia <1,000 IU/mL
Veit et al. [47] Am J Transplant 2021	28 SOT (all lung)	Refractory infection (57%), confirmed antiviral resistance (43%)	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	Decrease in viral load within median 17 days and subsequent clearance in 82%; treatment failure in 18%
Schubert et al. [48] Eur J Clin Microbiol Infect Dis 2021	5 SOT (3 kidney, 2 heart) In addition, two HSCT and two other immunosuppressed patients included	refractory infection (11%), intolerance to other antivirals (67%), confirmed resistance (22%)	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	Decrease in viral load to <200 IU/mL within median 23 days seen in 78%
Ortiz et al. [49] Clin Transplant 2022	4 SOT (3 SPK, 1 kidney)	Intolerance to (val)ganciclovir (50%), confirmed antiviral resistance (50%)	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	Viral clearance reached in 75%, and decrease in viral load to <200 IU/mL in 25%, after 4–9 weeks of treatment
Phoompoung et al. [50] Transplantation 2020	4 SOT (lung), in addition one HSCT included	Refractory infection (50%), intolerance to other antivirals (25%), confirmed antiviral resistance (25%)	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	Decrease in viral load to <200 IU/mL within 3–6 weeks in 75%, treatment failure in 25%
Turner et al. [51] Antimicrob Agents Chemother 2019	4 SOT (2 lung, 2 heart) CMV retinitis in all	confirmed antiviral resistance	720 mg OD, dose titrated up to 960 mg in one patient	All showed clinical improvement, virological treatment failure in 75%
Aryal et al. [52] Transplant Infect Dis 2019	2 SOT (lung, heart) In addition, 7 patient included with LTV prophylaxis	confirmed antiviral resistance	480 or 240 mg OD (based on tacrolimus or cyclosporine use)	viremia clearance in 50%, treatment failure in 50%
Boignard et al. [53] Antiviral Ther 2022	2 SOT (heart)	intolerance to other antiviral (50%), confirmed resistance (50%)	480 mg OD	Viremia clearance in 50%, treatment failure in 50%

inferior to valganciclovir in preventing CMV disease (frequency 10.4% in the letermovir vs. 11.8% in the valganciclovir group). Importantly, letermovir resulted in lower toxicity compared to valganciclovir, especially lower rate of leukopenia (11.3% vs. 37%) or neutropenia (2.7% vs. 16.5%), and lower rate of drug discontinuation due to adverse events (4.1% vs. 13.5%) [43]. The study results are very convincing for the good efficacy of letermovir also in the SOT setting, when used as prophylaxis, and have recently led to the expanded indication mentioned above, by the US FDA.

Letermovir for Treatment of CMV Infections, Background

Larger industry-driven studies have all addressed the use of letermovir only as CMV prophylaxis, but due to lack of suitable alternatives for treating resistant CMV infections until recently, there has similarly been interest on using letermovir for treatment of CMV infections. However, as the drug does not block viral DNA synthesis, but inhibits events later in the viral cycle, some concerns have been raised about the potential to promote resistant viral strains, especially when used in case of high-level viremia. Indeed, several mutations in the pUL56 subunit of the terminase complex have been described after exposure to letermovir, potentially causing resistance to the antiviral action of the drug [44]. Interestingly however, in the phase 3 kidney transplant trial, no letermovir resistance-associated substitutions/mutations were detected in the letermovir arm, in comparison to nine patients in the valganciclovir arm, who developed ganciclovir resistance-associated mutations [45].

Letermovir for Treatment of CMV Infections, Real-World Experience

Table 2 briefly summarizes published case series of studies using letermovir as treatment of CMV infections. Most common dose has been 480 mg once daily PO, but also higher doses (up to 960 mg daily) have been used. In these studies, 76% of the cases with CMV infection treated with letermovir resulted in either viral clearance or decrease to viremia <200 IU/mL, and treatment failure was seen in 24% of cases. Although letermovir was mainly effective and resulted in lowering of viremia or viremia clearance, recurrent infections were common. In the multicenter retrospective study by [46], viral suppression was more likely when letermovir was started at a viral load of <1000 IU/mL. Therefore, another option worth considering would be to treat the viral load to low levels with another agent such as foscarnet, and then switch to letermovir to maximize the chance of clearance and minimize foscarnet toxicity.

Significant interaction with tacrolimus was noted, and tacrolimus dose needed to be adjusted (reduced significantly) in many cases. Letermovir is a moderate inhibitor of CYP3A *in vivo* [54], and therefore leads to increase in tacrolimus and cyclosporine (and sirolimus) concentrations. In phase 1 studies, coadminstration of letermovir with tacrolimus or cyclosporine resulted in 2.4- and 1.7-fold increases in area under the plasma concentration-time curves, and 1.6- and 1.1-fold increases in maximum plasma concentrations, respectively [55].

The use of letermovir as an antiviral agent in preemptive therapy after solid-organ transplantation has been so far addressed in only one early proof-of-concept phase 2a study, in which antiviral efficacy was shown despite using much lower doses than the current recommendation (only 80 mg/day) [56]. Some more experience of successful use of letermovir as preemptive therapy after HSCT has been described [57].

Combination therapy with letermovir and (val)ganciclovir or CMV IvIG has also been reported. In the largest study reporting combination therapy so far, eight kidney or kidney-pancreas recipients with persisting low-level viremia despite >90 days of valganciclovir were treated with valganciclovir 900 mg twice daily together with letermovir 480 mg once daily. In this study, the use of adjunctive letermovir did not result in viral clearance, and median viral load did not change during 12 weeks of follow-up.

Suggested or confirmed genotypic resistance to letermovir was described in some of the case series, and in addition in case reports. In total at least seven genotypically resistant cases have been published to date after solid-organ transplantation, with mutations seen in UL56 gene [46, 47, 51, 58]. Similarly, mutations in UL56 have been described in patients who received letermovir prophylaxis after HSCT [59]. However, the vast majority of CMV infections treated with letermovir have not resulted in resistance concerns.

Future Directions

Based on the published experience so far and our own clinical experience, letermovir can be considered for treatment of R/R CMV infections. Favorable results will more likely be reached if treatment is initiated at low-level viremia, but recurrence and development of resistance are remaining concerns. In cases of poor tolerance to valganciclovir due to leukopenia or neutropenia, the potential to use letermovir as secondary prophylaxis after clearance of viremia could be further explored. However, some concerns about breakthrough infections and emergence of letermovir resistance have been raised in small case series [52, 60].

CMV-Specific Adoptive T Cell Therapy

Rational for CMV-Specific Adoptive T Cell Therapy

T cell immunity is essential for CMV control [61, 62]. In SOT recipients, T cell immunity is weakened by immunosuppressive drugs, making direct restoration of immunity by infusion of CMV-specific T cells ("adoptive" T cell therapy) attractive [63].

To date, most clinical data on CMV-specific T cell therapies derive from phase 1/2 studies in allogeneic HCT recipients in which cells were infused for CMV-prophylaxis or treatment of R/R CMV [64]. Different protocols for T cell generation and application including intrathecal administration [65] were demonstrated to be safe and treatment for R/R CMV was successful in around 70% [64, 66]. Despite these promising data, the safety and efficacy still need to be confirmed in phase 3 studies. Additionally, there is very little data on SOT recipients.

T Cell Donors

Traditionally, CMV-specific T cells were harvested from the HCT donor. This limited the treatment to HCT recipients with CMV seropositive donors. More recently, peripheral blood cells from only partially HLA-matched CMV seropositive third-party donors were also successfully used [67]. This enabled therapy also in SOT recipients. Third-party cells were either collected prior and stored for "off-the-shelf" use [67] or collected upon request from pre-screened individuals in donor registers [68, 69]. Despite concerns about limited proliferative capacity due to continued immunosuppression, studies have shown successful expansion of autologous virus-specific T cells [70–73].

Preparation and Availability

Ex vivo steps are required to exclusively select CMV-specific T cells from the original donor product [64]. Complex and time intensive laboratory expansion protocols of minimum 10 days but up to 30 days are used to obtain high numbers of specific T cells [72, 74]. Alternatively, CMV-specific donor-derived white blood cells are directly isolated *ex vivo* using immunomagnetic methods (e.g., direct sorting using peptide-HLA multimers, cytokine-capture system or based on T cell activation molecules) [75–77].

Adoptive T cell therapies are still mainly restricted to specialized academic centers and few commercial companies due to the complexity of donor search and selection and the requirement of "good manufacturing practice"-accredited laboratories to prepare the cells *in vitro*. However, in recent years, increasing number of centers were able to offer "off-the-shelf" products to their patients as part of multicentric trials (e.g., NCT04390113 and [67]).

Safety

Virus-specific adoptive T cell therapies are generally reported to be safe. For allogeneic products, graft-versus host disease is a potential concern despite viral-specificity of most cells and was reported in around 5%–16% [64]. Independent of cell source, cytokine release syndrome and graft failure due to T cell mediated inflammation may occur but have rarely been reported [73, 78]. An open issue is the co-administration of immunosuppressive drugs, which affects the expansion and function of T cells *in vivo* after infusion into the patient. The optimal timing and composition of immunosuppression at the time of virus-specific T cell infusion remains to be determined.

CMV-Specific Adoptive T Cell Therapy in SOT

At this time, data from 19 SOT recipients treated with CMV-specific T cells have been reported, including one pediatric patient of 16 years of age, 11 lung, 6 kidney, 1 heart, and 1 liver transplant

TABLE 3 | Case reports and one case series reporting the use of CMV-specific adoptive T cell therapy in SOT.

Author/journal/year	Type of SOT and number of patients	Reason for treatment with CMV-specific T cells	T cell donor/Strategy	Outcomes
Smith et al. [72] Clinical Infectious Diseases 2019	13 SOT (4 kidney, 8 lung, 1 heart)	Recurrent, refractory and/or resistant CMV infection/disease or any CMV infection/disease with drug intolerance	Autologous *Ex vivo* expanded 1–6 doses; 22.2–224 × 10^6 T cells/dose. 8/13 with concomitant antiviral therapy after infusion	Objective improvement of symptoms, including reduction/resolution of DNAemia in 85% (11/13). Adverse events were of grade 1 (nausea, malaise, fatigue, altered taste sensation) and 2 (fatigue, halitosis, microangipathic hemolytic anemia)
Brestrich et al. [73] Am J Transplant 2009	1 SOT (lung)	Recurrent, refractory CMV-pneumonia on mechanical ventilation	Autologous *Ex vivo* expanded One dose as treatment (1 × 10^7 cells/m^2), 2nd dose as secondary prophylaxis	Virologic and clinical response after 1st dose. Recurrent pulmonary CMV disease 6 weeks later. Died from CMV-negative graft failure
Holmes-Liew et al. [71] Clin Transl Immunology 2015	1 SOT (lung)	Recurrent, resistant CMV infection after resolved CMV disease (hepatitis, pancytopenia)	Autologous *Ex vivo* expanded Four doses (3 × 10^7 T cells/dose)	CMV PCR undetectable at time of infusions and for 16 months following infusion
Pierucci et al. [70] J Heart Lung Transplant 2016	1 SOT (lung)	Recurrent, resistant CMV infection with intolerance to cidofovir	Autologous *Ex vivo* expanded Three doses (1.9–2.2 × 10^7 T cells/dose)	CMV titer reduction but no clearance. Died from unrelated fungal infection
Macesic et al. [69] Am J Transplant 2015	1 SOT (kidney)	Recurrent, resistant CMV disease (glomerular thrombotic microangiopathy)	Allogeneic (3/6 HLA matched third-party donor from a donor bank) *Ex vivo* expanded One dose (1.6 × 10^7 T cells/m^2). Concomitant artesunate	Virologic and clinical response but remained dialysis dependent. Mild fever following infusion
Miele et al. [79] Microorganisms 2021	1 SOT (liver)	Recurrent, refractory CMV disease (leukopenia, thrombocytopenia, interstitial pneumonia)	Allogeneic (5/6 HLA matched mother) *Ex vivo* expanded Two doses (1st dose with 1 × 10^6 cells/kg)	Virologic and clinical response (leukopenia resolved). No CMV relapse in the following 10 years
Stuehler C., Khanna N. et al. University Hospital of Basel, Switzerland (unpublished data)	1 SOT (kidney)	Recurrent, refractory CMV infection after CMV disease (leukopenia, pneumonia)	Allogeneic (6/6 HLA matched daughter) Immune magnetic sorting using cytokine capture assay One dose (3.5 × 10^4 cells/kg)	Clinical response (leukopenia resolved). Partial virologic response with ongoing low-level replication under valganciclovir

recipient (**Table 3**, including one unpublished case from our institution) [69–73, 79]. All recipients were treated for R/R CMV infection (n = 5) or disease (present or recent, n = 14). Anti-CMV drug resistance was reported in 12 cases. All protocols collected T cells from peripheral blood and most used *ex vivo* expanded cells. At our institution, we have successfully used the cytokine-capture system to isolate CMV-specific T cells.

Sixteen patients received autologous T cells and interestingly, it was possible to harvest CMV-specific T cells from patients with CMV D−/R− and D+/R− serostatus at time of transplantation [72]. In one patient, the immunosuppressive treatment was reduced specifically for cell harvesting, and the authors recommended this measure 2–3 weeks prior to cell collection [70].

Three patients received fully or partially HLA-matched third-party allogeneic T cells; our patient received the cells from his HLA-matched daughter, the pediatric patient received cells from his mother who was not the SOT donor [79], and another patient received cells from a third-party donor who was selected from a donor registry [69].

One to six doses of CMV-specific T cells were infused per patient with single doses between 0.24×10^7 and 3×10^7 cells. After infusion, some trials observed rapid *in vivo* expansion of CMV-specific T cells with simultaneous drop in viral load [73], however, other protocols could not observe these dynamics [70].

Infusions were generally well tolerated. Smith et al observed in their case series only grade 1 and 2 adverse events with potential association to the T cell infusion [72]. No graft-versus-host disease was observed with the allogeneic products, however, one patient had a mild fever following infusion which was potentially associated with cytokine release [69]. Of note, in the very first reported case, a lung transplant recipient with a drug-resistant CMV pneumonia on mechanical ventilation initially responded clinically and virologically after a first infusion of autologous CMV-specific T cells, could be discharged, and received a second infusion for prophylaxis,

TABLE 4 | Refractory/resistant CMV treatment strategies at Helsinki University Hospital, Johns Hopkins University, and University Hospital of Basel.

	Helsinki University Hospital, Finland	Johns Hopkins University, United States	University Hospital of Basel, Switzerland
Testing	Genotypic test for drug resistance only in selected cases with risk factors and failure to respond despite to 21 days of adequately dosed therapy	Genotypic test for drug resistance in patients without response despite 14 days of adequately dosed therapy	Genotypic test for drug resistance in patients without response despite 14 days of adequately dosed therapy
Current strategy to treat refractory/ resistant CMV	Letermovir has been used in selected cases with success. Generally try to avoid foscarnet due to nephrotoxicity. Until recently, Maribavir has not been available	Maribavir is now considered first-line therapy for R/R CMV infections at many centers. However, if the starting CMV viral load is extremely high, some clinicians may try to decrease the CMV viral load with another agent such as foscarnet first, then switch to maribavir after a drop in viral load and before significant toxicity has occurred	Foscarnet. In some cases addition of CMV specific immunoglobulins. Early discussion of treatment with adoptive CMV-specific adoptive T cell therapy from third party donor (ongoing phase 1/2 study). Maribavir was not readily available until to date
Planned adaption to the strategy	Maribavir as first line therapy in r/r CMV infection and disease	Maribavir as first line therapy in r/r CMV infection and disease. In future also hope to use maribavir for those with CMV recurrences and prior neutropenia during CMV treatment	Maribavir as first line therapy in r/r CMV infection and disease
Personal view	Most of the r/r CMV infections can be successfully treated with (val)ganciclovir together with mild reduction in immunosuppression and long enough courses of treatment, but leukopenia during long treatment is a problem	Collaboration between transplant teams and transplant infectious disease specialists essential; reduction of immunosuppression; Ig supplementation for hypogammaglobulinemic patients. Need further study of benefits/risks of secondary prophylaxis	Close management within interdisciplinary teams including transplant care team and infectious disease specialists recommended. We generally omit cidofovir due to nephrotoxicity

however, he subsequently died few weeks later from CMV-negative graft failure and it was not possible to fully exclude an association with the T cell therapy [73]. No changes in graft status were observed in the other cases.

As cases were not controlled and concomitant antiviral-drug regimen were often present, larger and controlled studies are necessary to estimate and prove treatment efficacy (e.g., as for BK virus in kidney transplantation, NCT04605484).

In summary, CMV-specific adoptive T cell therapy is an appealing option for R/R CMV in SOT. However, safety and efficacy need to be confirmed in controlled trials. Additional data is needed to identify the best protocols in terms of T cell generation and optimal time point of application and the influence of different immunosuppressive therapies on treatment efficacy should be investigated. At this point, we recommend that CMV-specific T cell therapies should be preferentially offered within clinical trials in order to close the knowledge gaps.

Other Options

Other options for treatment of R/R CMV in SOT have been discussed in the latest guidelines [10, 11]; brincidofovir, an oral conjugated form of cidofovir, is US FDA approved for smallpox as bioterrorism agent but no longer available [80] after it failed as prophylaxis for CMV in a phase 3 trial in HCT [81]. Use of leflunomide [82] or artesunate, both with *in vitro* efficacy against CMV remains anecdotal [83, 84]. And although 31% of respondents in a recent survey among mainly European SOT centers reported that they add CMV-specific immunoglobulins to the antiviral therapy for ganciclovir-resistant CMV [16], this approach is controversial. The current guidelines state that randomized trials are needed to adequately investigate the role of CMV-specific immunoglobulins [10, 11].

Reduction of immunosuppressive drug doses to lowest doses compatible with graft survival remains fundamental in CMV treatment. However, type of immunosuppression might also play a role; data of a recent meta-analysis suggested that compared to calcineurin inhibitors alone the addition of everolimus may be associated with lower risk for CMV infection and similar trends were observed with other mTOR inhibitors [37]. In contrast, mycophenolate mofetil might increase risk for CMV disease [85] and therefore, many clinicians hold the drug during R/R CMV episodes.

CONCLUSION

While R/R CMV remains an important complication in SOT, new therapeutic options became available in the recent years (**Table 1**).

Best evidence on efficacy and safety is available for maribavir and we therefore recommend maribavir as first-line treatment for R/R CMV in SOT. However, although maribavir was superior to standard therapies for R/R CMV, many patients did not achieve sustained viral clearance and symptom control. Especially patients with high initial viral loads and patients without genotypic resistance might be at risk for suboptimal responses, and, because of poor drug penetration, patients with CMV encephalitis and retinitis were completely excluded from the pivotal trial. Additionally, maribavir resistance and drug-drug interactions might become more relevant with broader use. This underlines the need for alternative strategies and still legitimates use of the conventional second-line drugs, foscarnet and cidofovir, depending on the individual patient situation.

More studies are needed to define the role of letermovir in R/R CMV; its best use may be in secondary prophylaxis. However, small case series reported a favorable response to treatment of R/R CMV infections.

Similarly, few data are currently available on safety and efficacy of CMV-specific T cell therapy in SOT. Until further data are available, we recommend treatment in clinical trials.

Authors' institutional guidelines and personal insights are shown in **Table 4**.

AUTHOR CONTRIBUTIONS

Focus on maribavir: RA. Focus on letermovir: IH. Focus on CMV-specific adoptive T cell therapy: CSW and NK. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

RA has received grant/research support from Aicuris, Astellas, Astra-Zeneca, Chimerix, Merck, Oxford Immunotec, Qiagen, Regeneron, and Takeda. NK is member of advisory boards of MSD Merck Sharp & Dohme, Pfizer and Gilead Sciences and member of the data safety management boards of Pulmocide and Idorsia Pharmaceuticals Ltd. IH holds research grants for investigator-initiated studies from MSD and Hansa Biopharma, and has ongoing consultancy agreements with Hansa Biopharma, MSD, Novartis, and Takeda. IH is an associate editor of Transplant International.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Prevention of Oncogenic *Gammaherpesvirinae* (EBV and HHV8) Associated Disease in Solid Organ Transplant Recipients

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Long-term risk for malignancy is higher among solid organ transplant (SOT) recipients compared to the general population. Four non-hepatitis viruses have been recognized as oncogenic in SOT recipients—EBV, cause of EBV-associated lymphoproliferative diseases; human herpes virus 8 (HHV8), cause of Kaposi sarcoma, primary effusion lymphoma and multicentric Castleman disease; human papilloma virus, cause of squamous cell skin cancers, and Merkel cell polyomavirus, cause of Merkel cell carcinoma. Two of these viruses (EBV and HHV8) belong to the human herpes virus family. In this review, we will discuss key aspects regarding the clinical presentation, diagnosis, treatment, and prevention of diseases in SOT recipients associated with the two herpesviruses.

Keywords: human herpes virus 8, Epstein-Barr virus, Kaposi sarcoma, multicentic Castleman disease, primary effusion lymphoma, posttransplant lymphoproliferative disorders

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HUMAN HERPES VIRUS 8 IN SOLID ORGAN TRANSPLANTATION

Introduction

HHV8 is a DNA virus that belongs to the gamma-herpes virus subfamily. It was first discovered in 1994 as the etiologic agent of Kaposi's sarcoma (KS) [1]. Four types of KS are distinguished: classic-, endemic-, immunosuppression-associated-, and AIDS-associated KS [2]. Other HHV8 associated neoplastic disorders include primary effusion lymphoma and multicentric Castleman disease [3, 4].

In SOT recipients, KS is ~200 fold more frequent than the general population, with cumulative incidence of ~3%–5% in endemic areas, and <1% in non-endemic areas [5, 6]. Post-transplant KS is a consequence of reactivation of latent infection in seropositive recipients, or a primary donor derived infection in seronegative recipients [7].

Non-neoplastic disorders associated with HHV8 are peripheral cytopenias, hemophagocytic syndromes, acute hepatitis, and KS-associated herpesvirus inflammatory cytokine syndrome (KICS) [8, 9].

Epidemiology

The seroprevalence of HHV8 depends on the geographic region. African countries have the highest seroprevalence rates (>50%), whereas seroprevalence in Europe, North America, South and East Asia is lower [10–14]. In low seroprevalence regions, men who have sex with men (MSM) are at increased risk [15].

Both sexual and non-sexual transmission (including blood transfusion and organ transplantation) of HHV8 occurs. SOT recipients may be infected either before transplantation and reactivate the virus post-transplantation, or acquire the virus as a donor-derived infection. Primary HHV8 infection post-transplant increase the risk for HHV8-associated disease [16].

Non-Malignant HHV8 Disorders

HHV8 infection in immunocompetent individuals is generally asymptomatic, although occasionally associated with a febrile rash in children [17]. In immunocompromised individuals, HHV8 infection has been associated with fever, splenomegaly, maculopapular rash, lymphadenopathy and cytopenia [18] and rarely causes systemic disease with multi-organ failure post-transplantation [6]. Bone marrow suppression, with or without hemophagocytosis was linked to donor derived HHV8 infection in the early post-transplant period [19–21], and rare cases of sexually transmitted primary HHV8 infections post-transplantation were associated with hemophagocytosis [22].

Malignant HHV8 Disorders

Post-Transplant Kaposi Sarcoma (PT-KS)

PT-KS is the most commonly encountered HHV8-related neoplastic disease [23]. PT-KS mostly develops within the first year post-transplantation [6], and may cause skin lesions involving the extremities, the trunk and the oral cavity [6]. Lesions are characterized by red-blue or purple discoloration, representing the vascular nature of the disease [18]. Visceral involvement occurs in ~10% of PT-KS cases, with higher rates (up to 50%) in liver transplant recipients and associated with high a mortality [24, 25]. Disseminated disease without skin lesions exists, and lesions may appear at atypical localizations including the tonsils, urinary bladder and liver [26–28]. The disease can be rapidly-progressive, especially in donor derived cases [29]. In addition to primary infection, risk factors for KS in SOT have been described, with the most prominent factor being residence/origin in endemic countries. Other risk factors include (from higher to lower risk) older age, male gender, thoracic transplantation, and use of cyclosporine and antilymphocyte antibody [18, 30, 31].

Multicentric Castleman Diseases (MCD)

MCD is characterized by B-cell transformation to plasmablasts, which subsequently infiltrate multiple lymph nodes and distort their architecture. It typically presents with fever, lymphadenopathy, hepatosplenomegaly, and cytopenia [6]. MCD and PT-KS may occur concomitantly in SOT patients [32–34].

Primary Effusion Lymphoma (PEL)

PEL is a non-Hodgkin lymphoma that rarely develops after SOT and affects serous body cavities (pleura, pericardium, and peritoneum) [6]. The median time of presentation is 8 years after transplant, with a wide range from 5 months to 28 years [35]. It presents as a body cavity effusion in the absence of tumor masses. The prognosis is dismal [35].

Kaposi Sarcoma Herpes Virus (KSHV) Inflammatory Cytokine Syndrome (KICS)

KICS is a systemic inflammation that resembles MCD without pathologic findings in lymph nodes. Generally, patients with KICS also have KS and to a lesser extent may have PEL. Patients with KICS have more severe symptoms, and an increased risk of death [36]. Two cases of KICS have been reported in SOT recipients (**Table 1**) [8, 37].

Screening and Diagnosis of HHV8 Infection

Recent American society of transplant (AST) guidelines on HHV8 provide a weak recommendation for pre-transplant serological screening of donors and recipients in endemic areas in order to stratify the risk for HHV8 associated disease [6]. In non-endemic areas it is suggested to consider screening for at-risk donors and recipients only (i.e., MSM, people living with HIV or who inject drugs), or for immigrants from endemic countries [8].

The rationale behind recommending serologic screening in endemic settings is the increased risk for KS among seropositive kidney transplant recipients as compared to seronegative recipients (23%–28% vs. 0.7%) [38]. In addition, donor derived post-transplant HHV8 transmission from seropositive donors to seronegative recipients has been described. Nevertheless, HHV8 seropositive individuals are not excluded from organ donation [6]. Preventive reduction of immunosuppression has been suggested in D+R− cases [23].

Lack of standardization of serological assays, variable sensitivity and specificity of these tests, and the absence of an algorithm for management according to serologic findings, result in low rates of pre-transplant screening in practice. In a survey including 51 transplant centers, only one-third performed pre-transplant HHV8 serology. High HHV8 seroprevalence (>6% seropositivity), Italian centers, available protocols for post-transplant viral load monitoring, and having had a recent case of HHV8 disease were associated with screening.

In a study that assessed six different serologic HHV8 assays the Biotrin–DiaSorin IFA and ABI IFA showed the highest agreement with a reference standard of ≥2 concordant positive assays [39].

No AST recommendations are available to direct a schedule of blood viral DNA monitoring in D+R− or R+ SOT recipients, beyond a general recommendation for monitoring in these patients [6]. In a recent survey, 41% of centers reported performing HHV8 PCR monitoring post-transplant, with variable indications including symptomatic patients only, risk-based approaches or universal screening [40]. In case of detectable HHV8 DNAemia, most centers reduced the immunosuppression or changed from calcineurin inhibitors (CNI) to m-TOR inhibitors, with or without addition of antivirals [40]. For viremic patients, guidelines suggest immunosuppression reduction or change to mTOR inhibitors. The rationale for the latter is the antiviral and antiangiogenic

TABLE 1 | Case reports of KSHV Inflammatory Cytokine Syndrome (KICS) in solid organ transplant recipients.

Recipient	Donor	Organ	Presentation	Findings	KS
38 years old female, PSC and CKD, HHV8 IgG Negative	42 years old, HHV8 IgG positive	Liver and Kidney	Persistent fever 12 months after transplantation	Severe anemia and worsening of renal function, severe splenomegaly and small-sized generalized lymphadenopathy, HHV8 viral load ~189,000 copies/mL	No
54 years old male, TOF, HHV8 IgG Negative	39 years old, Eastern Europe, high risk sexual behavior, HIV negative, positive HHV8 IgG	Heart	Persistent fever 11 months after transplantation	Pancytopenia, ↑creatinine, bilateral pleural effusion, generalized lymphadenopathy, HHV8 viral load ~183,000 copies/mL	yes

CKD, chronic kidney disease; HHV8, human herpesvirus 8; HIV, human immunodeficiency virus; KS, Kaposi sarcoma; KSHV, Kaposi sarcoma Herpes virus; PSC, primary sclerosing cholangitis; TOF, tetralogy of Fallot.

TABLE 2 | Proposed approach for HHV8 screening pre- and post-transplant.

	Serology[a]	PCR[b]	ELISPOT	Physical exam	Management
Pre transplant	Yes	No	No	No	No
Post transplant	Among D+R– repeated serology may indicate seroconversion—no schedule suggested [40]	Among D+R–, PCR once every 2 weeks for 3 months followed by once monthly to complete 2 years- Among R+, PCR once monthly for 2 years [40]	Among D+R– or R+ may assist as adjunctive test to PCR	For D+R–, skin and mucosal surfaces routine examinations [6]	If PCR positive negative → reduction in immunosuppression or change to mTOR inhibitor [6] If ELISPOT negative → consider immunosuppression reduction [9]

[a]*If a screening approach is not implemented, the following signs and symptoms should merit an investigation for HHV8 if no other cause is found: fever, splenomegaly, maculopapular rash, lymphadenopathy and cytopenia.*

[b]*There is no gold standard serology assay.*

[c]*Quantitative cut-offs for PCR tests are missing; optimal testing frequency and duration of surveillance have not been determined. Whole blood may be more sensitive than plasma, because if inclusion of the cellular component. Screening is not routinely used by the authors of this review.*

effects of sirolimus, though no clinical benefit has been demonstrated in studies [6]. Screening for viral DNA in bronchoalveolar fluid has been suggested for lung transplant recipients and is now under investigation (NCT05081141).

Immune monitoring by HHV8 ELISPOT test is used by some centers as adjunct to HHV8 PCR monitoring in high-risk patients [40]. Absent anti-HHV8 cytotoxic T-cell response has been demonstrated in SOT recipients with KS. It has been suggested that ELISPOT may assist in identifying patients at higher risk for developing KS, and if negative, reducing the immunosuppression may be considered [9].

Table 2 provides a proposed approach for screening or HHV8 pre and post-transplant.

Diagnosis of HHV8 Associated Disease

The gold standard for diagnosing KS, MCD and PEL is histopathological examination of tissue. Immunohistochemical staining of HHV8 latency-associated nuclear antigen confirms the diagnosis. Tissue PCR for HHV8 may assist in confirming the diagnosis. There is no established role for peripheral blood PCR in diagnosing KS. Positive PCR supports the diagnosis of KS, however, it may be negative in ~20% of KS cases [41]. Highest DNAemia levels were reported in MCD, followed by PEL. Hence, PCR may be more sensitive in these cases, and it has been suggested that negative HHV8 PCR may be used to exclude MCD [42]. High HHV8 DNAemia (>10,000 copies/mL) supports the diagnosis of MCD over KS [43]. In patients with PEL, high viral loads have been demonstrated in effusion fluids [42]. Due to limitations of serology discussed above, it is not currently indicated for diagnosis of HHV8 associated disease [44].

Patients with KICS are almost universally DNAemic. The diagnosis of KICS is based on high levels HHV8 DNAemia, exclusion of other possible causes, and possibly detection of HHV8 in involved organs (bone marrow, liver, and others) [9, 36]. A cutoff value of viral load in plasma ≥1,000 copies/mL or ≥100 copies/10^6 cells in peripheral blood mononuclear cells has been suggested for diagnosis of KICS [36].

Prevention

(Val)ganciclovir, cidofovir and foscarnet inhibit the replication of human herpes viruses, including HHV8. Among HIV patients, (val)ganciclovir proved to decrease the incidence of KS [45]. However, effectiveness of these drugs as pre-emptive therapy in cases of positive HHV8 PCR has not been demonstrated.

The need for a vaccine to prevent HHV8 associated malignancies in susceptible populations has been recently raised by the National Cancer Institute. Since the HHV8 genome is highly conserved, it is possible that a single vaccine would provide protection worldwide [46].

Treatment of HHV8 Related Diseases

Treatment of HHV8 associated malignancies and non-malignant conditions in SOT recipients should first include reduction in immunosuppression (RIS) and/or change from CNI to mTOR

inhibitors [47, 48]. Older studies demonstrated between 70% and 100% complete response (CR) of KS following a change from cyclosporin to sirolimus, and 20%–50% CR of KS with RIS [5, 38, 49].

In a more recent study, including 145 SOT recipients with KS, immunosuppression reduction with/without switch to mTOR inhibitors, resulted in a response in >80% of patients [5].

Systemic chemotherapy with an anthracycline or paclitaxel is usually required for KS patients with visceral involvement, extensive lymph node or mucocutaneous involvement, and for patients not responding to reduction/change in immunosuppression [6, 9]. Immunomodulatory therapy with interferon-α is avoided in the SOT setting because of the risk for rejection [50]. Specific chemotherapy regimens are routinely used for the management of MCD and PEL, in addition to immunosuppression reduction [9, 45].

Immunological (ELISPOT) and virological (HHV8 PCR) tests are suggested as part of follow up in the management of KS and other HHV8 related diseases [9].

Several antivirals have *in-vitro* activity against HHV8, including ganciclovir, foscarnet, and cidofovir, while acyclovir is not highly active [51]. Recent NIH guidelines for HIV management do not recommend antivirals as part of KS therapy, based on studies showing limited efficacy [45]. For the treatment of PEL, antiviral drugs may be used as a possible adjunctive therapy, with a CIII level of recommendation [45]. For MCD, two retrospective studies demonstrated remissions using ganciclovir as part of the treatment regimen in HIV patients [45]. This is supported by the rationale of lytic HHV8 infection being present in MCD [52]. There is limited data to support the use of anti-IL6 inhibitors for MCD with no recommendation for general use of these drugs for this indication [45]. Adoptive immunotherapy with cytotoxic T-lymphocytes specific for HHV8 could have a therapeutic role, though there is currently no commercial product available [9].

EPSTEIN-BARR VIRUS IN SOLID ORGAN TRANSPLANTATION

Introduction

Epstein–Barr virus (EBV) is a double-stranded DNA virus of the γ-herpesviridae subfamily [53]. The virus was discovered in 1964 from cultured lymphoblasts of Burkitt's lymphoma biopsies before being identified as the causative agent of mononucleosis in 1968 [54, 55]. EBV was the first known human oncogenic virus and it efficiently transforms human B-lymphocytes [56–58]. Upon infection, EBV establishes life-long latency in memory B-cells [59, 60]. The pathogenesis of EBV-associated oncogenesis is complex and it is related to the ability of the virus to transform and immortalize B-cells and to impede apoptosis of infected cells [53, 61]. EBV is associated with a large spectrum of diseases, including benign diseases (infective mononucleosis, oral hairy leukoplakia), a number of lymphoproliferative disorders (Burkitt's lymphoma, some Hodgkin lymphomas, EBV-positive diffuse large B-cell lymphomas, natural killer/T-cell lymphoma, nasal type angiocentric lymphomas, chronic active EBV), epithelial cancers (nasopharyngeal carcinoma, some forms of gastric cancer), smooth muscle cell tumors, and diseases related to immune dysfunction (multiple sclerosis, EBV-associated hemophagocytic lymphohistiocytosis) [61, 62].

In SOT patients, EBV is known to play a major role in the development of EBV-positive post-transplant lymphoproliferative disorders (PTLD), one of the most devastating complications of organ transplantation [53, 63, 64].

Epidemiology

Seroepidemiologic surveys indicate that >90% of adults are infected with EBV [65, 66]. In developed countries, primary EBV infection tends to occur later nowadays as compared to the past [67–69]. In the transplant setting, donor transmitted EBV infection is common in EBV mismatched (donor EBV+/recipient EBV−) patients. Children are more likely to be EBV-negative, and may acquire the virus from the donor organ or by natural infection, putting them at increased risk for post-transplant primary infection.

EBV Associated Diseases in SOT Recipients

Post-Transplant Lymphoproliferative Disorders (PTLD)

Since the first description of five lymphoma cases in kidney transplant recipients (KTR) in 1969, PTLD has been recognized as a serious complication of SOT [70]. PTLD encloses a heterogeneous spectrum of conditions characterized by lymphoproliferation after transplantation. These disorders range from uncomplicated infectious mononucleosis-like pathology to true malignancies [71]. PTLD is categorized according to the World Health Organization (WHO) 2017 classification, based on its histopathological appearance (**Table 3**) [77]. Additionally, PTLD is classified according to its temporal occurrence: early-onset PTLD arises within the first year post-transplant, whereas late-onset PTLD occurs thereafter [78]. In contrast to late-onset PTLD, most cases of early-onset PTLDs are associated with EBV [72, 79, 80]. While the incidence rate for EBV-positive PTLD is highest early after transplant, the incidence rate of EBV-negative PTLD is low immediately after transplantation and increases after 4–5 years, resulting in a biphasic pattern of overall PTLD occurrence [81, 82].

A major risk factor for development of EBV-positive PTLD is EBV-seronegativity pre-transplant (hazard rate 5–18 as compared to EBV-seropositive individuals) [80, 83–87]. However, in liver transplant recipients the association of EBV-seronegativity and PTLD risk is less pronounced [87]. As children are more likely to be EBV-seronegative before transplantation, PTLD is more common in pediatric SOT recipients. Further, the risk is affected by the type of transplanted organ with intestinal transplant recipients (~18%) being at highest risk for developing PTLD [88, 89], followed by lung (3%–10%), heart (2%–8%), liver (1%–6%), and kidneys (1%–2%) [90]. In the current era, there was no conclusive association between the type of induction therapy and PTLD risk [91, 92]. The contribution of each immunosuppressive agent to PTLD development is unclear,

TABLE 3 | Overview of post-transplant lymphoproliferative disorders.

WHO 2017 category	EBV-association	Clonality	Frequency	Clinical features
Non-destructive PTLD - Plasmatic hyperplasia - Infectious mononucleosis-like PTLD - Florid follicular hyperplasia	~100% [72, 73]	No	~5%	Early-onset, Benign
Polymorphic PTLD	~90% [72, 73]	Variable	~10%	Early and late-onset
Monomorphic PTLD B-cell neoplasm - Diffuse large B-cell lymphoma - Burkitt (like) lymphoma - Plasmablastic lymphoma - Plasmacytoma like lymphoma - Others	~50% [72]	Yes	~80%	Early > late
T-cell neoplasms - Peripheral T-cell lymphoma - Others	~20%	Yes	<5%	Late-onset
Hodgkin/Hodgkin-like lymphoma	~90% [74]	Yes	<5%	Early and late-onset

Early-onset, within 1 year post-transplant. Late-onset, >1 year post-transplant. EBV, Epstein-Barr virus; PTLD, post-transplant lymphoproliferative disorder; WHO, world health organization.

TABLE 4 | Proposed approach for EBV screening pre- and post-transplant.

	Serology	PCR	ELISPOT	Physical exam	Management
Pre transplant	Yes	No	No	No	No
Post transplant	Among D+R– repeated serology may indicate seroconversion—in clinical practice, measurement of EBV DNA in peripheral blood has largely replaced serology for the diagnosis of primary EBV infection	Among D+R–, PCR once every 2–4 weeks for 12 months [75, 76] (author's personal opinion, week evidence)	For research purpose only	Check for lymphadenopathy during routine clinical controls (author's personal opinion, no evidence)	Reduction in immunosuppression if high EBV DNAemia[a] (author's personal opinion, week evidence) Actively search for PTLD if EBV DNAemia is persistently high[b]

[a]*There is no uniformly accepted EBV DNAemia uniform cut-off for reduction in immunosuppression. This is related to the different types of samples (whole blood vs. EDTA plasma) used for EDTA monitoring and the considerable inter-laboratory variations in EBV DNAemia measurements (even when using the WHO standard).*
[b]*There is no established EBV DNAemia cut-off (neither DNAemia level nor duration of persistent DNAemia) for triggering radiologic examinations.*

since patients receive multiple agents in different doses at different times [91]. However, concerns regarding the use of belatacept in EBV-seronegative transplant recipient have been raised [93]. It is for this reason that belatacept is contraindicated in patients who are EBV-seronegative or whose EBV serostatus is unknown prior to transplant [94].

The clinical presentation of PTLD is heterogeneous and depends on the type (non-destructive-, polymorphic-, monomorphic-PTLD) and the localization of disease. Non-specific constitutional symptoms such as fever, unintended weight loss, night-sweats, and fatigue are common. Lymphadenopathy, tonsillar hypertrophy, dysfunction of involved organs, or compression of surrounding structures may occur. More than half of cases presents with extranodal involvement [72, 83, 95]. PTLD frequently involves the gastrointestinal tract (20%–30%), the allografts (10%–15%), and the central nervous system (CNS, 5%–20%) [72, 83, 95]. Therefore, not only lymphadenopathy but also gastrointestinal bleeding or ulcers, allograft dysfunction in combination with masses, and focal neurological signs should rise suspicion for PTLD.

EBV-Associated Smooth Muscle Cell Tumor (EBV-SMT)

EBV-SMT is an uncommon neoplasm of immunocompromised individuals [96]. The role of EBV in the tumorigenesis is poorly understood. EBV-SMT is thought to be derived from myogenous vascular smooth muscle cells [97]. The clinical presentation of EBV-SMT is unspecific and depends on the localization of the tumor [98]. Biopsies of smooth muscle tumors in SOT recipients should be evaluated with EBV-encoded small nuclear RNA (EBER) stains, to establish the diagnosis of EBV-SMT [98] and the differential diagnosis should include KS and mycobacterial spindle cell pseudotumor [96].

Non-Malignant EBV-Associated Disease After SOT

The features of these EBV manifestations may include infective mononucleosis, oral hairy leukoplakia [99], and end-organ infections such as encephalitis/myelitis [100] or hepatitis [101]. Some of these manifestations may share clinical features of PTLD (e.g., encephalitis vs. CNS PTLD). Therefore, careful evaluation of these cases is warrant.

Due to the overwhelming clinical importance of PTLD, we will focus on aspects related to PTLD in this review.

Diagnosis of Post-Transplant Lymphoproliferative Disorders (PTLD)

The diagnosis of PTLD is based on the histopathological examination of appropriate tissue biopsies. Assessing the presence of latent EBV infection of affected cells by (preferably) RNA-in-situ-hybridization targeting EBV-encoded small RNAs (EBER) or by immunohistochemistry targeting latent membrane protein 1 (LMP1) is essential for the diagnosis of EBV-associated PTLD [102]. Preceding to tissue sampling, radiographic imaging is a crucial initial step to come to a tentative diagnosis. The radiographic evaluation is similar to that used in the evaluation of suspected lymphoma in the non-transplant population [103]. A computed tomography scan (neck to pelvis) is the first step in most centers. MRI may be the preferred modality for suspected cerebral PTLD [104]. Positron emission tomography-computerized tomography has emerged as a useful imaging modality for detecting suspicious lymph nodes and extranodal lesions and may be helpful to identify optimal sites for biopsy [105]. Establishing a PTLD diagnosis can be difficult and occasionally multiple attempts for getting conclusive tissue biopsies are necessary (especially for gastrointestinal PTLD). In SOT recipients with persistent gastrointestinal symptoms, PTLD should be part of the differential diagnosis and endoscopy with biopsy of ulcers/lesions should be performed [106].

Studies evaluating the diagnostic test characteristics of EBV DNAemia measurements for diagnosing EBV-positive PTLD are limited. In summary, EBV DNAemia above a specific threshold has good sensitivity (~90%) for detecting EBV-positive PTLD but lacks specificity [107–109] and EBV PCR is not useful for detection of EBV-negative PTLD.

Prevention of EBV Associated Disease in SOT Recipients

Monitoring EBV DNAemia With Reduction of Immunosuppression for Prevention of EBV-Positive PTLD

A monitoring strategy of repeated EBV DNAemia measurement with RIS if a certain threshold is reached or if DNAemia is increasing, is applied by many transplant centers [110], especially for high-risk patients (EBV D+/R−) [108, 111–115]. However, the optimal way to apply this strategy remains unclear. This is also related to the inter-laboratory variability of EBV DNAemia measurements, despite previous efforts for harmonizing results by introducing an international standard [116, 117]. In clinical practice, EDTA plasma or whole blood is used for monitoring EBV DNAemia (**Table 4**). EBV DNAemia levels are higher when determined in whole blood as compared to EDTA plasma [118, 119]. Therefore, the sensitivity for detection of EBV DNAemia is higher when using whole blood. However, the specificity for detection of EBV-related disease is better when using EDTA plasma samples [120]. The controversy with respect to the preferred sample type for monitoring EBV DNAemia is ongoing. In our opinion, it is more relevant to ensure that the same type of sample is used and that DNAemia is determined in the same laboratory when longitudinally assessing EBV DNAemia, instead of focusing on the discussion about the preferred sample type. Even though there is no evidence from randomized-controlled trials supporting the usefulness of EBV DNAemia monitoring and RIS, there is some evidence from cohort studies supporting this approach [75, 76, 111]. However, the results of these studies have to be interpreted with caution because of using historic controls [75, 76] (problematic because of decreasing PTLD incidence over time, most likely related to less intense immunosuppression in contemporary versus historic cohorts [72, 111, 121] and the lack of statistical power to show differences due to the rarity of the disease [111]). Although it seems to be appealing from a pathophysiological point of view, there is no strong evidence supporting EBV DNAemia monitoring with RIS for prevention of EBV-positive PTLD. Furthermore, no specific cut-off value for EBV DNAemia to guide preemptive therapy is available, with some studies using any positive titer [122] while others using increasing loads (>10-fold or >1 log10 cp/mL) [122].

Antiviral Prophylaxis for Prevention of EBV-Positive PTLD

Several antiviral drugs such as (val)acyclovir, (val)ganciclovir, cidofovir, foscarnet and maribavir inhibit lytic EBV replication [123, 124]. However, these drugs have no effect on latent EBV infection. Since primary EBV infection after transplantation is a major PTLD risk factor, reducing donor-derived EBV transmission may have an impact on PTLD occurrence. A reduction of primary EBV infection was observed in a cohort of EBV seronegative pediatric KTRs on (val)ganciclovir prophylaxis versus no antiviral prophylaxis [125]. In another cohort of EBV mismatched adult KTRs, antiviral prophylaxis for 3–6 months delayed the rate of EBV primary infection at 100 days post-transplant, but the seroconversion rate 12 months post-transplant was identical with and without prophylaxis (72% vs. 74%) [126]. Recent cohort studies did not find a protective effect of antiviral prophylaxis on PTLD occurrence [72, 127]. These findings are consistent with results of a systematic review published in 2017, concluding that antiviral prophylaxis in high-risk EBV-naive patients has no effect on the incidence of PTLD [128].

Rituximab for Prevention of EBV-Positive PTLD

The preemptive use of rituximab for prevention of PTLD has become a common strategy in EBV viremic hematologic stem-cell transplant (HSCT) [129, 130]. B-cell depletion before or directly after HSCT, has shown to reduce EBV replication [131, 132] and the incidence of EBV-positive PTLD [133–135] in high-risk patients. The potential effect of rituximab on subsequent PTLD development may be attributable to the depletion of

$CD20^+$ B-cells, which represent the major reservoir for latent EBV infection. The reduced abundance of these cells at risk for malignant transformation might be linked to a lower PTLD risk [72]. Rituximab use is less well established for prevention of EBV-positive PTLD in SOT recipients. A recent multi-center cohort study reported that rituximab given as part of the induction regimen (mostly in ABO-incompatible kidney transplantation) is associated with a decreased risk for PTLD [72]. A single-center cohort study reported diminished PTLD rates with rituximab use in heart transplant recipients whose EBV DNAemia did not respond to RIS using a historic control group [75]. Similarly, EBV-mismatched KTRs with persistent EBV DNAemia or symptomatic EBV infection given rituximab simultaneously with RIS were less likely to develop PTLD compared to contemporaneous controls [114].

Treatment and Prognosis of PTLD

The first therapeutic measure in treatment of PTLD is RIS under close monitoring of the graft function. There are no evidence-based guidelines on how to reduce immunosuppression, but in clinical practice, stopping anti-proliferative agents and dose reduction of the CNI is the common approach [90]. Significant RIS may not be feasible in all cases and is especially difficult to achieve in thoracic organ transplant recipients due to the risk of life-threatening graft rejection [136]. RIS eradicates the majority of non-destructive PTLD cases. However, for polymorphic and monomorphic PTLD the response to RIS alone is often insufficient [137, 138]. A radiologic reassessment is performed two to 4 weeks after RIS, and if a CR is achieved no further treatment is needed.

In the following section, we summarize the treatment options for polymorphic PTLD and monomorphic diffuse large B-cell lymphoma (DLBCL) PTLD. Treatment of non-DLBCL monomorphic PTLD depends on the histologic classification of the respect lymphoma and follows the same chemotherapy regimens as for immunocompetent patients, and will not be reviewed here. Immunochemotherapy for treatment of DLBCL PTLD is associated with significant toxicity and many SOT recipients are not fit for highly intensive regimens [139]. Therefore, sequential and risk-stratified treatments are applied for treatment of $CD20^+$ monomorphic DLBCL PTLD. The PTLD-1 [140], the PTLD-1 third amended [141] and PTLD-2 [142] phase 2 trials are landmark studies that established sequential, risk-stratified PTLD treatment modalities. The PTLD-1 study proved the efficacy and safety of a sequential treatment of four cycles rituximab monotherapy followed by four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for patients who did not achieve complete remission with RIS [140]. The most favorable outcomes were seen in patients who achieved a response to rituximab alone prior to chemotherapy, indicating that these patients may belong to a "good-risk group". In consequence, the PTLD-1 third amended trial assessed a risk-stratified protocol: patients who achieved a CR after four doses of rituximab, received consolidation with rituximab alone while those who did not achieve CR were treated with four cycles of R-CHOP [141]. This trial proved that withholding chemotherapy and performing a rituximab consolidation in patients with CR to rituximab alone is safe and associated with less toxicity [141]. The PTLD-1 third amended trial identified two subgroups with poor prognosis: thoracic transplant recipients and patients with an *International Prognostic Index* (IPI) score >2 [141]. The PTLD-2 trial, *inter alia*, assessed treatment escalation (alternating R-CHOP and R-DHOAx-rituximab, dexamethasone, cytarabine, oxaliplatin) in these patients with poor prognosis [142]. However, the number of patients in this subgroup was low (n = 9), the outcome was poor and the treatment related toxicity was substantial [142].

For further information about novel, less established PTLD treatment options such as infusion of third-party EBV-specific cytotoxic T-lymphocytes, CAR-T cell therapy, proteasome inhibitors, burton-tyrosine kinase inhibitors, and histone deacetylase inhibitors in combination with antiviral nucleoside analogues we refer to the recent review of Atallah-Yunes et al. [143].

The introduction of rituximab, the administration of sequential risk stratified treatment regimens, and optimized supportive care have improved the outcome for patients with PTLD. In the PTLD-1 trial, the median overall survival was 6.6 years [140]. Patients with a CR to rituximab alone have better prognosis as compared to rituximab non-responders [141] and thoracic transplant recipients show less favorable outcome as compared to non-thoracic transplant recipients [141, 142].

AUTHOR CONTRIBUTIONS

AA and DY reviewed the HH8 literature, drafted the HHV8 part and critically reviewed the EBV part of the manuscript. CH reviewed the EBV literature, drafted the EBV part and critically reviewed the HHV8 part of the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Utility of the Interferon-Gamma Enzyme-Linked Immunosorbent Spot Assay to Predict Risk of Cytomegalovirus Infection in Kidney Transplant Recipients

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Non-specific interferon-gamma (IFN-γ) enzyme-linked immunosorbent (ELISpot) responses after solid organ transplant (SOT) and their relationship with cytomegalovirus (CMV) reactivation have hardly been investigated. Adult kidney transplant (KT) recipients underwent measurement of IFN-γ-producing T cells using the ELISpot assay before and 1 month after transplantation. Data for CMV infection episodes were collected. Risk factors for post-transplant CMV infection, based on IFN-γ responses, were analyzed using a Cox proportional hazards model. A total of 93 KT recipients were enrolled in the study and 84 evaluable participants remained at 1 month post KT. Thirty-three (39%) recipients developed subsequent CMV infection within 6 months post-transplant. At 1-month post-transplant, IFN-γ-producing T cells with <250 spot-forming units (SFUs)/2.5 × 10^5 peripheral blood mononuclear cells (PBMCs) were significantly associated with CMV infection (HR 3.1, 95% CI 1.4–7.1, p = 0.007). On multivariable analysis, posttransplant IFN-γ-producing T cells with <250 SFUs/2.5 × 10^5 PBMCs remained independently associated with CMV infection (HR 3.1, 95% CI 1.2–7.8, p = 0.019). Conclusions: KT recipients with low IFN-γ-producing T cells measured by the ELISpot assay are more likely to develop CMV infection after transplantation. Therefore, measurement of nonspecific cell-mediated immunity ELISpot responses could potentially stratify recipients at risk of CMV infection (Thai Clinical Trials Registry, TCTR20210216004).

Keywords: cytomegalovirus, cell-mediated immunity, immune monitoring, immunocompromised, solid organ transplant

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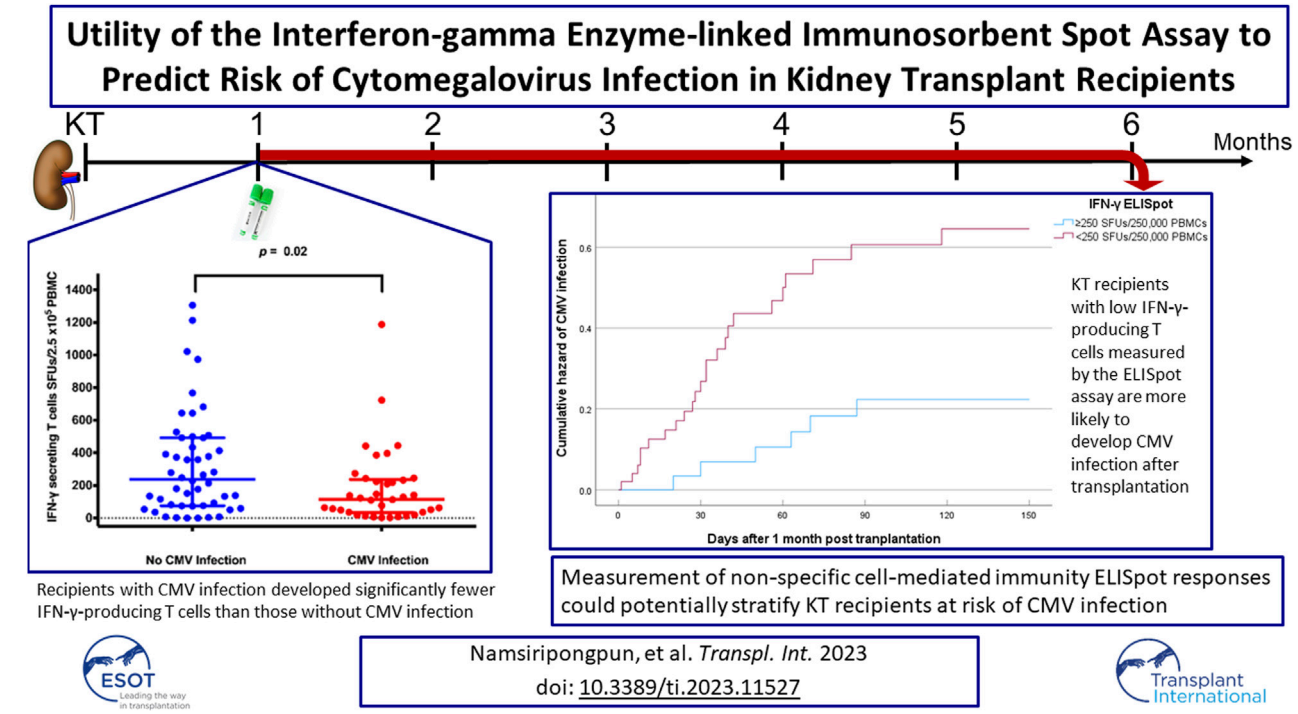
INTRODUCTION

Kidney transplantation (KT) has been widely performed over the past few decades and has improved quality of life and long-term survival among end-stage kidney disease patients requiring renal replacement therapy [1–3]. Immunosuppressants are administered to KT recipients to maintain allograft function and avoid rejection [4]. Although immunosuppressive drugs, especially those that



GRAPHICAL ABSTRACT

suppress cell-mediated immunity (CMI), provide the advantage of maintaining allograft function, they also place these vulnerable patient populations at increased risk of infection, especially opportunistic infection, after transplantation [5, 6]. As a result, clinicians need to balance the beneficial and deleterious effects of immunosuppressive therapy. Therefore, therapeutic drug monitoring is routinely performed during the course of transplantation to indirectly quantify the net immune status because subtherapeutic and supratherapeutic levels of immunosuppressants are correlated with allograft rejection and viral reactivation, respectively.

There has also been heightened interest in direct measurements of individual immunity. Interferon-gamma (IFN-γ) is an important cytokine with a significant role in antimicrobial and antiviral immunity [7]. Therefore, direct immune status evaluation through measurement of pathogen-specific or non-pathogen-specific IFN-γ-producing T cells has been proposed as a modality to predict specific types of infection in immunocompromised patients. The enzyme-linked immunosorbent spot (ELISpot) assay for IFN-γ measurement has been used for assessment of T cell immunity in response to stimulator cells from donors or third parties in solid organ transplant (SOT) recipients, and has been shown to predict poor long-term renal function in previous studies [8, 9]. However, data regarding non-specific IFN-γ ELISpot production responses to quantify the net state of immunosuppression from an infectious disease perspective are scarce. In the present study, we aimed to determine the utility of the IFN-γ ELISpot assay for measuring cellular immune responses and its correlation with post-transplant cytomegalovirus (CMV) infection in KT recipients.

PATIENTS AND METHODS

Population

A prospective clinical trial of adult KT recipients aged ≥18 years was conducted at Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, between December 2020 and December 2021. The inclusion criteria were adult patients who underwent KT during the study period. The exclusion criteria were surgical postponement regardless of etiology and inadequate peripheral blood mononuclear cells (PBMCs) from venous blood samples. Patients who provided informed consent were monitored clinically for 6 months post-transplant. Study-specific blood samples were collected prior to KT surgery and receiving induction therapy then at approximately 1 month after transplantation to assess for prediction of subsequent CMV infection. Data on demographic characteristics, comorbidities, transplantation types, immunosuppressive therapies, risk factors, and clinical outcomes were collected. Clinical outcomes of interest included CMV DNAemia, CMV syndrome and CMV end-organ CMV disease.

CMV-seropositive KT recipients underwent preemptive CMV monitoring every 2–4 weeks by plasma CMV quantitative real-

time polymerase chain reaction (qPCR) assays [CAP/CTM CMV (Roche, Branchburg, NJ, United States) or RealTime CMV (Abbott, Des Plaines, IL, United States)], or when clinically indicated, during the first 3 months. CMV-seromismatched (CMV-seronegative recipient receiving an allograft from CMV-seropositive donor) KT recipients or those who received anti-thymocyte globulin (ATG) for induction therapy or steroid-refractory rejection were provided intravenous ganciclovir or oral valganciclovir for anti-CMV prophylaxis for a period of 3–6 (CMV-seromismatched recipients) months, or were switched to preemptive CMV monitoring for 3 months by plasma CMV qPCR if they were unable to complete the course of therapy. According to our institutional guideline, CMV DNAemia is treated if CMV viral load is greater than 3,000 copies/mL. Both CMV DNAemia and CMV disease patients are treated with intravenous ganciclovir. Preemptive urine screening (i.e., urinalysis and urine culture) is routinely performed on days 3, 7, 10, and 14 after KT then twice weekly until additional 14 days following urinary stent or catheter removal. Trimethoprim/sulfamethoxazole (1 year or longer) for *Pneumocystis jirovecii* prophylaxis, acyclovir (6 months) for herpes simplex virus prophylaxis, and isoniazid (9 months) for latent tuberculous infection therapy were prescribed to all recipients.

The primary objective of the study was to determine the clinical utility of the non-specific IFN-γ ELISpot assay to measure cellular immune responses against phytohemagglutinin (PHA) and its correlation with post-transplant CMV infection in KT recipients. The secondary objectives were to assess risk factors and incidences of CMV infection within 6 months post-transplant.

IFN-γ ELISpot Assay

Venous blood samples were collected into two 4 mL tubes containing heparin. Sufficient PBMCs were separated by a Ficoll-Paque centrifugation technique and counted using an automated hematology analyzer. The final cell suspension was prepared at a density of 2.5×10^5 cells/100 μL. The IFN-γ ELISpot assay used in the study is the positive control part of the T-SPOT.TB assay (Oxford Immunotec, London, United Kingdom). The ELISpot assay was initiated by adding 100 μL of suspension and 50 μL of positive control solution containing PHA (Mabtech, Stockholm, Sweden) to commercially available pre-coated 96-well plates (Mabtech). The plates were incubated in a humidified incubator at 37°C with 5% CO_2 for 18 h. The distinct dark-blue spots produced as a result of antigen stimulation were evaluated and counted by an ImmunoSpot® Analyzer (Cellular Technology Ltd., Cleveland, OH, United States). The completely-developed assay plates were archived for potential re-examination in case of anomalies. The numbers of spot-forming units (SFUs) in paired wells were reported per 2.5×10^5 PBMCs.

CMV Infection

CMV Infection was diagnosed by clinical, microbiological, radiological, or pathological evidence. The first author determined the infection episode and a final decision was obtained from the corresponding author. Both are infectious disease specialists. CMV infection was defined as the detection of CMV deoxyribonucleic acid (DNA) in plasma and further classified into asymptomatic CMV DNAemia and CMV disease. The latter was subclassified into CMV syndrome or CMV tissue-invasive diseases according to AST IDCOP and the Transplantation Society International CMV Consensus Group [10, 11]. Data for all CMV infection that occurred within 6 months post-transplant were collected.

Statistical Analyses

The clinical characteristics were analyzed by descriptive statistics. Categorical and continuous variables were summarized as frequency and percentage, mean and standard deviation (SD), or median and interquartile range (IQR) as appropriate. Comparisons of two categorical outcomes were conducted using the chi-square test or Fisher's exact test. The Mann–Whitney U test or Student's t-test were used to analyze the differences between continuous outcomes. Numbers of IFN-γ-producing T cells were presented as dot plots with bars representing the median and IQR, as generated by GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA, United States). A receiver operating characteristic (ROC) curve was plotted to determine the IFN-γ ELISpot threshold. Clinical and immunological factors associated with CMV infection were analyzed using the Kaplan–Meier survival estimator and Cox proportional hazards model. Purposeful selection process algorithm was utilized by selecting any variable having a clinically significant univariable test at an arbitrary level of 0.1 to be a candidate for the multivariable analysis. Sensitivity analyses were performed by raising the threshold to 2,000 and 3,000 copies/mL. These cut-off values were selected because of its clinical significance according to our institutional guideline. Values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS® Statistics 18 (IBM, Armonk, NY, United States) and STATA 18 (StataCorp, College Station, Texas, United States).

Participant Consent Statement

The study protocol was approved by the Human Research Ethics Committee of Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (approval number: COA. MURA2020/1983). All patients signed an informed consent form before enrollment in the study. The study was registered in the Thai Clinical Trials Registry (TCTR20210216004).

RESULTS

Population

A total of 93 participants were recruited for the study and 81 samples were available for evaluation at 1 month post-transplant (**Figure 1**). The baseline characteristics of the 93 KT recipients are shown in **Table 1**. The majority of the recipients received an allograft from a deceased donor (73%) and underwent induction therapy with basiliximab (71%). The maintenance

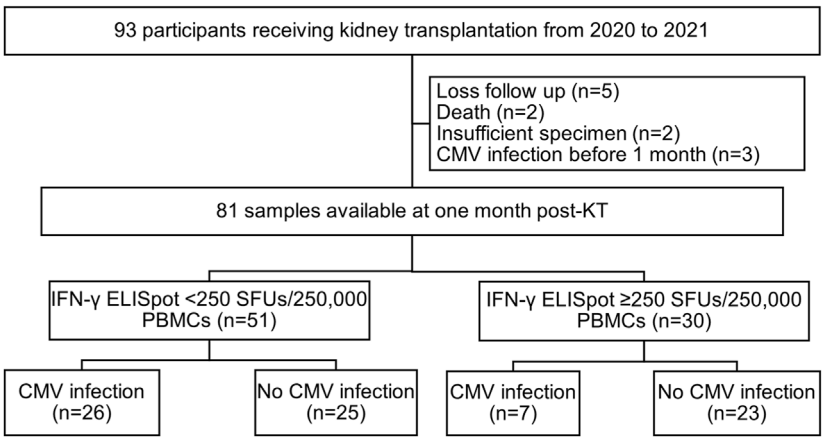


FIGURE 1 | Study flow chart. Abbreviations: KT, kidney transplantation; IFN-γ ELISpot, enzyme-linked immunosorbent spot assay for interferon-gamma; SFUs, spot-forming units; PBMCs, peripheral blood mononuclear cells.

immunosuppression rates were 93% for tacrolimus, 77% for mycophenolate mofetil, and 100% for prednisolone. Almost all participants (98.9%) carried CMV-seropositive status and underwent preemptive CMV DNA load monitoring for 3 months after the transplant. There was only one CMV-seromismatched participant who received ganciclovir prophylaxis for 2 weeks during the hospital stay and then switched to preemptive CMV DNA load monitoring to complete 3 months course. Three episodes of acute rejection occurred on days 6, 23, and 25 after KT.

CMV Infection

Among all 81 evaluable participants at 1 month post KT, 33 (41%) KT recipients developed CMV infection within 6 months post-transplant.

Nearly all CMV infection (30, 91%) were asymptomatic CMV DNAemia. The median (IQR) values of the first and peak CMV DNA load were 784 (223–2,334) and 1,934 (522–7,432) IU/mL. Three CMV diseases comprised one CMV syndrome and two CMV gastrointestinal diseases. The only one CMV-seronegative recipient receiving a CMV-seropositive graft developed CMV syndrome 70 days after transplantation. The patient was admitted and treated with intravenous ganciclovir induction for 1 month leading to clinical resolution and negative CMV viral load before discharge. The median (IQR) duration from transplant to CMV infection was 62 (41–90) days.

IFN-γ-Producing T Cells and Post-Transplant CMV Infection

The median (IQR) of absolute lymphocytes counts (ALC) before and 1 month after transplantation were 1,104 (861–1,442) and 1,133 (717–1,730) cells/mm^3, respectively ($p = 0.42$). The median (IQR) numbers of IFN-γ-producing T cells before and 1 month after transplantation were 763 (409–1,067) and 148 (54–389) SFUs/2.5 × 10^5 PBMCs, respectively ($p < 0.001$). The IFN-γ ELISpot of CMV-seromismatched participant were 395 SFUs/2.5 × 10^5 PBMCs before KT and 4 SFUs/2.5 × 10^5 PBMCs 1 month after KT.

The median (IQR) numbers of IFN-γ-producing T cells at 1-month post-transplant in the KT recipients with CMV infection is presented in **Figure 2**. Recipients with CMV infection developed significantly fewer IFN-γ-producing T cells than those without CMV infection (115 [33–237] vs. 238 [76–492] SFUs/2.5 × 10^5 PBMCs, $p = 0.019$).

The ROC curve analysis revealed that the IFN-γ ELISpot assay showed satisfactory test quality to discriminate between CMV infection and no CMV infection with an optimal cutoff value of 250 SFUs/2.5 × 10^5 PBMCs (AUC 0.65, sensitivity 50%, specificity 80.6%, positive predictive value 66%, negative predictive value 69%), as shown in **Table 2**. Baseline characteristics of KT recipients classified by IFN-γ ELISpot at 1 month post-transplant were shown in **Table 3**. Those with IFN-γ ELISpot <250 SFUs/2.5 × 10^5 PBMCs tend to receive more ATG for induction therapy (27.5%) compared to those with IFN-γ ELISpot ≥250 SFUs/2.5 × 10^5 (10%).

Factors Associated With CMV Reactivation

Cox proportional hazards model analyses were conducted to assess the clinical and immunological factors associated with CMV infection/reactivation within 6 months post-transplant (**Table 4**). IFN-γ ELISpot <250 SFUs/2.5 × 10^5 PBMCs was an independent determinant of CMV infection in both univariable and multivariable analyses.

On univariable analysis, the significant factors associated with CMV infection at 6 months post-transplant were pre-transplant PRA (HR 1.02, $p = 0.001$), ATG induction therapy (HR 3.04, 95% CI 1.53–6.06, $p = 0.002$), and IFN-γ ELISpot <250 SFUs/2.5 × 10^5 PBMCs (HR 3.30, 95% CI 1.36–8.03, $p = 0.008$). On multivariable analysis, IFN-γ ELISpot <250 SFUs/2.5 × 10^5 PBMCs was the only significant factor independently associated with CMV reactivation (HR 2.83, 95% CI 1.12–7.13, $p = 0.027$). Harrell's C value was 0.630 (95% CI 0.573–0.723) with a standard definition of CMV infection. The values increase as we raise

TABLE 1 | Baseline characteristics of the 93 kidney transplant recipients.

Characteristics	N (%) or mean ± SD
Female sex	38 (40.9)
Age (years)	44 ± 11
Comorbidities	
Hypertension	76 (81.7)
Diabetes mellitus	11 (11.8)
Hyperparathyroidism	29 (31.2)
HBV infection	4 (4.3)
Unknown	1 (1.1)
Transplant type	
DDKT	68 (73.1)
LRKT	25 (26.9)
BMI (kg/m^2)	22.6 ± 3.7
CMV serostatus	
D+/R+	88 (94.6)
D−/R+	2 (2.2)
D+/R−	1 (1)
D−/R−	0
Unknown donor CMV status/R+	2 (2.2)
Re-transplantation	7 (7.5)
HLA mismatch	
0	10 (10.8)
1–3	72 (77.4)
4–6	11 (11.8)
PRA (%)	
0–10	71 (76.3)
11–50	10 (10.8)
>50	12 (12.9)
Induction therapy	
Basiliximab	66 (70.9)
Anti-thymocyte globulin	22 (23.7)
None	5 (5.4)
Maintenance therapy	
Tacrolimus	86 (92.5)
Cyclosporine	7 (7.5)
Mycophenolate sodium	21 (22.6)
Mycophenolate mofetil	72 (77.4)
Prednisolone	93 (100)

Abbreviations: SD, standard deviation; HBV, hepatitis B virus; DDKT, deceased-donor kidney transplantation; LRKT, living-related kidney transplantation; BMI, body mass index; CMV, cytomegalovirus; D, donor; R, recipient; +, seropositive; –, seronegative; HLA, human leukocyte antigen; PRA, panel-reactive antibody.

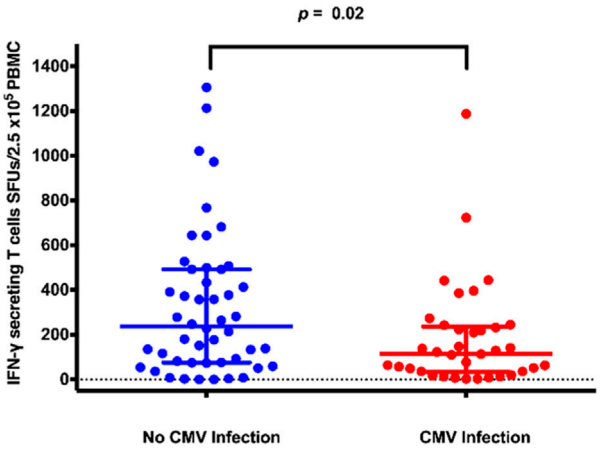


FIGURE 2 | IFN-γ ELISpot distribution plots for kidney transplant recipients with and without CMV infection. Abbreviations: IFN-γ, interferon-gamma; CMV, cytomegalovirus; IFN-γ ELISpot, enzyme-linked immunosorbent spot assay for interferon-gamma; SFUs, spot-forming units; PBMCs, peripheral blood mononuclear cells.

the thresholds to 2,000 and 3,000 copies/mL. The C values were 0.694 (95% CI 0.584–0.806) and 0.728 (95% CI 0.623–0.834), respectively.

The time to CMV infection stratified by IFN-γ ELISpot (<250 vs. ≥250 SFUs/2.5 × 10^5 PBMCs) was presented in **Figure 3** by a Kaplan-Meier curve (log-rank test < 0.05).

DISCUSSION

The present study prospectively evaluated non-specific CMI before and after receiving immunosuppressive drugs in KT recipients. IFN-γ-producing T cells after stimulation with PHA were quantified by the ELISpot assay. At a month post-transplant, a significant reduction in IFN-γ-producing T cell responses was observed among KT recipients. Low non-specific CMI, defined as <250 SFUs/2.5 × 10^5 PBMCs by ELISpot assay, was significantly associated with CMV infection after adjustment for a lymphocyte-depleting agent as induction therapy.

KT recipients are at risk of infection due to the complexities of immunosuppressive medications, instrumentation, and re-transplantation, as represented in our cohort [12]. Among opportunistic pathogens, herpesvirus and polyomavirus are predominant among KT recipients due to the pathogenesis of reactivation under an immunosuppressed state [5]. The significant association with CMV infection could be explained by the containment of this specific pathogen by T cells. The high prevalence of CMV seropositivity in our cohort allowed us to observe this relationship. This association was supported by several previous studies reported in the literature, in which a lack of innate or adaptive immunity was associated with an increased risk of CMV infection in SOT recipients [13–17].

For pathogen-specific immunity, CMV has been widely explored in previous studies. A lack of CMV-specific humoral immunity and CMI before and after transplantation was associated with CMV infection in KT recipients [18, 19]. Specifically, a lack of CMV intermediate early 1–specific CMI, defined as 40 IFN-γ spots/3 × 10^5 PBMCs at 2 weeks post-transplant, was correlated with CMV infection among KT recipients with basiliximab induction therapy. In the present study, non-specific IFN-γ-producing cells remained independently predictive of CMV infection in a cohort that was mainly composed of recipients with CMV-seropositive status. This finding may be explained by the underlying mechanism for how IFN-γ-producing cells contribute to protection against viral infections, especially the long-term control of viral infections [7, 20]. Immunosuppressants compromise this specific CMI, leading to loss of control and virus reactivation. Although a negative CMV-specific cell-

TABLE 2 | ROC curve analysis of IFN-γ ELISpot for distinguishing between CMV infection and no CMV infection.

IFN-γ ELISpot cutoff value (SFUs/2.5×10^5 PBMCs)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
234	50	75	59	67	65
240	50	78	62	68	66
244	50	81	66	69	68
255	48	81	65	68	67

Abbreviations: ROC, receiver operating characteristic; IFN-γ ELISpot, enzyme-linked immunosorbent spot assay for interferon-gamma; CMV, cytomegalovirus; SFUs, spot-forming units; PBMCs, peripheral blood mononuclear cells.
Area under the ROC curve = 0.65 (95% confidence interval 0.53–0.77).

TABLE 3 | Baseline characteristics of 81 evaluable kidney transplant recipients with IFN-γ ELISpot at 1 month post-transplant <250 or ≥250 SFUs/2.5 × 10^5 PBMCs.

Characteristics	IFN-γ ELISpot <250 SFUs/2.5 × 10^5 PBMCs *N* = 51 (%)	IFN-γ ELISpot ≥250 SFUs/2.5 × 10^5 PBMCs *N* = 30 (%)	*p*-value	Total (*N* = 81)
Female sex	22 (43.1)	12 (40.0)	0.78	34 (42.0)
Age (years)	45 ± 10	41 ± 11	0.07	44 ± 10
Comorbidities				
Hypertension	41 (80.4)	25 (83.3)	0.74	66 (81.5)
Diabetes mellitus	9 (17.6)	1 (3.3)	0.08	10 (12.3)
Hyperparathyroidism	17 (33.3)	8 (26.7)	0.53	27 (30.9)
Transplant type			0.66	
DDKT	38 (74.5)	21 (70)		59 (72.8)
LRKT	13 (25.5)	9 (30)		22 (27.2)
BMI (kg/m^2)	22.6 ± 3.6	22.1 ± 3.7	0.6	22.4 ± 3.6
CMV serostatus			0.49	
D+/R+	49 (96)	28 (93.4)		77 (95.1)
D−/R+	1 (2)	1 (3.3)		2 (2.5)
D+/R−	1 (2)	0 (0)		1 (1.2)
Unknown donor CMV status/R+	0 (0)	1 (3.3)		1 (1.2)
Re-transplantation	3 (5.9)	2 (6.7)	1.0	5 (6.2)
HLA mismatch			**0.01**	
0	2 (3.9)	7 (23.3)		9 (11.1)
1–3	41 (80.4)	22 (73.4)		63 (77.8)
4–6	8 (15.7)	1 (3.3)		9 (11.1)
PRA (%)			0.43	
0–10	38 (74.5)	26 (86.6)		64 (79)
11–50	6 (11.8)	2 (6.7)		8 (9.9)
>50	7 (13.7)	2 (6.7)		9 (11.1)
Induction therapy			0.12	
Basiliximab	35 (68.6)	24 (80)		59 (72.8)
Anti-thymocyte globulin	14 (27.5)	3 (10)		17 (21.0)
None	2 (3.9)	3 (10)		5 (6.2)
Maintenance therapy				
Tacrolimus	47 (92.2)	30 (100)	0.29	77 (95.1)
Cyclosporin	4 (7.8)	0 (0)	0.29	4 (4.9)
Mycophenolate sodium	13 (25.5)	6 (20)	0.57	19 (23.5)
Mycophenolate mofetil	38 (74.5)	24 (80)	0.57	62 (76.5)
Prednisolone	51 (100)	30 (100)	NA	81 (100)

Abbreviations: IFN-γ ELISpot, enzyme-linked immunosorbent spot assay for interferon-gamma; SFUs, spot-forming units; PBMCs, peripheral blood mononuclear cells; DDKT, deceased-donor kidney transplantation; LRKT, living-related kidney transplantation; BMI, body mass index; CMV, cytomegalovirus; D, donor; R, recipient; +, seropositive; –, seronegative; HLA, human leukocyte antigen; PRA, panel-reactive antibody.
Bold value Indicates the significant p-value <0.05.

mediated immunity (CMI) measured by QuantiFERON-CMV (QFT-CMV) assay at 1 month after immunosuppressant administration was associated with clinically significant CMV infection in non-transplant immunocompromised (systemic lupus erythematosus) patients with high CMV seroprevalence [21]. The utilization of CMV-specific CMI to predict the risk of infection among CMV-seropositive KT recipients remains to be elucidated and requires further exploration. At least a single time point of the use 1 month post-transplant QFT-CMV assays did not predict CMV DNAemia among KT recipients living in a high seroprevalence setting [22]. Therefore, we proposed that monitoring of overall (non-specific) CMI can better predict KT recipients at risk of CMV infection in the setting where CMV seropositivity is predominant [23].

TABLE 4 | Univariable and multivariable Cox proportional hazards model analyses of clinical and immunological factors associated with CMV reactivation after kidney transplantation.

Factors	Univariable analysis			Multivariable analysis		
	HR	(95% CI)	*p*-value	HR	(95% CI)	*p*-value
Female sex	0.87	(0.44–1.72)	0.697			
Age	1.03	(1.00–1.06)	0.095	1.00	(0.97–1.04)	0.830
BMI	1.06	(0.97–1.16)	0.171			
Hypertension	2.42	(0.74–7.92)	0.143			
Diabetes mellitus	1.38	(0.53–3.56)	0.505			
Hyperparathyroidism	1.12	(0.55–2.29)	0.753			
DDKT	2.09	(0.87–5.05)	0.099	1.65	(0.64–4.25)	0.303
Re-transplantation	0.98	(0.24–4.09)	0.979			
HLA mismatch	0.99	(0.76–1.28)	0.923			
PRA	1.02	(1.01–1.03)	0.001	1.01	(0.99–1.02)	0.538
ATG induction therapy	3.04	(1.53–6.06)	0.002	1.65	(0.42–6.53)	0.472
ALC at 1 month post-transplant ≤500 cells/mm^3	1.93	(0.84–4.43)	0.119			
IFN-γ ELISpot at 1 month post-transplant <250 SFUs/2.5 × 10^5 PBMCs	3.30	(1.36–8.03)	0.008	2.83	(1.12–7.13)	0.027

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; DDKT, deceased-donor kidney transplantation; HLA, human leukocyte antigen; PRA, panel-reactive antibody; ATG, anti-thymocyte globulin; ALC, absolute lymphocyte count; IFN-γ ELISpot, enzyme-linked immunosorbent spot assay for interferon-gamma; SFUs, spot-forming units; PBMCs, peripheral blood mononuclear cells.

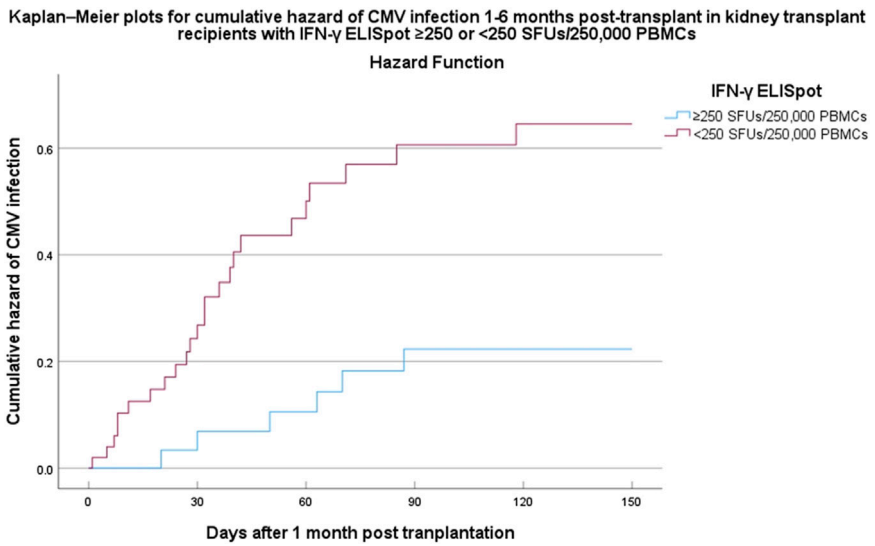


FIGURE 3 | Kaplan–Meier plots for cumulative incidence of CMV infection within 6 months post-transplant in kidney transplant recipients with IFN-γ ELISpot ≥250 or <250 SFUs/2.5 × 10^5 PBMCs. Abbreviations: CMV, cytomegalovirus; IFN-γ ELISpot, enzyme-linked immunosorbent spot assay for interferon-gamma; SFUs, spot-forming units; PBMCs, peripheral blood mononuclear cells; HR, hazard ratio; CI, confidence interval.

IFN-γ is an important cytokine synthesized by natural killer cells, CD4 T_H1 cells, and CD8 cytotoxic lymphocytes of the immune system in response to mitogenic and antigenic stimuli. IFN-γ plays a crucial role in antimicrobial and antiviral immunity [7]. There are several tools to measure the state of immunity in immunocompromised individuals. Virus-specific CMI can be measured by enzyme-linked immunosorbent assay (ELISA), ELISpot assay, or intracellular cytokine staining. Indeed, a lack of CMV-specific IFN-γ -producing T cell responses measured by ELISA, ELISpot, or intracellular cytokine assay was shown to be associated with CMV infection in SOT recipients. We demonstrated that IFN-γ ELISpot response to PHA in KT recipients at 1-month post-transplant was an independent biomarker predictive of CMV reactivation. The IFN-γ ELISpot assay is the positive control part of a commercially available and standardized TB-specific ELISpot assay, and can be routinely performed in a clinical laboratory. IFN-γ was shown to be predictive of acute allograft rejection in a previous study [24]. However, another study found that donor-specific IFN-γ ELISpot was not predictive of allograft loss [25]. The ELISpot assay has an advantage over other assays by measuring extracellular IFN-γ, which is believed to be more functional than measurement of intracellular components. Furthermore, a washing step that is unique to the ELISpot assay procedure may remove pre-existing

IFN-γ and other potential substances that could interfere with the results. International guidelines have encouraged the use of these tools to guide clinicians when treating and offering prevention strategies to SOT recipients [10, 11].

Several studies have investigated the role of non-pathogen-specific CMI in predicting the occurrence of CMV infection after transplantation. Immuknow assay, a commercially available assay, which provides an assessment of global cell-mediated immune responses revealed that those with impaired CD4 T cell responses were likely to develop significantly more CMV disease [16]. QuantiFERON monitor assay revealed that IFN-γ in solid organ (including kidney) transplant recipients at 1-month post-transplant was significantly lower in those with CMV disease [26]. Those findings were similar with our study which utilized different global immunity monitoring technique.

On the other way, a simple and practical way to indirectly measure non-specific CMI could be obtained from absolute lymphocyte count (ALC). Lymphopenia with an absolute lymphocyte count of <610 cells/mm^3 was correlated with an elevated risk of CMV reactivation in SOT recipients [27]. Severe lymphopenia (defined as ALC <500 cells/mm^3) during pretransplant [15] and early post-transplant periods [17] was an independent risk factor for CMV disease and early CMV infection, respectively. However, we did not observe an increased risk of post-transplant CMV reactivation in KT recipients with an ALC of ≤500 cells/mm^3. We believe being able to assess CMI function may possibly be a better option to stratify CMV risk in SOT population with CMV seropositivity.

The present study has several limitations. The small sample size and the relatively high proportion of dropouts at 1 month post-transplant were inadvertently aggravated by the COVID-19 pandemic. Only one case of CMV-seronegative recipient receiving a CMV-seropositive graft was recruited in our study. Thus, the correlation between non-specific IFN-γ ELISpot and CMV infection cannot be extrapolated to this transplant subpopulation. The statistically significant differences may not be translated into clinical practice because a quarter of participants with high non-specific CMI still developed CMV infection in our study. Furthermore, many recipients with CMV viral load above institutional threshold were not given antiviral therapy. Decreased immunosuppressive therapy led to resolution of CMV DNAemia in these patients. As a result, non-specific IFN-γ-producing cells should be further assessed in a larger cohort with a longer follow-up duration. The test could also have limited clinical utility because it is technically complicated and not available in a resource-limited diagnostic laboratory. However, we have demonstrated the potential role of overall immune monitoring in predicting CMV infection by the ELISpot assay in KT recipients with profound immunosuppression.

In conclusion, an intact overall net state of CMI in KT recipients early after transplantation is a protective factor against post-transplant CMV infection within the first few months. KT recipients with a low IFN-γ response are more likely to develop CMV infection. Therefore, measurement of non-specific CMI responses using the ELISpot assay could potentially stratify KT recipients at risk of CMV reactivation. Clinicians should be able to design prevention strategies, either by preemptive approaches or prophylaxis, based on the actual immune status in individual recipients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study protocol was approved by the Human Research Ethics Committee of Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (approval number: COA.MURA2020/1983). All patients signed an informed consent form before enrolment in the study. The study was registered in the Thai Clinical Trials Registry (TCTR20210216004).

AUTHOR CONTRIBUTIONS

Research design: WN and JB. Writing of the paper: WN and JB. Performing the research: WN, SK, and JB. Data analysis: WN and JB. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Cytomegalovirus Cell-Mediated Immunity: Ready for Routine Use?

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Utilizing assays that assess specific T-cell-mediated immunity against cytomegalovirus (CMV) holds the potential to enhance personalized strategies aimed at preventing and treating CMV in organ transplantation. This includes improved risk stratification during transplantation compared to relying solely on CMV serostatus, as well as determining the optimal duration of antiviral prophylaxis, deciding on antiviral therapy when asymptomatic replication occurs, and estimating the risk of recurrence. In this review, we initially provide an overlook of the current concepts into the immune control of CMV after transplantation. We then summarize the existent literature on the clinical experience of the use of immune monitoring in organ transplantation, with a particular interest on the outcomes of interventional trials. Current evidence indicates that cell-mediated immune assays are helpful in identifying patients at low risk for replication for whom preventive measures against CMV can be safely withheld. As more data accumulates from these and other clinical scenarios, it is foreseeable that these assays will likely become part of the routine clinical practice in organ transplantation.

Keywords: immune monitoring, cytomegalovirus management, innate immunity, preventive strategies, antiviral prophylaxis

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INTRODUCTION

Despite the implementation of effective antiviral therapies and sensitive molecular diagnostic assays, cytomegalovirus (CMV) infection remains as a major complication after solid organ transplantation (SOT), threatening both graft function and survival [1].

While relevant advances have been made in the understanding of the immunobiology of CMV infection in the context of organ transplantation, little translation to clinical practice has been done so far. In this regard, the T-cell arm of adaptive immunity (hereafter cell-mediated immunity [CMI]), especially CMV-specific $CD4^+$ and $CD8^+$ T lymphocytes, has been well-recognized as a major immune mechanism driving antiviral control [2, 3]. Robust evidence has showed a close association between CMV-CMI and the risk of developing CMV infection in different transplant settings [4–6]. Yet, current immune-risk stratification of CMV infection relies on the serological mismatch between donors and recipients, based on the premise that seronegative recipients receiving a seropositive graft (D+/R−) are

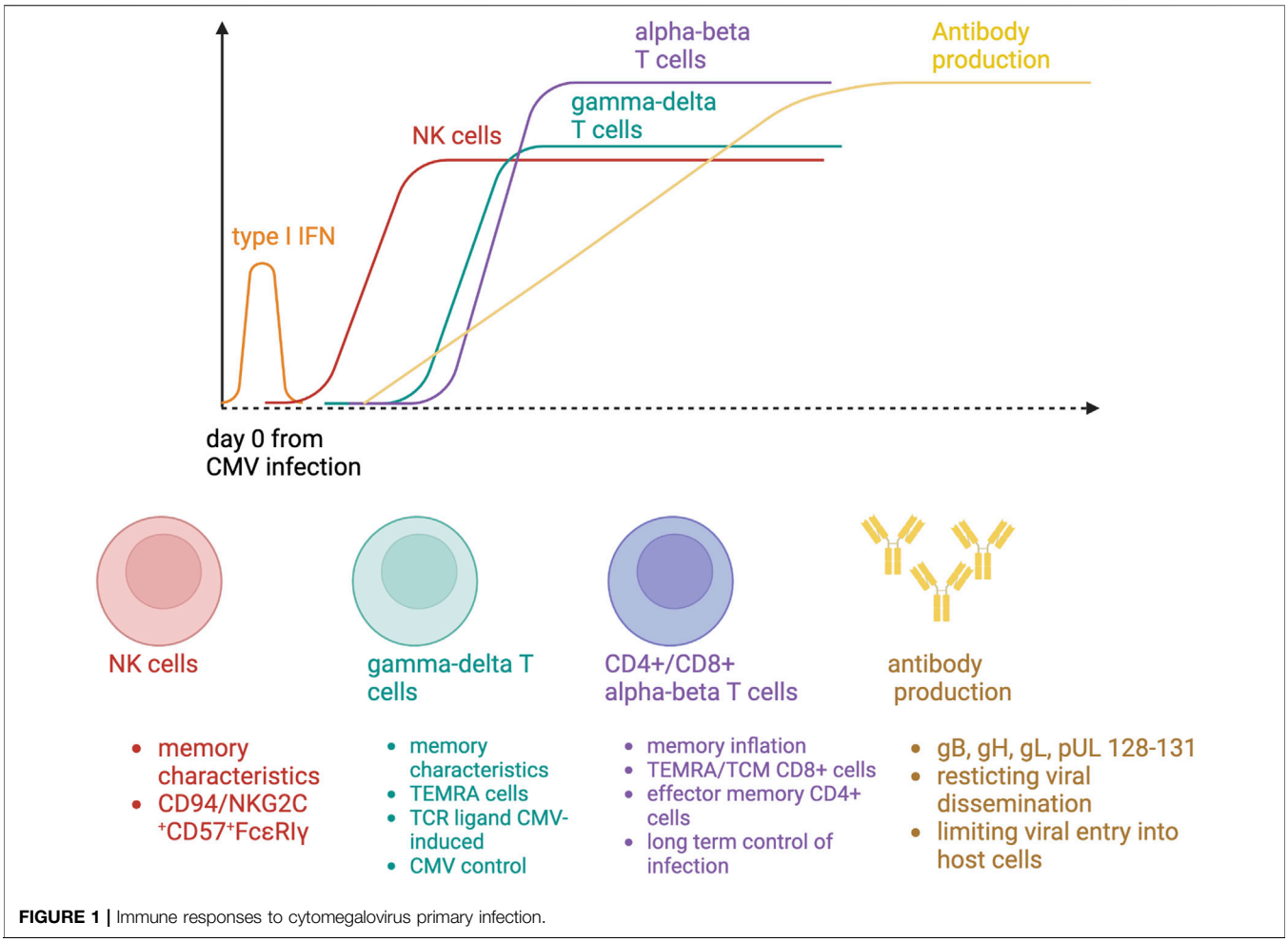

FIGURE 1 | Immune responses to cytomegalovirus primary infection.

at the highest risk of developing primary CMV infection due to their *naïve* immune status, whereas seropositive patients (R+) receiving seropositive grafts are at an intermediate risk because of previous viral immunization which should provide sufficient protection against viral replication [7]. While such paradigm has helped to predict the advent of CMV infection, this approach encompasses important limitations as a proportion of R+ individuals may unpredictably develop CMV replication and also because of the widespread use of T-cell depleting therapies that convert previously immunized patients into *naïve* individuals against CMV [8]. To minimize the development of CMV infection, the use of universal antiviral prophylaxis or preemptive assessment of viral replication are the two main preventive strategies used [7]. However, either approach is far from being accurate as they do not personalize the type and duration of such preventive strategies, since the dynamic immune status specific to CMV is not being considered.

Recently, novel immune assays have been used in transplantation showing their capacity to accurately measure CMV-CMI [4, 7]. While interesting clinical associations have been reported between CMV-CMI and the risk of CMV infection after transplant, the different methodological nature of these assays -which provide diverse biological insight on functionality of immune responses-, the so far limited data coming from clinical trials, as well as the distinct clinical transplant settings evaluated, makes it difficult to establish robust conclusions on how to implement these new technologies into clinical practice with the aim of improving transplant outcomes.

In this review, we first summarize the main mechanisms involved in the immunobiology of CMV in transplantation, to then address the major advances made with the assessment of CMV-CMI using different immune-monitoring assays as well as the major drawbacks currently limiting the implementation of these assays.

IMMUNOBIOLOGY OF CYTOMEGALOVIRUS INFECTION

CMV infection in SOT recipients results from primoinfection or reactivation. In these two situations, a complex multi layered cell response is required to inhibit CMV dissemination [9]. Five main cell types have been studied during CMV infection, three belonging to adaptive immunity (in particular $CD8^+$ and

$CD4^+$ T cells, and to a lesser extent the B cells) (**Figure 1**). Importantly, some patients do not develop CMV disease despite the absence of any CMV-specific $CD8^+$ and $CD4^+$ T cells, suggesting that other actors belonging to innate immunity (such as NK and γδ cells) could also be necessary for CMV control.

NK Cells

The monitoring of NK cells can be easily performed by flow cytometry with the following fluorochrome-coupled specific antibodies: CD3, CD16, CD56, NKG2C, CD57. In human, NK cell deficiency is associated with severe herpes viral infections, such as CMV [10]. Healthy human individuals with a history of CMV infection have an expanded population of NK cells expressing the activating CD94/NKG2C receptor [11]. In kidney transplant recipients, the number of circulating NK cell is correlated with NK cell-mediated cytotoxicity during CMV infection [12]. CMV R+ patients had preexisting memory-like NK cells ($NKG2C^+CD57^+Fc\varepsilon RI\gamma^-$) at baseline and a subset of pre-memory-like NK cells ($NKG2C^+CD57^+Fc\varepsilon RI\gamma^{low\text{-}dim}$) increases during CMV DNAemia. These cells expressed a higher cytotoxic profile than preexisting memory-like NK cells at the acute phase. At later phases of viremia, a subsequent accumulation of new memory-like NK cells has been reported [13]. NK cell clonal expansion is observed after CMV infection, leading to the development of immunological memory, two features belonging to an adaptive immune response. NK cell reactivity against CMV-infected cells results from a balance governed by the activation of receptors that sense alterations in the expression of ligands on the surface of CMV-infected cells. An increase in NK activating receptors could confer to the host a better protection against CMV infection.

γδ T Cells

In humans, γδ T cells are divided into two main subsets, based on their γ and δ T-cell receptor (TCR) chain expression: 1) the Vγ9Vδ2 γδT cells, expressing a δ2 chain, and 2) the non-Vγ9Vδ2 γδT cells. Initially, the involvement of non-Vγ9Vδ2 γδ T cells in the anti-CMV response was identified in the context of SOT or stem-cell transplantation. Five major observations suggest that non-Vγ9Vδ2 γδ T cells respond specifically to CMV:

- A longitudinal expansion of non-Vγ9Vδ2 γδ T cells is specifically observed in the peripheral blood of SOT recipients undergoing CMV infection [14, 15].
- CMV infection induces a restricted repertoire of non-Vγ9Vδ2 γδ T cells, suggesting an antigen-driven clonal selection [16].
- Non-Vγ9Vδ2 γδ T cells are poised for effector (particularly cytotoxic). During the course of CMV infection, non-Vγ9Vδ2 γδ T cells switch from a mainly naive phenotype ($CD27^+CD45RA^+$) towards a terminally differentiated effector memory (TEMRA) phenotype ($CD27^-CD45RA^+$), with the same kinetics than CMV-specific αβ T cells [17].
- The non-Vγ9Vδ2 T cell clones or cell lines can inhibit CMV dissemination and kill CMV-infected cells, *in vitro* [18]. Moreover, non-Vγ9Vδ2 γδ T cell expansion is associated with recovery from CMV infection without recurrence [15].
- Non-Vγ9Vδ2 T cells recognize native antigens, which are expressed at the cell surface during stress conditions (for instance CMV infection) such as reactive oxygen species (ROS) production, or AMP-activated protein kinase (AMPK)-dependent metabolic reprogramming. One example of CMV-induced γδ TCRs ligands is Annexin A2 [19].

Gamma-delta T cells can be easily monitored in clinical routine thanks to flow cytometry using a commercially available kit gathering fluorochrome coupled specific antibodies for CD45, CD3, Vδ2 and PAN-δ.

B Cells

While the advent of long-lasting humoral immunity toward a primary viral infection is universally accepted, the contribution of antibodies for protection against and control of CMV replication in transplant recipients is still a matter of debate. Data coming from experimental models suggest a key role of B cells through CMV-specific antibody release, particularly in restricting viral dissemination and in limiting disease severity [20, 21]. CMV-specific neutralizing antibodies appear during the first 4 weeks after primary infection and are mainly directed against CMV glycoprotein B, but also H, L, and pUL128-131, all of them involved in cell attachment, penetration, and fusion of the viral envelope to the cell membrane of the host [22]. The association shown between the former use of CMV-specific immunoglobulins as prophylaxis and better outcomes among liver transplant recipients also suggests to some extend a protective role of humoral immunity against viral replication [23].

Notably, in clinical transplantation, some R+ transplant individuals remain at high risk of CMV infection despite detectable humoral immunity, suggesting either a low avidity or poor neutralizing activity of the antibody response. Post-transplant IgM and IgG antibody seroconversion has been shown not to be a reliable predictor of CMV disease [24]. Furthermore, some of D+/R− patients (20%–30%) do not develop CMV infection after transplantation, suggesting either an optimal antibody seroconversion early after transplantation or the presence of preformed CMV-specific memory B cells prior to transplantation even though undetectable circulating CMV-specific IgG antibodies [25].

CMV-Specific $CD8^+$ T Cells

During primary infection, CMV-specific $CD8^+$ T cells exhibit an antigen-driven early-differentiating phenotype ($CD27^+CD28^+$ $CD45RO^+CD45RA^-$) armed for cytotoxicity [26, 27]. After viral clearance in healthy CMV R+ individuals, CMV-specific $CD8^+$ T cells can represent up to 10% of the memory $CD8^+$ lymphocyte pool, a process described as memory inflation [28]. There are two main subsets of CMV-specific $CD8^+$ T cells: a) a central memory cell population ($CD27^+$ $CD28^-$ $CD45RO^+$) with low cytotoxic potential but high proliferation ability, and b) a TEMRA cell population, representing up to 75% of CMV-specific

$CD8^+$ T cells ($CD27^-$ $CD28^-$ $CD45RA^+$), with a low proliferation ability but a major cytotoxic potential. TEMRA cells are resupplied from central memory cells and *naive* precursors.

During primary infection, the CMV-specific $CD8^+$ T cell population is polyclonal. On the opposite, few epitope-specific clones are predominant at the chronic phase. More than half of individuals have $CD8^+$ T cell recognizing CMV peptides from the three following open reading frames (UL48, UL83, UL123). UL123 (immediate-early [IE]-1)-specific $CD8^+$ T cells are associated with less CMV reactivation in SOT recipients, likely because UL123 is the first CMV protein to be expressed in infected cells. *In vitro*, CMV-specific $CD8^+$ T cells can kill autologous CMV-infected cells and inhibit CMV dissemination. In mouse models, late effector $CD8^+$ T cells maintain long-term control of viral replication [29].

CMV-Specific $CD4^+$ T Cells

After a primary infection in SOT recipients, CMV-specific $CD4^+$ T cells can be detected 1 week after the occurrence of CMV DNAemia [30], more specifically those $CD4^+$ CD28-granzyme B+ cells [30, 31]. At the chronic phase of infection after viral clearance, CMV-specific $CD4^+$ T cells represent up to 9% of the memory T lymphocyte pool. They exhibit an effector memory phenotype ($CD27^-$ $CD28^-$ $CD45RA^-$). More than half of individuals have $CD4^+$ T cells recognizing CMV peptides transcribed from the five following open reading frames (UL55, UL83, UL86, UL99, UL122). $CD4^+$ T cells play a central role in anti-CMV immunity by clearing cells loaded with CMV peptides, helping B cells to mount a specific humoral response against viral antigens and $CD8^+$ T cells to perform their effector functions [32].

Immunosuppressive Therapy and CMV Immune Response

CMV-CMI is abrogated for one to 3 months after anti thymocyte globulin induction [8] and reduced in patients having received high-dose steroids [33]. Rejection is usually treated by these two drugs and is therefore a risk factor for CMV disease [34, 35]. *In vitro*, tacrolimus is a potent inhibitor of CMV-specific cytokines release [36], and completely inhibits activation and proliferation of CMV-specific T cells [37]. On the opposite, belatacept demonstrated minimal inhibitory effects on CMV-specific T cells likely because of an absence of effect on cells lacking CD28 [36, 37]. While the antiviral immune response against CMV measured *in vitro* appears preserved under belatacept [38], high-risk belatacept-treated recipients show defects in sustaining CMV control [39], and exhibit high incidence of atypical life-threatening CMV diseases [40]. Further research is needed to elucidate this gap. Finally, a dysfunctional T-cell profile (with high PD1, low CD85j expression) has been observed in CMV-infected patients receiving mycophenolic acid. On the contrary, everolimus can improve T-cell fitness and transform dysfunctional into functional cells, along with better control of CMV [41]. In summary, the analysis of these five cells types could be useful for transplant physicians to understand the impact of the immunosuppressive regimen on CMV-specific T response.

OBSERVATIONAL DATA ON THE CLINICAL APPLICATION OF CMV IMMUNE-MONITORING

A growing number of observational studies have assessed in recent years the clinical usefulness of CMV-CMI monitoring to guide patient management in different SOT populations [42]. This research mainly includes single-center studies—with some multicenter experiences [8, 33, 43–47]— and has been performed in a wide range of clinical risk scenarios (**Table 1**). The most common methodologies used for the measurement of CMV-CMI is the reference technique of intracellular cytokine staining (ICS) by flow cytometry [42, 44, 45, 59, 61, 62, 67–71] and the different platforms for interferon (IFN)-γ release assay (IGRA) [4, 43, 46–56, 60, 63, 65, 66, 72–75]. Out of these immune assays, only three are currently commercially available: the quantiFERON®-CMV (QTF-CMV) (Qiagen, Hilden; Germany), the T-SPOT®.CMV (Oxford Immunotec, Abingdon, United Kingdom) and the T-Track®CMV (Mikrogen, Neuried, Germany). Available experience with the major histocompatibility complex (MHC)-tetramer staining method is more limited [64], whereas a few studies have compared the diagnostic accuracy of different approaches [54, 57, 76]. In most cases the primary study outcome is any CMV viremia, regardless of the presence or absence of symptoms or the level of DNAemia, or less often clinically significant viremia requiring antiviral therapy [46]. Since R+ patients typically have a low incidence of CMV disease [77, 78], the few studies that have primarily investigated the role of CMV-CMI monitoring to predict the occurrence of symptomatic infection (viral syndrome or end-organ disease) are focused on the high-risk group D+/R− patients [43, 48, 58]. Notably each platform has different readouts that are directly related to the nature of each immune assay. In general, all assays measure T-cell mediated effector immune responses of IFN-ɣ production in response to two main immunogenic CMV antigens, phosphoprotein 65 (pp65) and IE-1 [79]. Importantly, while ELISA-based assays do not provide the individual response to each CMV antigen, flow-cytometry and ELISpot-based assays do deliver such the specific immunes, thus better illustrating the global burden of immune responses against CMV.

As shown in **Table 1**, the available literature is not equally distributed across the different clinical scenarios involved. One of the most immediate applications of CMV-CMI monitoring is the individualization of the length of prophylaxis. Rather than the fixed-duration regimen of 3–6 months of valganciclovir—up to 12 months for lung transplant recipients—recommended by the current guidelines for high-risk patients [7, 80], the knowledge of the CMV-CMI functionality would allow for prematurely discontinuing prophylaxis in patients that have mounted a protective response, or prolonging it beyond the standard schedule in the presence of a negative (non-reactive) assay result. Manuel et al. provided early data on the usefulness of the QTF-CMV assay in a multicenter cohort of 127 D+/R− patients. The presence of a positive (reactive) assay at the end of valganciclovir prophylaxis was associated with a lower 12 months incidence of CMV disease as compared to negative or indeterminate results (6.4% versus 22.2%, respectively;

TABLE 1 | Summary of observational studies assessing the potential application of CMV-CMI monitoring in different clinical scenarios.

Clinical scenario	Predicted event	Supporting studies	Monitoring method	Proposed intervention
High-risk patients (D+/R–, T-cell-depleting antibodies, lung transplantation) during antiviral prophylaxis or at the time of discontinuation	Late-onset disease[a]	Yes [43, 46, 48–58]	QTF-CMV, ELISpot	Prolong antiviral prophylaxis or close monitoring for viremia if inadequate response
Pre-transplant assessment in intermediate-risk patients (R+ with no other factors)	Post-transplant viremia and/or disease	Yes [4, 44, 47, 51, 59, 60]	QTF-CMV, ELISpot, ICS	Initiate antiviral prophylaxis or close monitoring for viremia in patients with inadequate response ($D+/R_{NR}$)
Intermediate-risk patients (R+) on preemptive therapy with no concurrent viremia	Subsequent viremia and/or disease	Yes [42, 44, 49, 51, 52, 61–64]	ICS, QTF-CMV, ELISpot, MHC-tetramer staining	Reduce the frequency and/or discontinue monitoring of viremia if adequate response
Intermediate-risk patients (R+) on preemptive therapy with asymptomatic viremia	Spontaneous clearance	Yes [65, 66]	QTF-CMV	Withhold antiviral therapy if adequate response
Active CMV infection or disease during antiviral treatment	Response to antiviral treatment	No		Decrease immunosuppression and/or modify antivirals if inadequate response
Active CMV infection or disease after discontinuation of antiviral treatment	Post-treatment relapse	Yes [67]	ICS	Initiate secondary prophylaxis if inadequate response
Acute graft rejection treated with steroid boluses and/or T-cell-depleting antibodies	Disease following anti-rejection therapy	No		(Re)initiate prophylaxis if inadequate response

CMV, cytomegalovirus; D, donor; ELISpot, enzyme-linked immunosorbent spot assay; ICS, intracellular cytokine staining; QTF-CMV, QuantiFERON-CMV assay; MHC, major histocompatibility complex; R, recipient.

[a]*Refers to the occurrence of CMV, disease after discontinuing antiviral prophylaxis with ganciclovir or valganciclovir (usually administered for 100–200 days).*

p-value < 0.001), yielding a positive predictive value (PPV) for immune protection of 90% (95% confidence interval [95% CI]: 74–98). Interestingly, those patients with an indeterminate QTF-CMV result—suggestive of a profoundly abrogated immunity or absence of CMV peptide recognition—had the highest incidence of late disease [43]. These findings have been subsequently confirmed in different SOT populations [53, 57, 75]. On the other hand, a recent study has suggested that the predictive accuracy in this clinical scenario of commercially available ELISpot assays is superior of that of the QTF-CMV assay [57]. A similar conclusion may be drawn from a meta-analysis in kidney transplant recipients [81]. The next natural step is to apply this evidence to the clinical decision-making process. In addition to the interventional studies reviewed in the next section, a retrospective study in lung transplant recipients reported a lower incidence of high-level CMV replication by using a QTF-CMV-guided strategy of extended valganciclovir prophylaxis (5–11 months) as compared to a fixed 5 months regimen (43.1% versus 60.3%, respectively; *p*-value < 0.001) [55]. These results were replicated using the T-SPOT®.CMV in a distinct cohort of R+ lung transplant recipients [82].

Although the ability of the QTF-CMV assay to stratify the risk of late CMV disease following the discontinuation of prophylaxis has been demonstrated for the D+/R– constellation, some studies restricted to R+ kidney transplant recipients receiving T-cell-depleting induction therapy (ATG) [54] or R+ lung transplant recipients [56] failed to find significant differences in the occurrence of viral reactivation between patients with reactive or non-reactive results. It has been proposed that the diagnostic accuracy of the QTF-CMV assay to predict protection from low-level infection among R+ patients might be improved by increasing the threshold for IFN-γ production used to define a positive result [54]. In addition, more sensitive techniques not restricted to $CD8^+$ T-cell responses, such as ICS by flow cytometry and ELISpot-based assays, would perform better in this scenario, at the expense of being more time-consuming and costly [83].

The predominant population of R+ seropositive SOT recipients without ATG has been traditionally considered as an intermediate risk for CMV events, and either preemptive therapy or antiviral prophylaxis are recommended as prevention methods [7, 80]. A major contribution of the strategies for measuring the CMV-CMI has been the identification of a subgroup of R+ patients that lacks or displays very weak effective T-cell-mediated responses against CMV at the pre-transplant evaluation (non-reactive recipients [R_{NR}]) despite their positive anti-CMV IgG serological status. The proportion of R+ patients with no detectable baseline CMV-CMI has been estimated at about 20%–30% [44, 59, 60, 84, 85]. From a functional perspective, these patients should be considered closer to the seronegative recipients (R–) than to the so-called intermediate-risk (R+) group, which would result in a higher susceptibility to post-transplant infection if they receive an organ from a seropositive donor [25]. In a study in kidney and lung transplant recipients, Cantisán et al. found that $D+/R_{NR}$ patients faced a markedly increased risk of CMV replication as compared to R+ patients with a positive (reactive) pre-transplant QTF-CMV assay (adjusted odds ratio [OR]: 10.49; 95% CI: 1.88–58.46) [60]. Comparable results have been obtained with the ICS technique [44, 59] or an ELISpot assay [51, 85]. An early assessment at post-transplant day 15 provides a predictive capacity significantly higher than at the pre-transplant evaluation since some transplant recipients with robust preformed CMV-CMI may significantly decrease their functional CMV-CMI after induction immunosuppression therapy, even in absence of ATG [44]. In this regard and unlike the QTF-CMV assay, the knowledge of the specific CMV-CMI against each individual CMV antigen that is

TABLE 2 | Other immunological approaches proposed within the risk assessment for post-transplant CMV infection.

Immunological biomarker	Rationale	Diagnostic performance, advantages and limitations	Selected studies
Serum immunoglobulin levels	Severe IgG HGG (usually defined by the threshold of <400–500 mg/dL) as a quantitative surrogate of the humoral immune response	Easily available and economical (nephelometry). Potentially reversible by IVIg/SCIg replacement therapy. Lack of specificity for CMV infection risk	[92, 93]
Total lymphocyte count	Lymphopenia (usually defined by the threshold of <0.5–0.75 × 10^3 cells/μL) as a quantitative surrogate of the T-cell-mediated immune response	Easily available and economical. Lack of specificity for CMV infection risk	[94–97]
Peripheral blood lymphocyte subpopulations	Enumeration of peripheral blood $CD4^+$ and $CD8^+$ T-cell counts at different post-transplant time points by automated flow cytometry	Less time- and labor-consuming than CMV-CMI monitoring. Lack of specificity for CMV infection risk. Simultaneous risk assessment for other opportunistic infections. Of particular usefulness in patients receiving T-cell-depleting agents	[98, 99]
SNP in genes orchestrating innate and adaptive responses (pattern recognition receptors and interferons)	Protective effect associated to SNPs within *TLR9* and *IFNL3* genes. Risk-conferring effect associated to SNPs within *TLR2, MBL2, DC-SIGN, IL10* and *IFNG* genes	Attempts of polygenic risk scores (lacking external validation). Modest risk modification effect attributable to a given SNP. Lack of dedicated GWAS studies	[100–104]
Intracellular ATP production in $CD4^+$ T-cells	Quantification of intracellular ATP release in $CD4^+$ T-cells stimulated with a potent non-specific mitogen (phytohemagglutinin A), which would provide an overall functional evaluation of T-cell-mediated immunity	FDA-approved commercial assay (ImmuKnow®, Cylex). Lack of validated cut-off values to predict CMV infection. Time- and labor-consuming. Potentially affected by sample storage time	[56, 105]

ATP, adenosine triphosphate; CMV, cytomegalovirus; CMVCMI, cytomegalovirus-specific cell-mediated immunity; FDA, food and drug administration; GWAS, genomed-wide association study; HGG, hypogammaglobulinemia; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin; SNP, single-nucleotide polymorphism.

provided by ELISpot-based assays, may further help to better stratify patients according to three distinct immunological risks, this is, at low, high, and at intermediate risk if one response against one of the two antigen is absent or very low [33]. Some factors have been reported to be associated with the absence of QTF-CMV reactivity among R+ SOT candidates such as profound lymphopenia, younger age, the type of organ to be transplanted, presence of certain recipient HLA genotypes and of non-HLA-A1/non-HLA-A2 alleles [84]. The latter finding is not unexpected as the presentation to the $CD8^+$ T-cells of the viral epitopes contained in the "antigen tube" of the assay is restricted through some HLA class I alleles [86, 87].

Finally, some studies have been conducted to investigate the usefulness of post-transplant CMV-CMI monitoring among intermediate-risk recipients preemptively managed to predict protection against the development of CMV infection or, once established, the capacity of spontaneous clearance of viremia [42, 44, 49, 51, 52, 61–66]. These results pointed to the predominance of $CD8^+$ T-cells in the early response to primary infection—or re-infection in the D+/R+ constellation—and $CD4^+$ T-cells in the long-term control of latent infection [42, 44, 61]. The assessment of CMV-CMI at the onset of asymptomatic CMV viremia may be also useful to discern the patients that will spontaneously clear the infection from those who would eventually benefit from preemptive therapy. By applying the cut-off value for QTF-CMV positivity of ≥0.2 IU/mL of IFN-γ, Lisboa et al. reported a sensitivity and specificity in this clinical scenario of 82.8% and 75.0%, respectively, yielding a negative predictive value to predict virologic and/or clinical progression of asymptomatic viremia of 54.5% and a PPV of 90.9% to predict spontaneous clearance [65].

Few observational studies have also explored the role innate cells (NK and Non-Vγ9Vδ2 γδT cells) in different scenarios. For instance, pretransplant peripheral blood NKG2C+ NKG2A- NK cells could protect from CMV infection in kidney transplant recipients independently of the presence of CMV-specific T cells [88]. The NKG2C+ NK cell proportion in the bronchoalveolar lavage could also be a relevant biomarker for assessing risk of subsequent CMV viremia in lung transplant recipients [89]. During acute CMV infection, the NKG2C+ NK cells proliferate, become NKG2C(hi), and finally acquire CD57, a marker of "memory" NK cells that have been expanded in response to infection [90]. During CMV disease, non-Vγ9Vδ2 γδT cells expansion was correlated to the resolution of CMV infection and the emergence of CMV resistance in kidney transplant recipients, but more importantly was able to predict the absence of recurrence [15, 91]. A prospective clinical trial is ongoing to confirm this last finding (SPARCKLING study: NCT03339661).

Finally, as a complement to the assessment of the functionality of the CMV-specific T-cell response, other immunological biomarkers have been proposed to improve the process of risk stratification in the SOT population. This includes the assessment of antibodies targeting the pentameric complex (gH/gL/pUL128/pUL130/pUL131A), post-transplant hypogammaglobulinemia, absolute counts of total lymphocytes or peripheral blood subpopulations, as well as genetic markers. A detailed account of the advantage and limitations of these assays is summarized in **Table 2**.

TABLE 3 | Summary of the intervention studies on the application of CMV-CMI assays in SOT recipients.

Study author	Number of patients	Type of organ transplant	CMV serostatus	Cell-mediated immune assay	Intervention	Main results
[106]	118	Lung	R+ and D+/R–	QTF-CMV	Test at 5, 8 and 11 months, stop prophylaxis if test positive	Lower CMV replication in the allograft and longer duration of antiviral prophylaxis in the intervention group
[107]	150	Kidney	R+ on ATG	QTF-CMV	Test at 30, 45, 60, 90 days, stop prophylaxis if test positive	Similar incidence of CMV replication/disease, shorter duration of antiviral, lower incidence of neutropenia in the intervention group
[108]	185	Kidney (164) and liver (21)	R+ on ATG and D+/R–	T-Track-CMV	Test at 30, 60, 90 days (R+ and D+/R–), 120, 150, 180 (D+/R–), stop prophylaxis if test positive	Similar incidence of CMV replication/disease, shorter duration of antiviral in the intervention group
[109]	27	All SOT	R+ and D+/R–	QTF-CMV	Test at the end of therapy for CMV replication, add secondary prophylaxis in case of negative result	Lower incidence of CMV relapse in patients with a positive test
[110]	160	Kidney	R+	T-SPOT.CMV	Stratify patients at transplant in low vs. high-risk according to test result. Then randomize to preemptive vs. prophylaxis	Higher incidence of CMV replication in high-risk group. Better performance of antiviral prophylaxis strategy in both groups

ATG, anti-thymocyte globulin; CMV, cytomegalovirus; D, donor; QTF-CMV, QuantiFERON-CMV assay; R, recipient.

INTERVENTIONAL STUDIES EVALUATING CMV IMMUNE MONITORING STRATEGIES

The evidence generated by clinical trials on the use of CMV-CMI in transplant recipients is more limited. Most randomized controlled trials have focused on using the CMV-CMI assays for determining the duration of antiviral prophylaxis in intermediate or high-risk patients, particularly in kidney transplant recipients. In these studies, analysis of CMV-CMI has been performed using either the QTF-CMV or an ELISpot-CMV assay (**Table 3**).

In the study by [106] 118 lung transplant recipients were randomized to receive a fixed duration of antiviral prophylaxis (5 months), or a duration based on the results of the QTF-CMV assay, performed at 5, 8 and 11 months after transplantation. Antiviral prophylaxis was continued in case of a negative result of the assay in the intervention group. CMV replication measured by PCR in the bronchoalveolar lavage was observed in 58% in the control group as compared to 37% in the intervention group (p = 0.03), and this effect was probably due to the longer duration of prophylaxis in patients in the intervention group. A significant number of patients (39%), mostly D+/R–, remained with undetectable CMV-CMI at the end of prophylaxis period.

In the TIMOVAL trial [107], R+ kidney transplant recipients receiving induction therapy with ATG were randomized to receive a fixed duration of 3 months of prophylaxis (control group) or a duration based of immune-monitoring every 2–4 weeks using the QTF-CMV assay. Despite receiving ATG, up to 45% of patients had a QTF-CMV result as soon as 30 days after transplantation. Incidence of CMV infection (17% immune-monitoring vs. 13% control) was similar between groups while duration of antiviral prophylaxis was shorter in the intervention group. Incidence of neutropenia was lower in the immune-monitoring arm.

In the CMV-CMI study from Switzerland [108] 185 kidney or liver transplant R+ recipients receiving ATG or D+/R– were randomized to receive 3 or 6 months of prophylaxis (depending on the risk group) or immune monitoring once monthly with the T-Track-CMV®. Overall, the incidence of clinically significant CMV infections was similar between groups (30.9% immune-monitoring vs. 31.1% group) although non-inferiority was not proven (p = 0.06). The duration of antiviral prophylaxis was significantly shorter in the intervention group (−26 days, p < 0.001). The impact of the intervention was more pronounced in R+ patients.

Kumar et al. [109] performed a single-arm interventional study using a QTF-CMV assay at the end of antiviral therapy for clinically significant CMV infection (both CMV disease and asymptomatic replication). Patients with a positive QTF-CMV result did not receive additional antiviral therapy while patients with a negative result received valganciclovir for 8 additional weeks. Of the 27 SOT recipients included, 14 patients had detectable IFN-γ levels and 13 had undetectable levels. Only 1/14 (7%) patient with a positive assay result had a relapse of CMV replication in contrast with 9/13 (69%) in the group with a negative assay result.

Finally, in the RESPECT trial [26], Jarque et al. used the T-SPOT. CMV at the time of transplant to stratify patients as being low-risk (positive assay) or at high-risk (negative assay) based on IE-1 CMV-CMI for predicting post transplant CMV replication. Patients were then randomized to receive antiviral prophylaxis or a preemptive approach. Patients with a positive CMV-CMI test had significantly lower rates of CMV replication/disease irrespective of the preventive strategy used. However, the best performance of the assay was when performed at 15 days post transplant (81% of CMV infection if test negative vs. 9% if test positive).

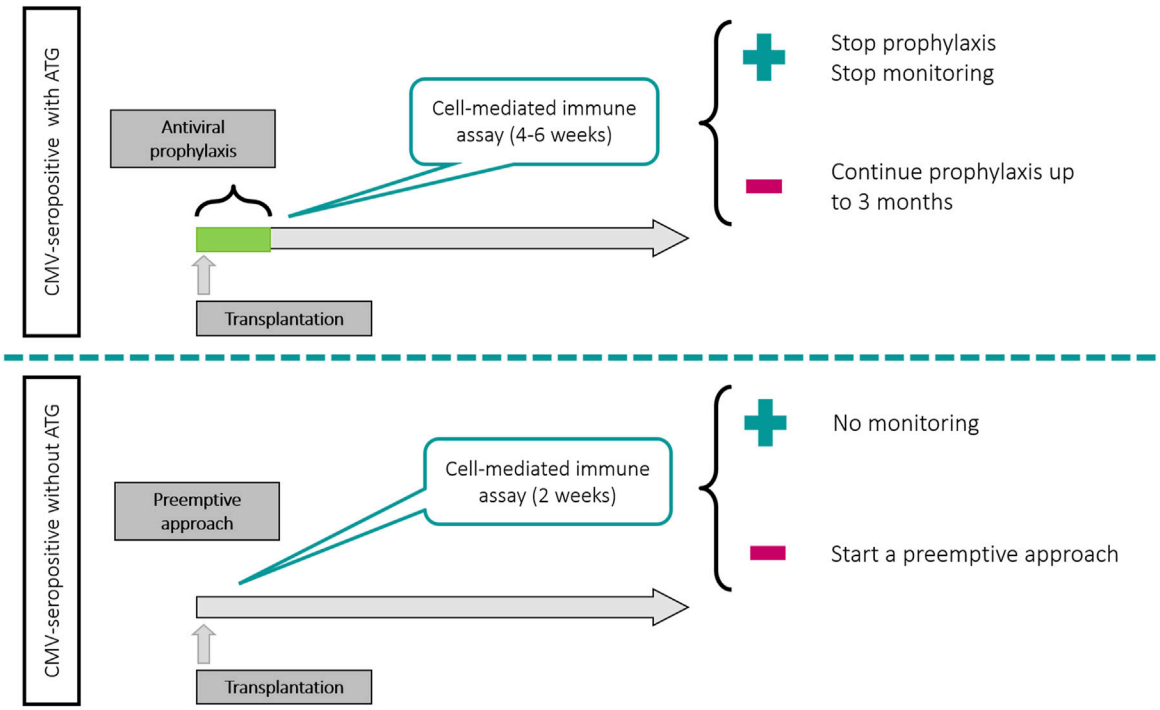

FIGURE 2 | Potential uses of CMV-CMI assays in CMV-seropositive patients according to preventive strategy and use of T-cell depleting antibodies.

Although more interventional studies would be desirable to better delineate the clinical scenarios for the use of CMV-CMI monitoring in SOT recipients, a summary of the main data available is provided below.

- A CMV-CMI assay can be used in the pre transplant period (if no T-cell depletion will be used) to identify those patients with a negative or low pre-transplant CMV-CMI and thus being at higher risk of CMV infection and therefore to choose the most appropriate preventive strategy against CMV. However, a positive CMV-CMI test prior to transplantation may lead to misleading predictive interpretations since a proportion of these patients may become high risk after transplantation due to induction immunosuppressive therapy.
- In patients receiving universal prophylaxis, the most appropriate population for using these assays seems to be the CMV-seropositive patients receiving ATG (as proposed in the TIMOVAL and CMV-CMI trials). According to these studies, as soon as 1 month post transplant, the majority of patients (45%–62%) mount a measurable CMI response against CMV, associated with a low risk for developing CMV disease. A potential strategy for these patients can be to perform a single-point assay at 4–6 weeks after transplant and to stop antivirals if the test is positive. In case of a negative result, an extension of prophylaxis or a preemptive approach could be applied. **Figure 2** illustrate a potential management of R+ patients according to the use of ATG.
- In patients managed with a preemptive approach, a CMV-CMI assay could be used in CMV-seropositive patients without receiving ATG (based on the RESPECT trial [110]). Here the risk of significant CMV replication is much lower and the probability to reach a detectable immune response much higher than in patients receiving ATG. A potential strategy for these patients can be to perform a single-point assay at 2 weeks after transplant and to stop PCR monitoring if the test is positive (**Figure 2**).
- There is limited data for high-risk D+/R− patients. In the CMV CMI study [108], the impact of the use of CMI assays was less visible in the high-risk group, mainly because the mounting of immunity was achieved later after transplant, and in only a minority of patients. A potential strategy in this population would consist in assessing CMV-CMI between 4 and 6 months post transplant and stop prophylaxis in case of a positive assay. Given the suboptimal sensitivity of CMV-CMI assays in this population, a negative result should not foster the extension of prophylaxis, but rather a closer follow-up after discontinuation of antivirals.

CONCLUSION

In this review we show the advances made in the field of CMV immune-risk stratification with the development of new sensitive assays measuring CMV-CMI. While most of the studies strongly suggest an added value of measuring CMV-CMI to better stratify the risk of CMV, in particular among R+ SOT recipients, yet some concerns arise when translating these immune tools into clinical practice; the precise predictive values illustrating the risk

at the patient-individual level should be noted with caution to ultimately establish safe, guided preventive strategies. Specific cut-offs, the biological insight provided by each type of assay, and the precise clinical settings where to be implemented need to be further investigated through the implementation of clinical trials.

With the implementation of artificial intelligence, including highly powerful machine-learning algorithms, the combination of distinct clinical as well as immunological variables at distinct biological level could further refine the individual risk of transplant patients to develop CMV infection. Notably, this is the ultimate goal of the large multicenter European project (HORUS[1]) by developing a dynamic multidimensional biomarker algorithm to robustly assess the risk of developing CMV infection.

Therefore, an effort should be made among the transplant community to confirm the added value of cell-mediated immune assays over current clinical management, as though if confirmed, they could revolutionize the management of CMV infection by personalizing the type and duration of preventive therapy against CMV infection after SOT.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

CONFLICT OF INTEREST

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REVIEW
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New Antibiotics Against Multidrug-Resistant Gram-Negative Bacteria in Liver Transplantation: Clinical Perspectives, Toxicity, and PK/PD Properties

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Antimicrobial resistance is a growing global health problem, and it is especially relevant among liver transplant recipients where infections, particularly when caused by microorganisms with a difficult-to-treat profile, are a significant cause of morbidity and mortality. We provide here a complete dissection of the antibiotics active against multidrug-resistant Gram-negative bacteria approved over the last years, focusing on their activity spectrum, toxicity profile and PK/PD properties, including therapeutic drug monitoring, in the setting of liver transplantation. Specifically, the following drugs are presented: ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, cefiderocol, and eravacycline. Overall, studies on the safety and optimal employment of these drugs in liver transplant recipients are limited and especially needed. Nevertheless, these pharmaceuticals have undeniably enhanced therapeutic options for infected liver transplant recipients.

Keywords: liver transplantation, BL/BLI, multidrug-resistant microorganisms, antimicrobial stewardship, metallo-beta lactamases

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INTRODUCTION

A significant challenge facing humankind in the 21st century is antibiotic resistance, and liver transplantation (LTx) is not immune to this threat [1]. Indeed, it is well-known how infections frequently occur in liver transplant recipients (LTR), with about 55% of them experiencing an infection within 12 months after transplantation [2]. This translates into relevant mortality, with infections being the most frequent cause of death 30–180 days after LTx [3]. Unfortunately, an increasing amount of these infections are caused by multidrug-resistant (MDR) bacteria [4]. Among them, MDR Gram-negative bacteria (MDRGNB) are responsible for most infections [5–8].

Colonisation by MDRGNB is a common condition in LTR, which reflects the long clinical history and exposure to antimicrobials and healthcare settings of these patients. The gastrointestinal tract represents the reservoir of MDRGNB, where resistance mechanisms are selected, maintained, and exchanged between species, leading to the so-called "gut resistome" [9].

Colonisation rates among LTR mirror the increasing frequencies observed worldwide in the general population [10]. This is reflected in an increased incidence of infections due to MDRGNB, with infection rate due to ESBL-producing Enterobacterales (ESBL-E) among colonised patients

seven times higher than in non-colonised [11]. Similarly, carbapenem-resistant Enterobacterales (CRE) infection rates have been estimated at 18.2% and 2% among colonised and non-colonised LTR, respectively [12].

Regarding outcomes, increased mortality has already been highlighted for liver transplant candidates on the waiting list colonised by MDRGNB compared to non-colonised (HR = 2.57, $p < 0.0001$) [13]. The same relevance has also been confirmed in the post-transplant setting, with patients developing post-transplant CRE infection having a 50% less chance of survival versus those uninfected (0.86, 95% CI, 0.76–0.97 vs. 0.34, 95% CI 0.08–1.0, $p = 0.0204$) [14] and several other studies confirming the role of MDRGNB in hampering survival [15, 16]. The same negative outcome has been associated with infection due to MDRGNB not belonging to the Enterobacterales genus, with recipients having carbapenem-resistant *Acinetobacter baumannii* (CRAB) infection showing a 60-day mortality of 46.4%, significantly higher than the one displayed by those not infected [17].

Notably, in the recent past, when the therapeutic armamentarium was limited to old or side-effects-prone antibiotics, colonisation by CRE was suggested as a reason for withdrawal from transplantation list, thus severely impacting the life expectancy of patients needing LTx [18].

Luckily, since 2014, several new antibiotics have entered the market: ceftolozane/tazobactam (C/T), ceftazidime/avibactam (CZA), meropenem/vaborbactam (MVB), imipenem/cilastatin/relebactam (I-R), cefiderocol (FDC), and eravacycline (ERV). They are an older beta-lactam (BL) plus a new beta-lactamase inhibitor (BLI) (CZA, MVB, I-R), a new BL plus an older BLI (C-T), a new siderophore cephalosporin (FDC), and a new tetracycline (ERV). Recently published guidelines from scientific societies regulate the use of these molecules in the general population [19–21]. We provide a complete dissection of these new molecules, focusing on their activity spectrum, toxicity profile and pharmacokinetic/pharmacodynamic (PK/PD) properties, including therapeutic drug monitoring, in LTx.

Table 1 provides an overview of common MDRGNB resistance mechanisms/profiles and the corresponding activity of new antibiotics. **Figure 1** compares the propensity of new antibiotic use in common infectious conditions in LTR according to the authors' opinions (personal view).

TABLE 1 | Activity spectrum of recently approved antibiotics against multidrug-resistant Gram-negative bacteria.

Antibiotic (year of approval by EMA)	ESBL	KPC	MBL	Amp-C	Oxa-48	P.aer-DTR	CRAb
Ceftolozane/tazobactam (2015)	✓	✗	✗	✓	✗	✓	✗
Ceftazidime/avibactam (2016)	✓	✓	✗	✓	✓	✓/✗	✗
Meropenem/vaborbactam (2018)	✓	✓	✗	✓	✗	✗	✗
Imipenem/relebactam (2020)	✓	✓	✗	✓	✗	✓	✗
Cefiderocol (2020)	✓	✓	✓	✓	✓	✓	✓
Eravacycline (2018)	✓	✓	✓/✗	✓	✓	✗	✓/✗

ESBL: extended-spectrum beta-lactamases; KPC: Klebsiella pneumoniae *carbapenemase; MBL: metallo-beta-lactamase; Amp-C: AmpC β-lactamases; OXA-48: OXA-48, carbapenemase; P. aer-DTR: difficult-to-treat* P. aeruginosa*; CRAb: carbapenem-resistant* Acinetobacter baumannii.

CEFTOLOZANE/TAZOBACTAM (C/T)

Activity Spectrum

C/T is an association between a fifth-generation cephalosporin, ceftolozane, and a well-known BLI, tazobactam [22]. Ceftolozane displays activity against Gram-negative bacilli, including those that produce β-lactamases. However, it is compromised by ESBLs, whose actions are overcome by adding tazobactam. Unlike other BLI such as avibactam, vaborbactam and relebactam, tazobactam does not inhibit carbapenemases, so C/T should not be used to manage CRE [23]. Instead, ceftolozane has an excellent capacity for penetration through porin canals and evades most resistance mechanisms displayed by *P. aeruginosa*, including efflux pumps, modification of penicillin-binding proteins and Amp-C expression. Due to these properties, C/T is primarily active against *P. aeruginosa* and ESBL-E [24].

C/T has been approved for the treatment of complicated urinary tract infections (cUTI) [25], complicated intra-abdominal infections (cIAI) [26] and ventilator-associated bacterial pneumonia (VABP) [27]. The licenced dose of C/T in patients with normal renal function is 1.5 g every 8 h for cUTI [4] and cIAI [5] and 3 g every 8 h for VABP [6]. Of note, dosages should be reduced in patients with impaired renal function.

Ceftolozane/Tazobactam in Clinical Trial and its Potential Application in SOT Recipients

Overall, C/T appears to be a novel BL/BLI combination particularly effective against serious infections caused by MDR and XDR *P. aeruginosa*, and most of the current studies address its use in this setting with promising clinical outcomes. However, there is little data on solid organ transplant (SOT) recipients and even less on LTR.

A good outcome for the use of C/T in *P. aeruginosa* infections with limited treatment options is reported in a multicentre retrospective study of 263 patients, achieving a composite clinical success in 70% of patients, confirmed in the SOT subgroup (60.8%, 4/23 patients). Only two patients were LTR in this study, and one in two achieved clinical success [28]. Similarly, Bassetti et al. performed a multicentre nationwide study of C/T for treating severe *P. aeruginosa* infections, with 83% of patients having a successful clinical outcome at the end of treatment. There were 11 SOT recipients in the population, but neither the transplanted organ nor the disaggregated outcome is available [29]. The efficacy of C/T in the treatment of MDR *P. aeruginosa* and MDR Enterobacterales infections is also demonstrated by Ronda et al., who describe 30.1% treatment failure and 30-day and 90-day all-cause mortality of 8.6% and

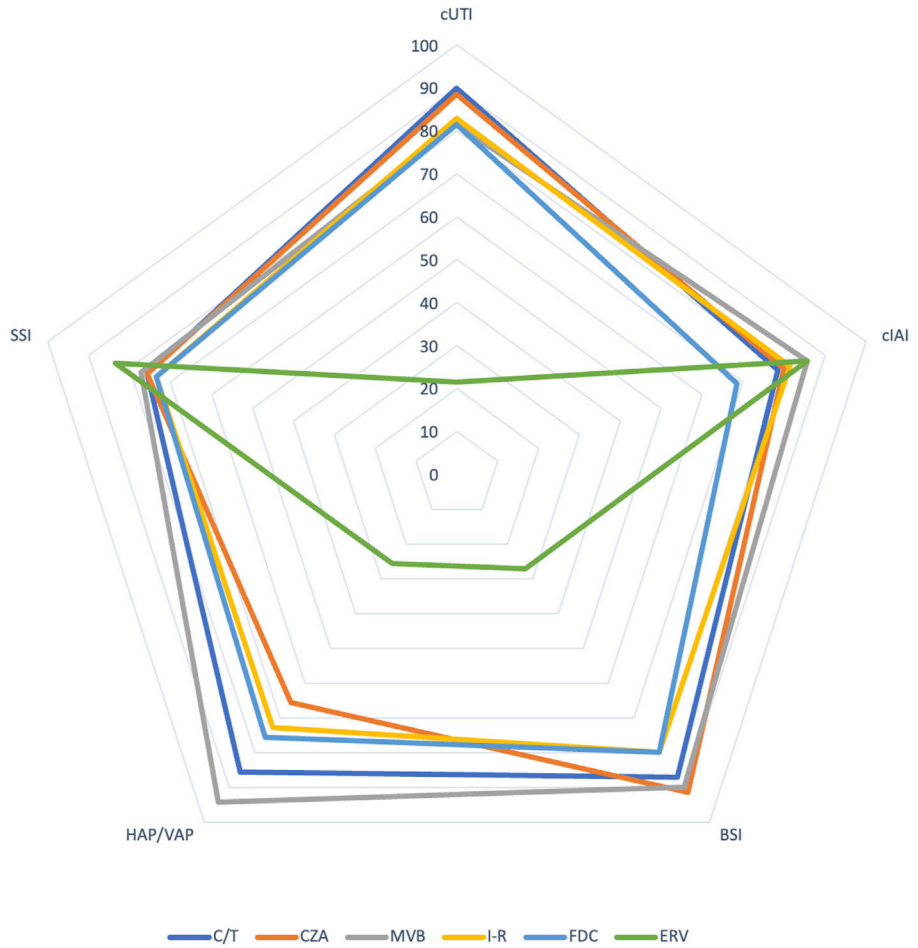

FIGURE 1 | Comparison of propensity to new antibiotic use in common infectious conditions among LTR according to authors' opinion (Personal view). Based on a hypothetical fully susceptible microorganism toward the antimicrobial considered. (0 = totally against use, 100 = totally in favour of use) (HAP/VAP: hospital-acquired pneumonia/ventilator-associated pneumonia, BSI: bloodstream infection; cIAI: complicated intraabdominal infection; cUTI, complicated urinary tract infection; SSI: surgical site infection; C/T: ceftolozane/tazobactam; CZA: ceftazidime/avibactam; MVB: meropenem/vaborbactam; I-R: imipenem/relebactam; FDC: cefiderocol; ERV: eravacycline).

17.2%, respectively. Interestingly, most of the 96 episodes analysed occurred in immunosuppressed patients (57.9%), of whom 17 (22.4%) were SOT recipients, including one LTR [30].

Promising news for LTR treated with C/T comes from real-world data, as reported by Escolà-Vergé et al. in their review of cIAI caused by MDR *P. aeruginosa*, which presents the cases of a 70-year-old LTR with liver abscesses and a 44-year-old LTR with septic shock due to cholangitis, with both patients reaching clinical cure and microbiological eradication [31].

Adverse Events and Limitations

There is limited information on using C/T with immunosuppressive agents in SOT recipients. Ceftolozane is not expected to have clinically significant drug-drug interaction as it is neither a substrate nor a modulator of the cytochrome P450 system at therapeutic concentrations. Instead, tazobactam is a substrate of the organic anion transporters 1 and 3, and the coadministration of drugs that may inhibit these transporters may increase its plasma concentrations. In a study evaluating the physical compatibility of C/T with selected intravenous drugs during simulated Y-site administration, Thabit et al. found that C/T was incompatible with cyclosporine due to turbidity changes [32].

C/T is generally well tolerated, with the most common adverse events being nausea, vomiting, and diarrhoea [3]. It is almost eliminated as an unchanged form by the renal route (92%) and is not extensively metabolised by the liver, making it a good candidate for use in LTR [2].

Key Messages

Despite the paucity of data on the use of C/T in LTR, the available studies suggest that it is a valid option for MDR and XDR *P. aeruginosa* infections in cUTI, cIAI and VABP, with promising clinical success and limited treatment failure also described in SOT recipients. Further studies are needed to assess its efficacy, pharmacokinetics, and tolerability in this population.

CEFTAZIDIME/AVIBACTAM (CZA)

Activity Spectrum

CZA is a combination of the third-generation anti-pseudomonal cephalosporin ceftazidime and avibactam, a non-β-lactam BLI, which restores *in vitro* activity of ceftazidime against Ambler class A, class C and some class D (e.g., OXA-48) β-lactamases [33]; however, it remains inactive against metallo-β-lactamases (MBLs). To treat infections caused by bacteria with this latter resistance mechanism, CZA is used in combination with aztreonam to take advantage of its synergistic effect [34].

CZA is currently approved for treating cIAI, UTI and nosocomial pneumonia [35].

The licenced dose of CZA in patients with normal renal function is 2.5 g every 8 h, with dose reduction in patients with impaired renal function.

Ceftazidime/Avibactam in Clinical Trial and its Potential Application in SOT Recipients

Data on using CZA in SOT recipients are limited to case reports and case series, mainly focusing on lung and kidney transplant recipients. Evidence in LTR is even scarcer and relies on retrospective real-world data analysis (**Table 2**). A Chinese case series of 21 LTR investigating the use of CZA in infections by KPC-producing Enterobacterales (KPC-E) [36] showed clinical response in adult patients at 14 days and 30 days of 70.6% (12/17) and 58.8% (10/17), respectively, while in paediatric patients was 75% at both time points. Three patients relapsed within 30 days. Most patients (66%) were treated with combination therapy (carbapenems, aztreonam, metronidazole, and polymyxin B), and no cases of CZA resistance were identified. Of note, three patients (3/21, 14.3%) developed acute kidney injury, and no other significant adverse event was reported. A similar study on six paediatric LTR [37] evaluated the efficacy and safety of CZA as salvage therapy for cIAI and bloodstream infections (BSI) caused by CRE, mostly KPC-E, and showed clinical success in all patients, without recurrence or development of resistance. CZA was mainly used as monotherapy (66%), and there were no serious adverse events.

An international, retrospective cohort compared CZA with the best available therapy (BAT) in a cohort of 149 SOT recipients with KPC-Kp bloodstream infection (BSI) [39]. Liver (44.3%) and kidney (40%) were the most common SOT. Eighty-three patients received CZA, 37 of whom were LTR. Patients treated with CZA had a significantly higher rate of clinical success at day 14 than those treated with BAT (80.7% vs. 60.6%), particularly in the high mortality risk stratum according to the INCREMENT-SOT-CPE score [40]. The same trend was observed for clinical success at day 30, with significant differences observed between patients receiving CZA versus BAT in the treatment cohort. No stratification by SOT type was available.

Notably, CZA therapy was also associated with increased survival in the CAVICOR study, the most extensive series to date evaluating the impact of CZA on mortality in CRE infections. However, only 45/339 (13.2%) patients analysed were SOT recipients, and no stratification by SOT type was present [41].

In contrast, Di Pietrantonio et al. [38], analysing a cohort of 81 patients, 8 of whom were LTR, receiving CZA for infections mainly due to KPC-E, found that a significantly higher proportion of patients with clinical failure were LTR and that LTx emerged as an independent predictor of treatment failure. These differences may be due to the populations' heterogeneity and the infection's severity. Furthermore, the study was not designed to focus its analysis and results on a specific population such as LTR.

Adverse Events and Limitations

Interactions with CZA and immunosuppressants are not expected, and no cases of induced hepatotoxicity have been reported in the Livertox database [42].

Monitoring renal function is warranted, especially when CZA is combined with other nephrotoxic molecules such as polymyxins or aminoglycosides.

Key Messages

In conclusion, CZA may be a useful therapeutic option in LTR for treating infections caused by MDRGNB, particularly KPC-producing strains. New studies are needed to analyse the use of CZA in LTR, focusing on its efficacy versus BAT and examining its safety profile in this population. Caution is required in monitoring the emergence of CZA resistance during treatment of KPC-3-producing *K. pneumoniae*, as has already been reported [8, 9]. Finally, further evidence must be gathered on CZA combined with aztreonam for treating infections due to MBL-producing bacteria.

MEROPENEM/VABORBACTAM (MVB)

Activity Spectrum

MVB is a new BL/BLI active on carbapenemases with a broad spectrum of enzyme inhibition. It combines meropenem (MEM), a carbapenem antibiotic, with vaborbactam, a highly specific BLI that targets KPC-β-lactamase (including KPC-8 and KPC-3) and other class A beta-lactamases. In addition, combination with vaborbactam has been shown to reduce MEM minimum inhibitory concentration (MIC) in Enterobacterales with low MEM susceptibility harbouring ESBL or AmpC-type β-lactamases [43, 44]. In contrast, MVB is inactive against class D or B carbapenemases [45]. The activity of MVB against other difficult-to-treat Gram-negative and anaerobic bacteria is variable: in general, the activity against *P. aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia* is comparable to that of MEM alone [46, 47].

Meropenem/Vaborbactam in Clinical Trial and its Potential Application in SOT Recipients

Currently, two Phase 3 clinical trials have evaluated the efficacy and safety of MVB: the TANGO I [48] and TANGO II [49] studies. In the latter, immunocompromised patients, including SOT recipients, were enrolled, representing 32% of the total

TABLE 2 | Overview of real-life studies describing ceftazidime/avibactam use among LTR.

Author, year	Country	Study design	Pathogen	Infection type	Main results	AE
Chen 2021 [36]	China	Retrospective observational study on 21 LTR (including 4 paediatric patients)	CRE KPC	IAI, BSI, PN	Mortality • 14 days: 28.6% • 30 days: 38.1% • All-cause: 42.9% Clinical response • Adult patients, 14 days: 70.6% (12/17); 30 days was 58.8% (10/17) • Paediatric patients, both 14 days and 30 days: 75% Relapse in 3 patients after 30 days CZA resistance not detected in any case	3 (3/21, 14.3%) acute kidney injury, 2/21 patients received haemodialysis after CZA treatment Transient increase in ALT and AST blood levels was reported
Wang 2022 [37]	China	Retrospective observational study on 6 paediatric LTR (≤12 years)	CRE KPC	IAI and BSI	Clinical success was achieved in all patients, no recurrences	Minor AE reported: vomiting (1/6), skin rash (1/6), increased GGT (2/6), (2/6), and alkaline phosphatase (3/6)
Di Pietrantonio 2022 [38]	Italy	Retrospective study on 81 pts receiving CZA for Gram-negative infections (8 LTR)	KPC	IAI, BSI, PN, VAP	Clinical failure for 7/8 (87.5%) patients Significantly higher proportion of patients with clinical failure received LT (p = 0.003), mechanical ventilation (p = 0.049) or had pneumoniae (p = 0.009) In multivariate logistic regression analysis, only LT is an independent predictor of treatment failure [OR 12.100 (1.369–106.971), p = 0.025]	Not reported
Perez-Nadales 2023 [39]	Spain, Italy, Brazil, United States	Retrospective study on 149 SOT recipients with KPC BSI (66 LTR)	KPC	BSI	Comparison between CZA and BAT. Clinical success • Day 14: CZA vs. BAT (80.7% vs. 60.6%) • Day 30, CZA vs. BAT (97.4% vs. 60.6%) All-cause mortality: CZA vs. BAT (13.3% vs. 27.3%)	Not reported

AE: adverse event; LTR: liver transplant recipient; CRE: Carbapenem-resistant Enterobacterales; IAI: intra-abdominal infection; BSI: bloodstream infection; PN: pneumonia; VAP: ventilator-associated pneumonia, CZA: ceftazidime-avibactam; BAT: best available therapy; LT: liver transplant; ALT: alanine transaminase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase.

cohort and 40% of those with microbiologically confirmed CRE infection. Within the microbiologic carbapenem-resistant Enterobacterales modified intent to treat population, the cure rate was higher in the MVB group than in the BAT group at both the end of treatment and test of cure (65.6% vs. 33.3% and 59.4% vs. 32.7%, respectively). Despite not reaching statistical significance, mortality at 28 days was numerically lower with MVB than with BAT. The favourable outcome with MVB treatment is also confirmed when considering different infection categories. However, few patients in this cohort had cIAI (4, 8.5%), which limits the transferability of the results in the liver transplantation setting. Again, in additional subgroup analysis in immunocompromised patients, MVB had a higher cure rate at test of cure than BAT (63% vs. 0%). Overall, in this study, MVB emerged as an interesting treatment for CRE infection among LTR, although details on the type of SOT and immunosuppression were not specified.

A few case reports have demonstrated the use of MVB in clinical practice in LTR. One case report described MVB as salvage therapy for CZA-resistant *K. pneumoniae* abdominal abscess in an LTR [50]. The authors described an LTR with KPC-Kp BSI in the early post-transplant period, cured with CZA. Subsequently, the patient had a new BSI with an onset of *de novo* CZA resistance requiring discontinuation of CZA treatment, initiation of tigecycline and polymyxin B followed by gentamicin. Blood cultures were cleared, but CZA-resistant *K. pneumoniae* was recovered from the abscess fluid. MVB was initiated with complete recovery, allowing re-transplantation in the following days. In this case, MVB was efficacious in infection with a high bacterial inoculum.

Shield et al. [51], in 2019, described the use of MVB in 20 patients 11% SOT, type not specified and reported only in abstract presentation [52] with Enterobacterales

TABLE 3 | Suggested dosages and infusion modalities for maximising PK/PD target of novel antibiotics, with particular focus to the LTx setting. Adapted from [99, 100].

Antibiotic	PK/PD target adopted in pivotal trials	Scheduled infusion modality	Optimised PK/PD target (maximise efficacy, suppress resistance development)	Stability in solution	Suggested dosage for maximising PK/PD target[a]	Considerations for LTx setting
Ceftolozane/ tazobactam [103]	30% $fT_{>MIC}$	II over 1 h	100% $fT_{>4 \times MIC}$	24 h	LD: 2 g/1 g MD: 2 g/1 g q8h CI	• negligible hepatic metabolism, not expected to be affected by hepatic impairment. No dose adjustment recommended as per SPC • TDM-guided approach may be useful in ACLF and/or high MELD score
Ceftazidime/ avibactam [104]	50% $fT_{>MIC}$	II over 2 h	100% $fT_{>4 \times MIC}$	12 h	LD: 2 g/0.5 g MD: 2 g/0.5 g q8h CI	• no relevant hepatic metabolism. No dose adjustment as per SPC (no PK data of ceftazidime in patients with severe hepatic impairment; no PK data of avibactam in patients with any degree of hepatic impairment) • TDM-guided dose should be obtained in deep-seated infections, ACLF and/or high MELD score
Meropenem/ vaborbactam [105]	45% $fT_{>MIC}$	EI over 3 h	100% $fT_{>4 \times MIC}$	12 h	LD: 2 g/2 g MD: 2 g/2 g q8h CI	• no relevant hepatic metabolism. No dose adjustment as per SPC (hepatic function monitoring recommended in patients with pre-existing liver disorders due to the risk of hepatic toxicity) • TDM-guided dose should be obtained in ACLF and/or high MELD score
Imipenem/ relebactam [106]	40% $fT_{>MIC}$	II over 0.5 h	100% $fT_{>4 \times MIC}$	3.5 h	500 mg/250 mg q6h EI over 3 h	• no relevant hepatic metabolism. No dose adjustment as per SPC (hepatic function monitoring recommended in patients with pre-existing liver disorders due to the risk of hepatic toxicity) • TDM-guided dose should be obtained in ACLF and/or high MELD score
Cefiderocol [89]	75% $fT_{>MIC}$	EI over 3 h	100% $fT_{>4 \times MIC}$	6 h	LD: 2 g MD: 2 g q8h CI	• no relevant hepatic metabolism. No dose adjustment as per SPC • TDM-guided approach may be useful in ACLF and/or high MELD score
Eravacycline [89]	*f*AUC/MIC ratio	II over 1 h	N/A	12 h	as per SPC	• No dose adjustment as per SPC • Exposure may be increased in patients with Child-Pugh Class C (twofold increase in AUC, half-life prolonged from 16 to 21–26 h), particularly if obese and/or also being treated with potent CYP3A inhibitors. In these patients, no recommendation on posology given • TDM-guided approach not available

LTx: liver transplant; PK/PD: pharmacokinetic/pharmacodynamic; MIC: minimum inhibitory concentration; II: intermittent infusion; EI: extended infusion; CI: continuous infusion; LD: loading dose; MD: maintenance dose; SPC: summary of product characteristics (EMA); TDM: therapeutic drug monitoring; ACLF: acute on chronic liver failure; MELD: Model for End-Stage Liver Disease.

[a]*For patients with normal renal function.*

infections, reporting KPC production in 90% of isolates. Survival rates at 30 and 90 days were 90% and 80%, respectively, and success rates were 63% in patients with BSI and 67% in patients with pneumonia. Clinical success was achieved in 65% (13/20) of patients. A significant rate of microbiologic failure was observed (6/20; 35%) due to recurrent CRE infection, respiratory colonisation, breakthrough during treatment, and persistent BSI. In two cases, microbiologic failure was associated with intra-abdominal abscess. In 50% of cases of recurrence, MIC for

MVB increased significantly, and KPC-3 *K. pneumoniae* isolated in patients with intra-abdominal infection also acquired resistance to MVB. This point is relevant for LTR, where abdominal abscesses are frequent and may create an environment favourable for selecting antibiotic-resistant strains.

Adverse Events and Limitations

Regarding adverse events (AE), in the TANGO I trial [48], patients in MVB discontinued treatment in 2.6% of cases because of AE. The most common AE reported was headache (8.8%), and liver toxicity was reported in a low percentage of cases (1.5%). In the TANGO II trial [49], AE associated with MVB included diarrhoea, anaemia, and hypokalaemia. Interestingly, MVB treatment experienced a lower level of renal insufficiency than BAT. A lower incidence of renal insufficiency was also described when MVB was compared to CZA [53]. No other side effects have been reported in studies of this drug. In addition, there are no known interactions with immunosuppressive medications, but real-life experience is needed to understand mechanisms better.

Key Messages

MVB use in LTR is promising, especially for its anti-KPC activity, but more real-world data are needed. Its use in infections with high bacterial inoculum, requiring prolonged antibiotic therapies and source control, will require further investigation. In this setting, the toxicity of prolonged exposure and the potential development of resistance must be evaluated. In addition, more data are needed on interactions with immunosuppressive drugs.

IMIPENEM/RELEBACTAM (I-R)

Activity Spectrum

-R is a new drug that is an intravenous combination of imipenem/cilastatin and relebactam, a non-β-lactam BLI. Relebactam (REL) is an inhibitor of class A and C β-lactamases [54]. Although REL has no intrinsic antibacterial activity, it can protect imipenem from degradation by Ambler class A and class C β-lactamases and *Pseudomonas*-derived cephalosporinase [55]. Instead, REL is inactive against class B MBLs or D oxacillinases [56, 57]. In addition, some *in vitro* studies have shown that REL is unaffected by efflux pumps at basal level of expression and does not suffer from inoculum effect [58].

Imipenem/Relebactam in Clinical Trial and its Potential Application in SOT Recipients

There is a lack of data on using I-R in LTR [59]. I-R has been evaluated in two phase-2 clinical trials, two phase-3 clinical trials and a small amount of real-world clinical experience, but LTR and SOT were usually excluded.

Phase 2 clinical trials evaluated I-R in cases of cIAI [60] and cUTI [61] and demonstrated a favourable clinical response in both cases. However, the phase 3 studies raise interesting questions regarding the efficacy in SOT recipients. In RESTORE-IMI 1 [62], which compared the efficacy and safety of I-R versus colistin (COL) plus IMP in patients with IMP-susceptible hospital-acquired or ventilator-associated pneumonia (HAP/VAP), cUTI or cIAI, favourable overall responses were achieved in both arms (I-R, 71%; COL + IMP, 70%). Only patients with HAP/VAP and cUTI, but none with cIAI, achieved a favourable overall response. Of note, this data is biased by the small number of patients with cIAI enrolled [4], with one out of two patients in both arms experiencing an unfavourable overall response due to missing/undefinable data.

In addition, the recent RESTORE-IMI 2 study [63] evaluated I-R versus piperacillin-tazobactam (TZP) in patients with HAP/VAP. Unfortunately, immunocompromised patients were excluded per protocol, limiting the applicability of the study results to the LTR population. Overall, I-R was non-inferior to TZP for the primary (28-day all-cause mortality) and secondary endpoint (favourable clinical response at the end of follow-up). In a subgroup of patients with severe disease, 28-day mortality and end-of-treatment cure were higher in patients treated with I-R. In addition, patients with *P. aeruginosa* infection had a lower clinical response rate and higher 28-day mortality rate in the I-R arm, although both treatment arms had comparable microbiologic eradication rates at the end of treatment (67% I-R vs. 72% TZP) [62–65].

Few studies have published real-world experience with I-R. Konho et al. [64] described the experience with I-R in patients with cIAI and cUTI infections and evaluated safety and efficacy. They enrolled 83 patients (cIAI = 39, cUTI = 44). Adverse events occurred in 74.1% of cases, the most common being diarrhoea. Four patients discontinued treatment due to AE, but no serious AE was considered related to the study treatment. A favourable clinical and microbiological response was achieved in 85.7% of patients with cIAI at the end of treatment and 82.1% at the test of cure visit (5–9 days and 14 days after completion of treatment). Microbiologic response was achieved in all patients with cUTI at the end of treatment and 59% at the test of cure visit. Of 16 cUTI patients with an unfavourable microbiological response, 13 had a favourable clinical outcome.

The last real-world evidence study described the emergence of resistance to I-R in patients with *P. aeruginosa* HAP/VAP treated with this molecule [65]. The main observation was that 5 of 19 patients had the emergence of I-R non-susceptible *P. aeruginosa* during treatment or within 30 days after treatment. All five patients had failed prior antibiotic regimens, including two who received I-R after treatment-emergent resistance to C/T. At whole-genome sequencing, the *P. aeruginosa* isolate did not harbour MBLs or other ß-lactamase enzymes conferring resistance to I-R. However, in all patients, I-R non-susceptibility coincided with the emergence of mutations in *P. aeruginosa* efflux operons. In two patients, the *P. aeruginosa* strains were ST235 and ST244, known to be high-risk MDR clones [66]. All these mutations occurred during antibiotic treatment between 8 and 23 days of therapy, resulting in a shift of the I-R MIC to higher values. Further studies in real-life settings with patients with multiple comorbidities and a variety of potential drug interactions are needed to define the role of I-R in *P. aeruginosa* infections occurring among LTR.

Adverse Events and Limitations

Regarding AE, similar data were reported in the available studies. In phase 2 [60] and phase 3 studies [62, 63], the most common AE were nausea, diarrhoea, and elevated liver enzymes. Focusing on liver toxicity, in RESTORE IMI-1, the incidence was between 2% and 3%, while in RESTORE IMI-2, the incidence was 2.3% [62, 63]. In general, in the RESTORE IMI-1 study, three patients (19%) in the COL + IMP arm and none in the I-R arm discontinued treatment due to AE, while in the RESTORE IMI-2 study, six patients (2.3%) in the I-R arm and four (1.5%) in the TZP arm discontinued treatment due to drug toxicities [62, 63].

Regarding renal toxicity, I-R was associated with a more favourable renal safety profile than COL-based therapy in RESTORE IMI-1. These data were also confirmed by a subsequent retrospective study conducted with RESTORE IMI-1 data using two assessment criteria for acute kidney injury, strengthening, as expected, how I-R had a better safety profile than IMP-COL [62].

Concerning drug interactions, it is essential to know that I-R may interact with other antimicrobial and antiviral treatments. The use of I-R with amikacin, azithromycin, aztreonam, COL, gentamicin, levofloxacin, linezolid, tigecycline, tobramycin, or vancomycin has been tested, and it is allowed. Instead, I-R should not be used concomitantly with ganciclovir due to the increased risk of seizures unless the potential benefit outweighs the risk [67]. Given the many concomitant medications LTR need, more data on this issue is needed.

Key Messages

I-R could be a promising drug in the LTx setting, mainly because of its broad spectrum of activity, covering anaerobes, *Enterococcus faecalis*, Enterobacterales and *P. aeruginosa* strains, even in the MDR setting. This feature is handy in intra-abdominal infections, a frequent complication after LTx. However, several issues remain to be clarified—first, the efficacy and emergency of non-susceptible I-R strains. LTR have often experienced multiple lines of antibiotic treatment, are often colonised or infected by MDRGNB, and sometimes experience deep infections requiring source control and prolonged antibiotic therapy. Knowing whether exposure to antibiotics could select for resistant strains is critical in this setting. Second, the liver toxicity described in RESTORE-IMI 2 needs to be investigated in-depth, and drug-drug interactions, especially with immunosuppressive treatment, need to be evaluated, given the higher rate of interactions with other molecules. Specifically, the contraindication to use ganciclovir concomitantly may be a limitation in this setting, given the frequent, ongoing treatment for CMV.

CEFIDEROCOL (FDC)

Activity Spectrum

FDC is a novel siderophore cephalosporin antibiotic that is indicated for treating infections due to aerobic Gram-negative organisms in adults with limited treatment options [68]. FDC bind to free iron molecules, and it is actively transported across the outer membrane of bacteria by their iron-transport system, thus leading to the accumulation of the antibiotic inside the microorganism [69]. Exploiting this strategy, FDC can overcome resistance mechanisms due to efflux pumps, particularly common in MDRGNB such as *P. aeruginosa* [70]. Moreover, FDC potent activity against MDRGNB is also related to its high stability against various extended-spectrum-lactamases (ESBLs) and carbapenemases [71]. Clinical data for FDC are promising, with several studies demonstrating its efficacy in treating various infections caused by multidrug-resistant bacteria, including cUTI, HAP, and BSI [72–74]. Notably, FDC displayed a significant activity in infections due to MBL-producing bacteria, a condition with minimal therapeutic opportunities [75].

Cefiderocol in Clinical Trial and its Potential Application in SOT Recipients

Regarding LTx, there is limited data on using FDC, with all data coming from case reports/series.

In their case series of difficult-to-treat infections due to MDRGNB treated with FDC, Bavaro et al. [76] included one LTR who received a combination therapy with FDC plus COL plus tigecycline followed by FDC plus fosfomycin for CZA-resistant KPC-Kp strain, causing liver abscess with bloodstream involvement. FDC was administered for 28 days, with a successful clinical outcome.

Klein et al. [77] reported the case of an LTR who underwent re-transplantation 10 years after receiving the first graft and who had a complicated clinical course with carbapenem-resistant *Enterobacter cloacae* BSI, initially treated with MEM and COL and subsequently with FDC alone. Within 21 days of therapy, the germ became resistant to FDC, and the patient died due to uncontrolled infectious focus.

Bodro et al. [78] presented instead a case of persistent BSI related to an infected transjugular intrahepatic portosystemic shunt caused by an extensively drug-resistant *P. aeruginosa*, resistant to ceftazidime, C/T, and MEM in a kidney transplant recipient who subsequently underwent a combined kidney-liver transplant. The patient received initial combination therapy with FDC plus COL for 2 weeks, followed by FDC alone for 4 weeks, resolving the infection.

Adverse Events and Limitations

Limited information regarding potential drug interactions between FDC and immunosuppressive drugs commonly used in liver transplantation is available. FDC is primarily eliminated unchanged in the urine and is not extensively metabolised by the liver [68]. As such, the risk of significant drug interactions with immunosuppressive drugs primarily metabolised by the liver may be low. In the CREDIBLE-CR study, liver-related adverse events (specifically increased liver enzyme concentrations) were reported more frequently in patients treated with FDC than with the best available therapy. It should be noted how the study included a relevant number of patients with ongoing hepatic disease (moderate/severe liver disease 11/101, hepatitis 12/101), how the adverse events were of mild/moderate severity and transient in duration and how no cases met the clinical and biochemical criteria for Hy's law or drug-induced liver injury [74]. Instead, in the APEKS-NP study, no notable differences

between the treatment groups (MEM vs. FDC) were identified in the occurrence of liver-related adverse events. In contrast, in the NCT02321800 trial (a multicenter, double-blind, randomized clinical study to assess the efficacy and safety of FDC in hospitalized adults with cUTI caused by Gram-negative pathogens), liver-related adverse events were not described [72, 73]. Of note, currently, there are no reported cases of liver toxicity due to FDC reported in the Livertox database [79].

FDC may cause renal impairment, which could be exacerbated by the concomitant use of nephrotoxic drugs commonly used in liver transplantation, such as calcineurin inhibitors (e.g., tacrolimus, cyclosporine) [80]. Therefore, it may be necessary to monitor renal function closely and adjust the dose of immunosuppressive drugs accordingly [68].

Finally, therapeutic and supratherapeutic doses of FDC had no apparent clinically significant effect on the QTc. Thus, no specific monitoring with electrocardiography is required during FDC therapy [81].

Key Messages

Overall, while there is limited data specifically on the use of FDC in liver transplantation, the available evidence suggests that it may be a safe and effective treatment option for multidrug-resistant infections, especially when due to MDRGNB harbouring MBLs and *P. aeruginosa* DTR. However, further studies are needed to confirm these findings and evaluate its optimal employment in this patient population.

ERAVACYCLINE (ERV)

Activity Spectrum

ERV is a novel, fully synthetic fluorocycline belonging to the tetracycline class. It has a broad-spectrum activity against aerobic and anaerobic Gram-positive and Gram-negative microorganisms and was explicitly designed to maintain stability against efflux pumps and ribosomal protection proteins. ERV is active against various MDR pathogens such as methicillin-resistant *Staphylococcus aureus* strains, vancomycin-resistant *Enterococcus faecium*, *Enterococcus faecalis*, ESBL-E, and AmpC-producing Enterobacterales [82]. On the other hand, it shows limited activity against *P. aeruginosa* and *Stenotrophomonas maltophilia*.

ERV exerts its antimicrobial action by primarily binding to the ribosomal 30 s subunit, interrupting the elongation phase of protein synthesis. *In vitro* shows a ten-fold higher activity at a four-fold lower drug concentration than other tetracyclines. Similarly, data from the CANWARD surveillance study demonstrated that ERV carries an *in vitro* activity equivalent to or 2- to 4-fold greater than tigecycline against Enterobacterales and Gram-positive bacteria [83].

Eravacycline in Clinical Trial and its Potential Application in SOT Recipients

ERV has been approved in several countries, including the EU and United States, for treating adult patients with cIAI. Two randomised, double-blind, non-inferiority phase 3 trials [84, 85] evaluated its efficacy in treating subjects with cIAI, acknowledging this drug as non-inferior to intravenous ertapenem or MEM, respectively, at the test-of-cure visit in terms of clinical response rates in all prespecified populations. Unfortunately, none of the trials included data on the efficacy of ERV in treating CRE and/or MDR *Acinetobacter spp*.

ERV has also been investigated in cUTI: two trials compared it with ertapenem and levofloxacin, respectively, reporting lower cure rates [86, 87]. In this setting, its use is not recommended.

Regarding treating infections in the setting of LTx, there is still no specific data on the use of ERV. A recent retrospective, multicentre study evaluated ERV clinical use in a cohort of 66 patients with infections by MDRGNB or Gram-positive cocci, with 7 of them being SOT recipients. Most subjects received the drug for an off-label indication, and overall, a good clinical response was reported (63/66 patients, 95.5%) [88].

Adverse Events and Limitations

There is limited information regarding potential drug interactions between ERV and immunosuppressive drugs commonly used in LTx. The absence of data is supported by the fact that clinical trials did not include immunosuppressed subjects. ERV is metabolised by liver cytochrome CYP3A4 and flavin-containing monooxygenase and excreted in urine and faeces. Therefore, concomitant administration of immunosuppressive drugs generally metabolised by the liver should be considered and closely monitored. Both the Food and Drug Administration and the European Medicines Agency suggest increasing ERV dose when co-administered with strong CYP3A4-inducers; on the other hand, coadministration with CYP3A4-inhibitors (e.g., tacrolimus) is not likely to cause a clinically significant increased exposure. Moreover, *in vitro*, ERV has been displayed to be a substrate for the transporters P-gp, OATP1B1 and OATP1B3. This kind of interaction cannot be excluded *in vivo*, and therefore, coadministration of ERV with drugs that inhibit these transporters (e.g., cyclosporine) could increase ERV serum levels [89].

Regarding side effects, ERV has demonstrated an acceptable tolerability profile, with infusion site reactions, nausea, vomiting, and diarrhoea being the most common AE.

Regarding hepatotoxicity, data from preclinical trials report mild to moderate aminotransferase elevations. The literature does not report cases of drug-induced liver injury associated with ERV use [42].

Considering the described elimination and excretion features, ERV does not seem to cause renal impairment.

Therapeutic and supra-therapeutic doses of ERV had no apparent clinically significant effect on electrocardiographic traces (e.g., increase in QTc interval); thus, no specific monitoring with electrocardiography is required during ERV therapy [90].

Key Messages

Overall, while there is still no data on the specific use of ERV in LTx, the available evidence in the setting of cIAI and the peculiar drug features suggest that it may be a safe and effective treatment option for infections caused by difficult-to-treat bacteria.

However, studies are needed to confirm these findings and evaluate its optimal employment in this patient population.

PK/PD of New Molecules

All the above-described antibiotics, except ERV, belong to the beta-lactam class. They all demonstrate time-dependent killing with the PK/PD parameter of efficacy related to the amount of time that the unbound drug concentration remains above the MIC of the infecting organism ($fT_{>MIC}$) [91]. It is suggested that 50% $fT_{>MIC}$ is likely enough to obtain standard efficacy, while in critically ill immunocompromised individuals, up to 100% $fT_{>4 \times MIC}$ should be ensured for optimal drug exposure and suppression of resistance development [92–94].

LTx candidates with end-stage organ failure and SOT patients in the early post-operative period are characterised by profound pathophysiological alterations that resemble those of critically ill patients. These alterations significantly impact the PK/PD of BLs [91, 92, 94, 95]. Indeed, conditions frequently encountered in the LTx period could either increase Vd (capillary leakage and oedema, fluid therapy, ascites, hypoalbuminemia) or enhance renal clearance (hyperdynamic condition of the early phase of sepsis, use of hemodynamically active drugs), leading to the risk of drug underdosing. On the contrary, reduced renal clearance due to renal failure bedridden or concomitant nephrotoxic drugs may expose them to antibiotic overdosing and toxicity [91, 92, 94, 95]. Extracorporeal support techniques such as continuous renal replacement therapy (CRRT) also contribute to antibiotic concentration variability [95]. In addition, critically ill patients with decompensated cirrhosis have a unique PK variability that can affect serum drug concentrations and compromise target attainment. Severe acute on chronic liver failure (ACLF) frequently presents circulatory and renal dysfunctions and low serum protein levels, features that contribute to ascites and frequently anasarca. This setting will likely significantly affect both clearance and Vd of antibiotics. Population PK models have shown that increasing MELD score values reduce MEM and tigecycline clearance, demanding a reduction in drug doses [96, 97]. ACLF was found to increase MEM Vd by lowering peak concentrations. Consequently, higher loading doses of MEM have been suggested [97].

Clinicians must face these remarkable PK/PD issues when antibiotics are administered to critically ill patients. Strategies to overcome these issues and optimise beta-lactam efficacy include continuous/extended infusions (C/EI) and therapeutic drug monitoring (TDM).

The duration of BL infusion has been shown to influence their $fT_{>MIC}$ [94]. Several studies and systematic reviews reported PD benefits for target attainment of C/EI of beta-lactams, especially in infections by MDRGNB [98–101].

Vardakas et al. [98] conducted a meta-analysis of 22 randomised controlled trials comparing C/EI versus short-term infusion of antipseudomonal beta-lactams in sepsis, involving 1876 patients. C/EI was associated with lower all-cause mortality than short-term infusion (RR 0.70, 95% CI 0.56–0.87). Almost all subgroup and sensitivity analyses showed that C/EI was associated with at least a trend towards lower all-cause mortality than short-term infusion [98].

Bartoletti et al. [101] performed a secondary analysis of the BICHROME study, a prospective multicentre study conducted in 19 tertiary centres across five countries designed to describe the epidemiology of BSI in cirrhotic patients. The authors reviewed 119 patients treated with TZP or carbapenems as empirical treatment and observed a significantly lower mortality rate in those who received C/EI (after adjusting for severity of illness: HR 0.41, 95% CI 0.11–0.936). A significant reduction in 30-day mortality was also found in the subgroups of patients with sepsis (HR 0.21, 95% CI 0.06–0.74), acute-on-chronic liver failure (HR 0.29, 95% CI 0.03–0.99), and MELD score ≥25 (HR 0.26, 95% CI 0.08–0.92) [101].

Among novel beta-lactams, EI was considered in developing clinical trials only for MVB and FDC, which nowadays are the only two novel beta-lactams licensed to be administered by EI over 3 h. However, administration by intermittent infusion could lead to failure in achieving even the most conservative PK/PD target adopted in pivotal trials, especially in critically ill patients or infections by MDRGNB [100]. Real-world evidence on using novel beta-lactam antibiotics by C/EI in clinical scenarios when achieving aggressive PK/PD targets is challenging has been thoroughly reviewed [99, 100].

TDM had been historically instituted for aminoglycosides and glycopeptides to reduce the rate of drug toxicity. Because of the excellent safety profile of BLs, TDM was thought unnecessary for these antibiotics. More recently, challenges in achieving "optimal" drug concentrations in critically ill patients have suggested BL TDM as a valuable strategy to optimise PK/PD exposure, especially in infections by MDRGNB, immunocompromised patients and those undergoing CRRT or with augmented renal clearance [92, 95].

Focusing on critically ill patients with suspected or proven sepsis, Pai Mangalore et al. [102] conducted a systematic review and meta-analysis on TDM-guided dosing and clinical outcomes. TDM-group was associated with increased target attainment (RR 1.85, 95% CI 1.08–3.16) and improved clinical cure (RR 1.17, 95% CI 1.04–1.31), microbiological cure (RR 1.14, 95% CI 1.03–1.27) and treatment failure (RR 0.79, 95% CI 0.66–0.94) [102].

Table 3 summarises scheduled and suggested administration modalities for maximising novel BL antibiotics' PK/PD target, focusing on the LTx setting.

CONCLUSION

Overall, the scientific and clinical community has warmly received the availability of a discrete number of new molecules active against MDRGNB, as it represents a significant breakthrough in addressing the urgent need for effective antibiotics in the face of rising antimicrobial resistance. This holds particularly true within the setting of LTx, wherein the prevalence of infections caused by MDRGNB is considerable, and patients undergo extensive surgical procedures while concurrently receiving immunosuppressive therapy.

Despite the high anticipation surrounding the introduction of these medications, substantial evidence regarding their safety, effectiveness, and optimal utilisation in LTR is limited or lacking. Given the underrepresentation of this patient population in

conventional registration studies, the transplantation community must collaborate to collect the necessary data to optimise their usage.

AUTHOR CONTRIBUTIONS

AL, DM, and AB conceived the study. AL, LA, EP, GV, AT, and DM wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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GLOSSARY

ACLF	acute on chronic liver failure
AE	adverse events
BAT	best available therapy
BL	beta-lactam
BLI	beta-lactamase inhibitor
BSI	bloodstream infection
C/EI	continuous/extended infusions
C/T	ceftolozane/tazobactam
cIAI	complicated intra-abdominal infections
COL	colistin
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CRRT	continuous renal replacement therapy
CRE	carbapenem-resistant Enterobacterales
cUTI	complicated urinary tract infections
CZA	ceftazidime/avibactam
ESBL-E	ESBL-producing Enterobacterales
ESBL	extended-spectrum-β-lactamases
ERV	eravacycline
FDC	cefiderocol
HAP	hospital-acquired pneumonia
I-R	imipenem/cilastatin/relebactam
IMP	imipenem
LTR	liver transplant recipients
LTx	liver transplantation
KPC-E	KPC-producing Enterobacterales
MBL	metallo-β-lactamases
MDR	multidrug-resistant
MDRGNB	multidrug-resistant Gram-negative bacteria
MEM	meropenem
MIC	minimum inhibitory concentration
MVB	meropenem/vaborbactam
PK/PD	pharmacokinetic/pharmacodynamic
REL	relebactam
SOT	solid organ transplant
TDM	therapeutic drug monitoring
TZP	piperacillin-tazobactam
VABP	ventilator-associated bacterial pneumonia
VAP	ventilator-associated pneumonia

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REVIEW
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Burden and Management of Multi-Drug Resistant Organism Infections in Solid Organ Transplant Recipients Across the World: A Narrative Review

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Solid organ transplant (SOT) recipients are particularly susceptible to infections caused by multidrug-resistant organisms (MDRO) and are often the first to be affected by an emerging resistant pathogen. Unfortunately, their prevalence and impact on morbidity and mortality according to the type of graft is not systematically reported from high-as well as from low and middle-income countries (HIC and LMIC). Thus, epidemiology on MDRO in SOT recipients could be subjected to reporting bias. In addition, screening practices and diagnostic resources may vary between countries, as well as the availability of new drugs. In this review, we aimed to depict the burden of main Gram-negative MDRO in SOT patients across HIC and LMIC and to provide an overview of current diagnostic and therapeutic resources.

Keywords: solid organ transplant, multidrug-resistant Gram-negative bacteria, epidemiology, clinical impact, diagnosis and treatment, new anti-infective agents

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INTRODUCTION

Solid organ transplant (SOT) recipients are at high risk for acquiring colonization and/or infection with multi-drug resistant organisms (MDRO) with associated high morbidity and mortality rates [1–3].

In the last 10 years, Enterobacterales, *P. aeruginosa,* and *Acinetobacter baumannii* have emerged as critical threats due to a progressive widespread pattern of resistance, impacting patient survival, mainly among vulnerable populations [4]. The present review will focus on these pathogens.

Abbreviation: SOT, solid organ transplantation; MDRO, multi drug resistant organisms; ESBL-E, extended spectrum beta-lactamase producing enterobacterales; ESCR-E, extended-spectrum cephalosporin resistant-enterobacterales; CRE, carbapenem resistant enterobacterales; CPE, carbapenemase producing enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-beta-lactamase; NDM, New Delhi metallobetalactamase; VIM, verona-integron-metallo beta lactamase; IMP, imipenemase; MDR, multi-drug-resistant; XDR; extensively drug resistant; PDR, pan-drug resistant; DTR, difficult-to treat resistance; CR-Pa, carbapenem resistant *Pseudomonas aeruginosa*; CR-Ab, carbapenem resistant *Acinetobacter* baumannii; HIC, high income countries; LMIC, low and medium income countries; OLT, orthotopic liver transplantation; KT, kidney transplantation; LuT, lung transplantation; HT, heart transplantation; UTI, urinary tract infection; DDI, donor derived infection.

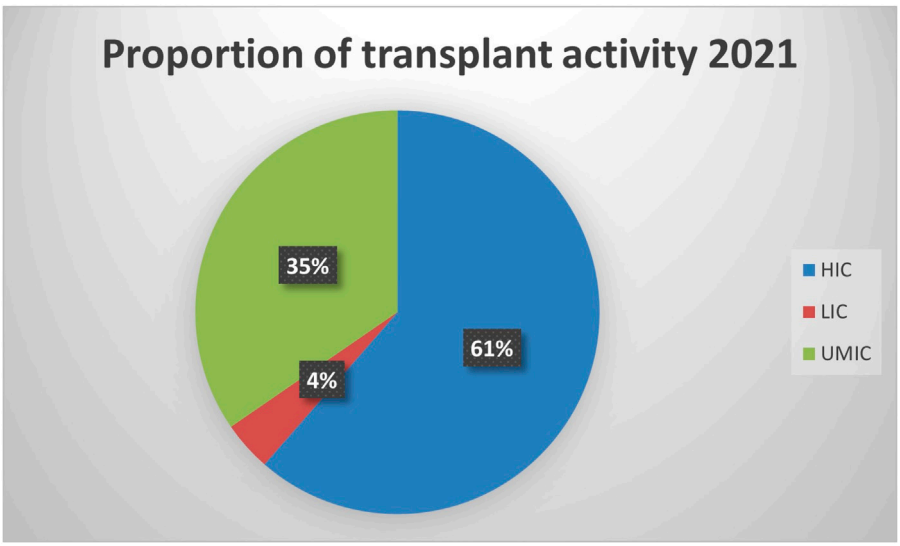

FIGURE 1 | Proportion of transplant activity in high-, lower- and upper middle-income countries.

The objective is to provide an overview of the epidemiology of these MDROs in SOT recipients in different regions of the world. Diagnostic and treatment strategies will be also reviewed considering differences in the access to new diagnostic tools and new antibiotics across high- and low-medium-income countries.

METHODS

We conducted a narrative review by a computer-based PubMed search using as keywords "Solid Organ Transplantation," "multidrug resistance," "extended-spectrum β-lactamase producing" or "extended-spectrum cephalosporin resistance," "carbapenem resistance" or "carbapenemase-producing," "difficult to treat resistant *P. aeruginosa,*" "carbapenem-resistant *A. baumannii*" to identify published all-language literature between June 2013 and June 2023. A pre-established chart was used to extract epidemiological data. MDRO was defined according to Magiorakos criteria and new DTR concept [5,6]. HIC and LMIC were defined according to world bank classification [7]. To estimate MDRO prevalence in SOT recipients across countries, we included studies reporting the number of infections by each specific MDRO, as well as the number of transplanted patients during the same period. Studies that only reported colonization or laboratory-based descriptions without clinical data were excluded.

RESULTS

Epidemiology of MDRO Infections After SOT

Compared to high-income countries (HICs), data on MDRO infections among SOT patients is relatively scarce in low and middle-income countries (LMICs). In these regions, the number of transplants per million people is lower when compared to Western Europe and the US. However, in absolute terms, 39% of all transplants are performed in these countries (see **Figure 1**) [8]. Significant discrepancies in donor referral and transplantation exist between HICs and LMICs. In the latter, the proportion of living-donor transplants is higher, especially in Asia [9]. Moreover, the rates of MDRO infections among SOT recipients are highly influenced by the local epidemiology. For instance, Brazil, Turkey, India, China, and Argentina are described as countries with the highest prevalence of CRAB infection [10] Moreover, India and China have a high prevalence of ESCR-E and CRE, mainly NDM-producing [10,11]. Thus, it is expected that LMIC bear a high burden of these diseases, which are likely underreported due to deficiencies in diagnosis, lack of microbiology laboratory infrastructure, and limited resources to make post-transplant infection rates public. Finally, there is a lack of representativity from countries in the Middle East and Africa. Taking into account these considerations, an overview of the worldwide prevalence of infection by most common MDROs per 1,000 transplant-recipients is shown in **Figure 2**.

ESBL-Producing Enterobacterales

ESBL-E infection is the most commonly reported MDR Gram-negative infection, with a prevalence ranging from 3% to 11% and an aggregate rate of 7% among all bacterial infections in all types of SOT; however, in KT recipients the prevalence of ESBL-E, mainly in urinary tract infections (UTIs) may be >30% in high endemic centers [12–33] (**Table 1**). Data from the Swiss Transplant Cohort showed that, ESBL production was observed in 11.4% Enterobacterales isolated from 1072 SOT recipients [70]. Enterobacterales infections occurred at a median of 69 days after transplant, interestingly patients were

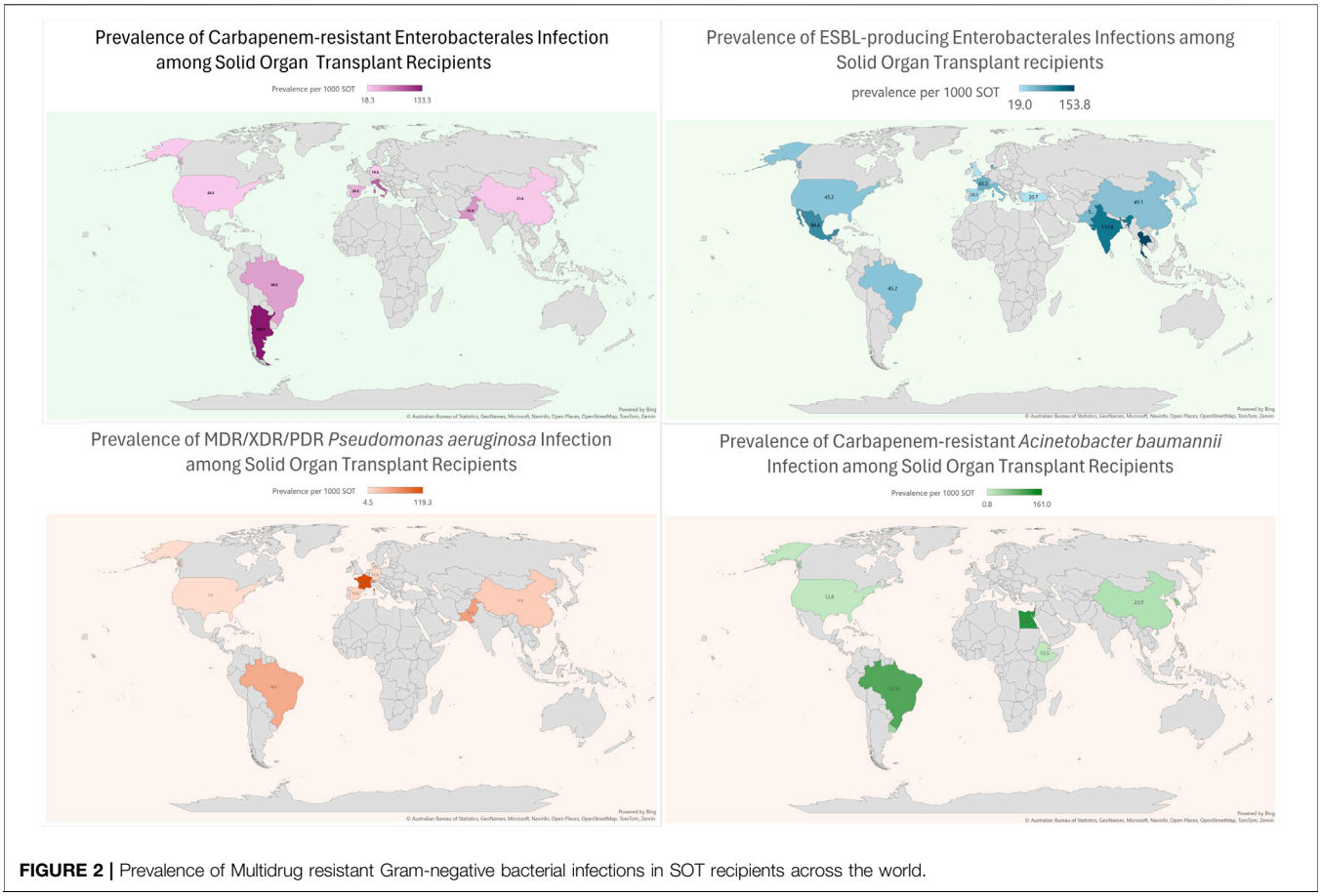

FIGURE 2 | Prevalence of Multidrug resistant Gram-negative bacterial infections in SOT recipients across the world.

TABLE 1 | Prevalence of MDRO infections in SOT recipients reported in studies from low- and medium-income and high-income countries.

Type of resistance	Low and medium-income countries				High-income countries			
	All infections	BSI	UTI[a]	LRTI	All infections	BSI	UTI	LRTI
ESBL	7.0% (4.4%–11.2%)	3.4% (0.9%–11.7%)	14.4% (5.6%–21.6%)	NA	5.5% (2.2%–13.6%)	12.8% (7%–40%)	5% (1%–6%)	NA
CRE	4.0% (0.9%–15.7%)	2.0% (0.9%–7.8%)	2.8% (0.8%–7.7%)	1.3% (1%–2.1%)	6% (1.9%–10.3%)	8%	NA	NA
DTR-Pa	1.4% (0.8%–3.9%)	3.1% (1.5%–8.0%)	1.1% (0.8%–1.5%)	3.2%	7%	10%	NA	9% (3%–15%)
CR-Ab	4.1% (0.8%–28.6%)	1.4% (1.1%–28.6%)	NA	5.8% (3.8%–9.7%)	1%–6%	NA	NA	NA

[a]*Rates of UTI, are mainly obtained from studies including kidney transplant recipients.*
References: ESBL LMIC [13,16–21,34,35]; ESBL HIC [22–33,36–41]; CRE LMIC [14,16,20,42–47]; CRE HIC [39,48–53]; DTR-Pa LMsIC [14,16,46,54–58]; DTR-Pa HIC [2,22,49,52,59–61]; CR-Ab LMIC [15,16,20,46,57,62–65]; CR-Ab HIC [22,66–69].

predominantly outpatients. Higher prevalence of ESBL-E has been reported in studies analyzing SOT recipients with BSI and UTI [36,37,71]. In a study assessing the epidemiology of UTI in a cohort of 4388 SOT recipients in Spain, the prevalence of ESBL in *E. coli* was 26% [38].

Two large studies have investigated molecular characteristics of MDR-E isolated in SOT recipients, from Spain and US each. In the Spanish study, 541 MDR-E isolates were collected. The main microorganisms were *E. coli* (46.2%), *K. pneumoniae* (35.3%), *E. cloacae* (6.5%) and *C. freundii* (6.3%). Overall, 78.0% of strains harbored ESBL genes, CTX-M-group-1 being the most prevalent (53.3%) followed by CTX-M-group-9 in 15.4%. Among ESBL-producers, 2.1% of *E. coli*, 47.3% of *K. pneumoniae* and 11.1% of *E. cloacae* harbored a carbapenemase gene. Hyperproduction of chromosomal-AmpC was detected in *E. cloacae* (57.7%), *C. freundii* (82.6%) and other MDR-E species (39.1%) [72]. In

the US study on 88 transplant recipients, 20% of patients were colonized with MDR-E (ESCR-E only $n = 23$; CRE only $n = 12$; both $n = 5$), 52% of ESCR-E carried blaCTX-M. Post-transplant MDR-E infection rate was 10%, the attack rate was higher following CRE than ESCR-E colonization (53% vs. 21%, $p = .05$) [39].

Main risk factors for ESBL-E infections after SOT are reported in **Table 2** [73]. In this regard, the role of targeted perioperative antibiotic prophylaxis (T-PAP) is still an open issue [74]. Two studies, from France and Thailand each, showed a reduction of ESBL-E infections in patients receiving T-PAP after OLT and KT, respectively [13,40]. However, both of them showed several limitations including observational design, heterogeneity in drugs used in the OLT study, and consideration of asymptomatic bacteriuria as an endpoint in the KT cohort. Furthermore, it should be remarked that carbapenem exposure is the main driver for carbapenem resistant infections.

ESBL-E infections are associated with increased length of stay, mainly in case of initial inappropriate therapy [34,35]. In addition, high recurrence rates have been reported ranging from 25% for BSI to 79% for UTI, mainly in KT recipients [34,90]. Factors associated with relapse were inappropriate empirical therapy, advanced age, and persistent bacteriuria [41,70].

Carbapenem-Resistant Enterobacterales

The prevalence of CRE infection after SOT varies according to the type of organ, being higher among liver (2%–10%) and lung (5%–7%) transplant recipients [91]. These rates seem to be a little higher in HIC than in LMIC (see **Table 1**) [42–45,49–52]. The rate of CRE infection is on average 30% among CRE carriers [53]. Usually, CRE infection occurs in the first 4–8 weeks after transplant, earlier infections (within 2 weeks) are observed in pre-transplant carriers and/or in donor derived infections (DDI) [48,53,92]. Notably, incidence of DDI due to CRE is high in China, one study focused on KT patients reported that possible DDI increased the risk of CRE infection by more than six times [75]. Authors reported varying prevalence rates of CRE among donor or preservation fluid cultures, ranging from 1.6% to 19.2% [93–95].

CRE infection after SOT often presents as severe infection with BSI and/or lung involvement [76,91].

Carbapenemases show significant geographical variation—*K. pneumoniae* carbapenemases (KPC) remain the commonest in United States, the metallo-beta-lactamases (MBLs) are most common in the countries of South and Southeast Asia and OXA-48-type carbapenemases in the Middle East, Mediterranean and northern African countries [96–98]. In the two studies assessing molecular characteristics of MDR-E isolated from SOT recipients, the main mechanisms of carbapenem resistance were OXA-48 in Spain accounting for 78% of the isolates, and KPC in US detected in 72% of CRE [39,72]. These mechanisms were mostly detected in *K. pneumoniae* isolates. Few studies in LMICs investigated this issue. The proportion of strains with carbapenemase-producing is reported to be 46%–84% among OLT recipients and 83% among KT recipients. KPC-producing CRE appears to be the most frequent. The second most common carbapenemase is NDM, which corresponded to 28% in an OLT cohort in China and 2% in a KT cohort in Brazil. Despite, CRE post-transplant infection rates are high in India, details about the proportion of NDM and KPC are not available [99]. Other carbapenemases, such as IMP, are less frequent and often associated with outbreaks [77,78,100,101].

Risk factors for CRE infection have been usually investigated in specific organ transplant settings and most commonly in OLT recipients (see **Table 2**) [48,75,79,80]. Carriage, either acquired before or after transplant, and peri-surgical complications have been associated with highest risk of developing CRE infection [48,77]. For pre-transplant carriage, shorter the time of detection before SOT, higher is the risk of infection after SOT [81]. For post-transplant carriage, it is worth mentioning that this occurs 2-3 times as more frequently than pre-transplant carriage, thus in high endemic areas it could be considered to repeat the screening for rectal carriage, which is usually done before or at transplant time, also during the post-transplant period during ICU or hospital stay. Conversely, the role of T-PAP for CRE is under debate [74,82].

Rates of mortality and graft failure in patients developing CRE infection after SOT are as high as on average 40% and 20%, respectively. After adjusting for confounding variables CRE infection was found as a significant predictor of poor outcome [83].

Difficult-To-Treat Resistant P*seudomonas aeruginosa*

Assessing the burden of difficult-to-treat resistant (DTR) *P. aeruginosa* (DTR-Pa) in SOT recipients is difficult for several reasons including: i) different drug resistance definitions used across centers and study periods; ii) analysis of respiratory isolates generally available only for LuT recipients while for other types of transplant most data come from studies on BSI; iii) cumulative data on drug resistance provided including also other pathogens; and iv) lack of large multicenter studies.

With this premise, DTR-Pa appears to be the MDRO with the lowest prevalence among SOT in LMIC, described from 0.8% to 3.9% in KT and OLT recipients (**Table 1**) [54–58]. In HIC, Pa generally ranked first among pathogens isolated from LuT recipients, with rates of MDR ranging from 7% to 50% [59,60,84]. In a single-center Spanish study, including 318 consecutive episodes of BSI in a cohort of non-lung SOT recipients, 44 (15%) BSI were caused by Pa with 31 (63%) strains classified as XDR [61]. The most frequent source was UTI, and the median time from transplantation to BSI was shorter for XDR episodes (66 vs. 278 days). Independent risk factors for XDR Pa BSI were prior transplantation, nosocomial acquisition and septic shock [85]. Only colistin and amikacin maintained activity against XDR strains. Compared to patients with susceptible-Pa BSI, those with XDR-Pa BSI received more frequently inappropriate empirical treatment (58% vs. 22%), and had higher 7-day (20.7% vs. 8.5%) and 30-day (38% vs. 16%) mortality rates.

Few data are available about the mechanisms underlying DTR and CR phenotypes in Pa. In a recent study including CR-Pa from

TABLE 2 | Risk factors for MDRO infection and for mortality.

Type of resistance	Risk factors for infection	Risk factors for mortality
ESBL-E [13,34,40,70,71,73]	*General Characteristics* - Female gender - Kidney Transplant - MELD score >25 *Colonization status* - ESBL-Enterobacterales carriage in the prior 1 year *Pre-SOT antibiotic exposure/prophylaxis* - Pre-operative prophylaxis for spontaneous bacterial peritonitis - Carbapenems prophylaxis - Exposure to third-generation cephalosporin, TMP/SMX or echinocandins in the prior 6 months *Post-SOT condition* - Acute rejection in prior 3 months - Reoperation - Corticosteroid containing immunosuppressive regimen	*Severity of patient and/or condition* - Pitt bacteremia score - Mechanical ventilation at the time of infection diagnosis
CRE [42,43,48,74–83]	*General Characteristics* - Male gender - Older age - Time of hospitalization - Lung transplant - Liver transplant - Multiple infected organisms or sites - Previous infections - Dialysis - MELD score >32 - Median lymphocytes count under 700 cell/mm3 *Colonization status* - Pre/post-transplant CRE carriage - Multisite colonization - Colonization by more than one species of CRE *Pre-SOT antibiotic exposure* - Carbapenem use (OR 2.53, OR 2.80) *Post-SOT condition* - Combined transplant - Prolonged mechanical ventilation - Possible donor -derived infection - Delayed kidney function/Ureteral stent - CMV infection - Re -transplantation - Rejection - Mycophenolate use	*General Characteristics* - older age - CMV disease - Lymphocytes ≤600 U/mm^3 - Pitt bacteremia score - Graft failure *Severity of patient and/or condition* - Septic shock - High SOFA score - Multiple infected organisms or sites - Genitourinary source - No source control - INCREMENT-CPE mortality score ≥8 *Antibiotic exposure* - Appropriate empiric therapy (protective) - Polymyxin exposure in the prior 6 months
DTR-Pa [54,59–61,84,85]	*General Characteristics* - *Hospital stay > 10 days* - *Lower median lymphocyte counts* - *Central venous catheter* - *Urinary catheter* - *Prior transplantation* - *ICU admission in previous year* - *Septic shock* *Pre-SOT antibiotic exposure* - *Prior carbapenem use* - *Prior ciprofloxacin use* *Post-SOT condition* - *re-transplantation* - *urological surgical procedure after Kidney transplant*	*Severity of patient and/or condition* - Bacteremia - creatinine >1,5 - onset of BSI while in ICU
CR-Ab [20,44,62,86–89]	*General Characteristics* - *Liver Transplant performed because of fulminant hepatitis* - *high preoperative serum levels of BUN* - *pre-operative hypoalbuminemia* *Post-SOT condition* - *Fungal culture positivity after SOT* - *long duration of surgery* - *tracheal intubation twice* - *longer cold ischemia time* - *post-Liver transplant need for dialysis*	*Severity of patient and/or condition* - *Platelet count < 50,000/mm3* - *Mechanical ventilation at the onset of CRAb* - *ICU-acquired infection* *Antibiotic exposure* - *Inappropriate empiric therapy* - *Colistin-carbapenem regimens*

FIGURE 3 | Spectrum of various novel agents active against carbapenem-resistant Gram-negative organisms (modified from: European Respiratory Review 2022 31: 220119) *This drug may retain activity against serine-type carbapenemases (e.g., GES) but are inactivated by metallobetalactamases This combination has been shown to be active *in vitro* against some MBL producing *P. aeruginosa* strains.

972 individuals (USA $n = 527$, China $n = 171$, south and central America $n = 127$, Middle East $n = 91$, Australia and Singapore $n = 56$), almost a quarter of strains were shown to produce a carbapenemase, mostly consisting of KPC-2 (49%) or VIM-2 (36%), with a prevalence varying across south and central America 69%, Australia and Singapore 57%, China 32%, Middle East 30%, US 2% [4]. In a study on 163 clinical *P. aeruginosa* isolates in adult cystic fibrosis and LuT in Australia, 32 (19.6%) were XDR, 82% of strains were susceptible to ceftolozane/tazobactam [102].

Mortality risk associated with DTR/XDR or CR Pa infection after SOT seems to be higher in patients with septic shock and/or multiorgan failure and ICU stay [61].

Carbapenem-Resistant *Acinetobacter baumannii*

The overall rate of CRAb infection among SOT recipients varies from 1% to 6% in HIC [66–69]. In a study conducted in US on 248 patients with *A. baumannii* infection, CRAb rates were higher among SOT compared to non-SOT patients (43% vs. 14%) [103].

CRAb prevalence after SOT in China and Brazil can reach 29% [10,16,62,63,86]. A systematic review focused on uro-pathogens among KT recipients highlighted *A. baumannii* as the third most frequently encountered Gram-negative bacteria, displaying a prevalence rate of 8% in the Middle-East [104] Additionally, 4%–10% of OLT recipients have pneumonia attributed to CRAb in China, Brazil, Egypt and Uruguay [64,65,87,88] A Chinese study involving 107 LuT recipients found that CRAb was the predominant MDRO infection agent, accounting for 35% of Gram-negative MDRO [63]. Thus local epidemiology is pivotal in planning screening for CRAb before and after SOT.

A. baumannii is intrinsically resistant to a wide range of antibiotic classes, caused by simultaneous mechanisms of resistance [105]. Among these, decreased outer-membrane porins, constitutional expression of efflux pumps, intrinsic harboring of β-lactamases and plasmidial carbapenemase, has been widely described. Among carbapenemases, OXA-23-like are the most common. However, CRAb isolates harboring MBL, such as blaNDM-1 genes, has been associated with increased mortality rates in a study conducted from Pakistan [106–108]. Resistance to polymyxin is infrequent and appears to be linked to outbreaks [46,62,86,109].

Data about risk factors for CRAb infections were exclusively reported for OLT recipients from LMICs [87,88]. (**Table 2**) CRAb infection mortality rates are the highest among SOT MDRO infections and often exceed 40% (ranging from 20% to 47%) [62,86,87,89,110].

Diagnosis of MDRO Infections After SOT

Timely diagnosis of MDRO infections in SOT recipients is critically important to patient and allograft survival. Advanced diagnostic methodologies may aid in shortening the time to narrowest appropriate antibiotic administration; however, data on their optimal use and interpretation in this specific population are limited [111]. In addition, the availability of rapid diagnostics may vary by location.

In a survey among American Society Transplant (AST) members, 19 respondents indicated frequently ordering multiplexed molecular assays (82%) and antimicrobial susceptibility to new antibiotics (76%), and >80% of respondents reported to change treatment according to the results of such tests [112]. However, data from other countries are missing.

Preliminary data on the use of a multiplex PCR panel in 29 transplant recipients with 45 bloodstream infections remarked the possibility of off-target pathogens [113]. Indeed, a consensus conference to define the utility of these new diagnostics in SOT concluded that prospective multicenter studies are needed to

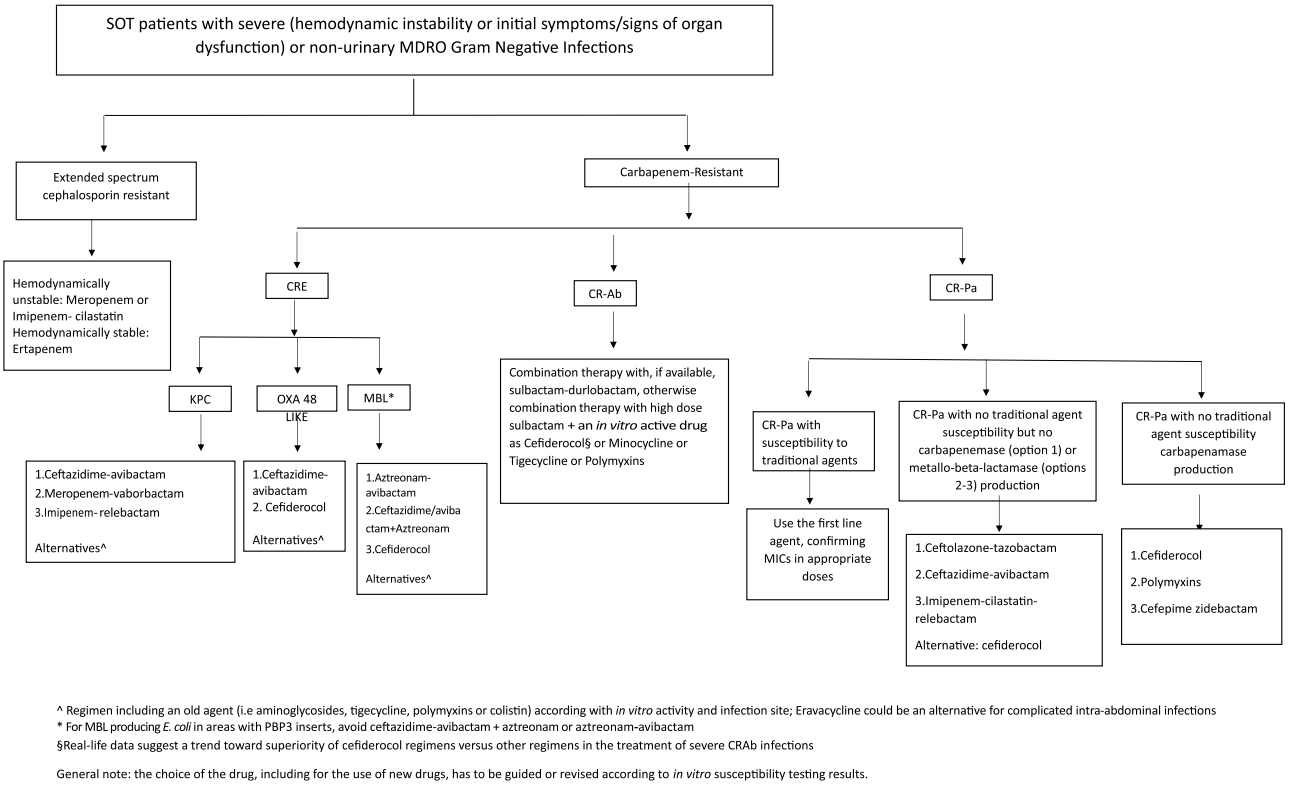

FIGURE 4 | Treatment flowchart.

investigate their performance and reproducibility compared to reference standards, the optimal timing of testing to predict and/or diagnose disease, the impact on clinical outcomes, and the cost-effectiveness also for point-of care applications [112].

ESBL-Producing Enterobacterales

Molecular detection of ESBL genes may aid in decreasing the time to diagnosis and initiation of targeted antimicrobials in SOT recipients. Several systems capable of detecting ESBL-producing Enterobacterales in lower respiratory tract specimens and blood are commercially available; however, not all genes responsible for ESBL production, including bla_{TEM} and bla_{SHV} are included on all panels. Moreover, assays used for rapid genotypic resistance detection display reduced accuracy in polymicrobial infections [111,112]. Rapid phenotypic antimicrobial susceptibility testing has also been demonstrated to reduce the time to optimal therapy among bacteremic non-transplant patients [111,114].Current recommendations underscore the need for conventional antimicrobial susceptibility testing to verify results of rapid genotypic and phenotypic testing when there is concern for a highly resistant phenotype and for polymicrobial infection [1,111].

Carbapenem-Resistant Enterobacterales

Several rapid diagnostic tests for carbapenem resistance are commercially available and include real-time polymerase chain reaction and nucleic acid tests such as the Xpert® Carba-R (Cepheid), Verigene® BC-GN (Luminex), and BioFire® FilmArray® Blood Culture Identification 2 Panel, which test for bla_{KPC}, bla_{NDM}, bla_{OXA}, bla_{VIM}, and bla_{IMP} gene sequences [115,116].However, this assays display reduced accuracy in polymicrobial infections [111,112]. Other methods for rapid diagnosis of CRE include chromogenic assays as RAPIDEC® CARBA NP (bioMérieux) and Rapid CARB Blue (Rosco Diagnostics) and matrix-assisted laser desorption ionization-time-of-flight mass spectroscopy (MALDI-TOF MS) [117–119]. While rapid diagnostic assays for the detection of carbapenem resistance may reduce the time to effective antimicrobial therapy, current guidelines and expert consensus recommendations recommend conventional antimicrobial susceptibility testing to confirm the diagnosis of a CRE infection [1,111].

According to local availability, antimicrobial susceptibility to old and new agents is advisable not only on the clinical isolate but also on the colonizing strain in order to start promptly an appropriate treatment upon the onset of infection symptoms/signs.

Difficult-To-Treat Resistant *Pseudomonas aeruginosa*

Difficult-to-treat resistance has been defined as *P. aeruginosa* which exhibits non-susceptibility to aztreonam, piperacillin-tazobactam, ciprofloxacin, levofloxacin, ceftazidime, cefepime, meropenem, imipenem-cilastatin [120].

Rapid diagnostic tests for the identification of *P. aeruginosa* are commercially available and include nucleic acid tests, MALDI-TOF MS, and peptide nucleic acid fluorescent *in situ* hybridization (PNA FISH; AdvanDx) [121]. However, given that DTR-Pa evolves due to multiple resistance mechanisms, current

guidelines recommend against rapid diagnostic testing to guide empiric treatment [1].

Carbapenem-Resistant *Acinetobacter baumannii*

In low-prevalence areas, use of rapid diagnostic and phenotypic tests for the detection of CRAB has posed clinical challenges. A recent study comparing the NG-Test CARBA 5 (NG-Biotech) version2 with the Xpert-Carba-R assay, modified carbapenem inactivation method (mCIM), and the CIMTris assay with whole-genome sequencing as the reference standard demonstrated that the NG-Test CARBA 5 and Xpert Carba-R had an overall percentage agreement of 6.2%, noting OXA-type carbapenemases are not included, and the CIMTris had an overall percentage agreement of 99%. In addition, approximately 96% of isolates incorrectly tested positive for IMP on NG-Test CARBA 5 [122]. Supplementary studies are being undertaken to identify opportunities for rapid diagnostics for CR-Ab infections [123,124].

Management of MDROs in SOT patients

The management of MDRO infections in SOT patients is not different from that recommended in other patients in view of choice agent/regimen and treatment duration. The outsized burden of AMR in the LMICs is further complicated by non-availability of recently approved antibacterial agents. For example, in the South Asian region, where carbapenem-resistant infections are very common, cefiderocol, sulbactam-durlobactam, meropenem-vaborbactam, imipenem-relebactam, eravacycline and plazomicin are not yet available. The treatment for severe infections, with bacteraemia as a prototype, is discussed here. Overall, spectrum of activity of various antimicrobial agents is shown in **Figure 3**. Selection of agents should be based on *in vitro* activity and local availability. An algorithm for treatment approaches is proposed in **Figure 4**.

Third-Generation Cephalosporin-Resistant Enterobacterales

Carbapenems are considered the drug of choice for the management of severe ESBL-E infections in SOT patients [120,125]. The MERINO trial compared piperacillin-tazobactam versus meropenem for the management of ceftriaxone-resistant *E. coli* and *Klebsiella* spp. bacteremia. Thirty-day mortality, was higher in the piperacillin-tazobactam group (12% vs. 4%; absolute risk difference 9%), failing to meet the non-inferiority margin [126]. The carbapenem superiority appears to be related to elevated piperacillin-tazobactam MICs with co-occurrence of narrow spectrum oxacillinases [127]. Ertapenem is generally deferred as an upfront therapy in critically ill patients [128]. Carbapenems including ertapenem, fluoroquinolones, TMP-SMX and aminoglycosides are options for stable patients with pyelonephritis and other UTI. Switch to oral regimens can be considered once clinical stability is achieved and susceptible oral agents with good intestinal absorption are available [125].

Klebsiella aerogenes, *Enterobacter cloacae* complex, and *Citrobacter freundii* are commonly associated with higher risk of AmpC-β-lactamase production [129]. Despite its limited ability to induce AmpC-β-lactamases, piperacillin-tazobactam is considered inferior for treatment due to the risk of hydrolysis [130]. MERINO 2, a small RCT evaluating piperacillin-tazobactam versus meropenem in bacteremia with presumed AmpC-producing organisms showed no difference between the two agents in clinical failure and mortality [131]. However, some observational data point to poorer outcomes with piperacillin-tazobactam [132–134]. Cefepime minimally induces AmpC β-lactamases and is relatively stable to AmpC hydrolysis. Some observational studies show higher mortality with cefepime MICs 4–8 μg/mL (susceptible dose-dependent range), probably correlating with co-production of ESBLs [135]. Carbapenems are stable against AmpC β-lactamases and are the drugs of choice for severe infections and/or upon isolates with MICs ≥4 μg/mL for cefepime [120].

Studies addressing the role of intestinal decolonization for SOT recipients colonized with ESCR-E are limited. One case-control study described the successful use of a 5-day course of norfloxacin in reducing the burden of ESBL-E in stool samples obtained from OLT recipients during an outbreak in a transplant unit [136]. However, other studies have described the development of colistin- and tobramycin-resistant *K. pneumoniae* after attempted decolonization with orally administered colistin [137,138]. Given the risk of selecting resistant organisms, this approach is not recommended [139].

Carbapenem-Resistant Enterobacterales

Once the CRE is confirmed, carbapenamase testing and antimicrobial susceptibility for all available agents are recommended. For KPC-producing CRE isolates, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam are the first line options of therapy [125]. Cefiderocol can be used provided susceptibility testing is available. For OXA-48 type carbapenemase-producing CRE, ceftazidime-avibactam is the preferred agent of choice. Cefiderocol is an alternative [140,141]. NDM-producing CRE is best treated with a combination of ceftazidime-avibactam and aztreonam. Aztreonam retains activity against MBL but is inactivated by coexistent ESBLs, AmpCs or OXA-48 like enzymes. Avibactam protects the aztreonam from these mechanisms. Cefiderocol is a potential option for treatment of NDM- and other MBL-producers if the isolate is susceptible to this agent. In MBL-producing *E coli,* presence of four-amino acid (YRIN or YRIK) inserts in Penicillin binding protein 3 (PBP3) are common in countries like India and China, reducing the interaction of aztreonam at that site, leading to higher MICs [142,143]. The efficacy of ceftazidime-avibactam plus aztreonam may not be retained in MBL producing *E coli* isolates with PBP3 inserts.

Few studies have assessed the efficacy of the new drugs specifically in SOT recipients. Most data are available for ceftazidime-avibactam as it was first introduced in Europe and US. A multicentre observational study of 210 SOT recipients with BSI due carbapenemase producing *K. pneumoniae*, 149 received active primary therapy with CAZ-AVI (66/149) or best available treatment (BAT) (83/149). Patients treated with CAZ-AVI had higher 14-day (80.7% vs. 60.6%, p = 0.011) and 30-day (83.1% vs. 60.6%, p = 0.004) clinical success and lower 30-day mortality

(13.25% vs. 27.3%, p = .053) than those receiving BAT. In the adjusted analysis, CAZ-AVI increased the probability of clinical success; in contrast, it was not independently associated with 30-day mortality. In the CAZ-AVI group, combination therapy was not associated with better outcomes [144].

There is a paucity of data regarding intestinal decolonization of SOT recipients colonized with CRE. A clinical trial on SOT colonized with MDRO failed to show a benefit from decolonization with oral colistin plus neomycin, conversely decolonization was associated with adverse events [145]. Thus, this approach is currently not recommended. The role of fecal microbiota transplantation in restoring intestinal microbial diversity in SOT recipients colonized with MDROs seems promising; however, more data on clinical effectiveness and safety are needed [146].

Difficult to Treat Resistant *P. aeruginosa*

Treatment of Pa with carbapenem resistance can be approached in three ways. If a traditional agent like piperacillin-tazobactam, cefepime, ceftazidime or fluoroquinolones remains susceptible with carbapenem resistance, they can be used in optimal doses [147]. This is primarily due to lack of functional OprD which is required for carbapenem entry.

If there is resistance to traditional agents and to carbapenems (e.g., a XDR or DTR strain), it is important to check for carbapenemases [148,149]. If carbapenemase testing is negative, ceftolozane-tazobactam is considered the drug of choice when *in vitro* activity is confirmed. For CR-Pa where resistance is mediated by a non-MBL carbapenemase (e.g., KPC, GES) ceftazidime-avibactam or imipenem-relebactam could be used; cefiderocol is an alternative option.

For CR-Pa isolates with documented MBL production, the therapeutic options are limited. Cefiderocol or polymyxins are generally the only drugs maintaining *in vitro* activity. However, data on clinical efficacy are controversial for cefiderocol, and generally poor for polymyxin/colistin mainly due to toxicity. The combination of ceftazidime-avibactam and aztreonam could be an option although clinical experience is limited [150,151]. Cefepime-zidebactam has been reported as a salvage option in these patients [152,153].

Carbapenem Resistant *Acineotacter baumannii*

The therapy of CRAb infections is particularly complex in view of difficulty in differentiating between colonization and invasive infection, especially in the lung, with extremely limited therapeutic options. There is no single antibiotic available as a preferred agent in the management of CRAb infections. One of the recent promising agents is sulbactam-durlobactam. In a phase 3 RCT, 28-day all-cause mortality was 19% in the sulbactam–durlobactam group and 32% in the colistin group, an absolute difference of −13.2%, meeting the non-inferiority criteria. In both groups, combination with imipenem-cilastatin was used. Most guidelines currently recommend sulbactam based therapy and wherever possible in combination with other *in-vitro* active agents [125]. Sulbactam is a competitive betalactamase-inhibitor with independent anti-*Acinetobacter* activity via saturation of PBP1 and PBP3 in high doses [154]. But the susceptible MIC range for sulbactam is not established. Also, changes in the above PBPs can decrease its affinity and result in resistance. Few studies have supported the benefit of ampicillin-sulbactam especially against polymyxins [105]. The options for combination therapy with sulbactam include minocycline, tigecycline, polymyxins and cefiderocol. Colistin is frequently active *in vitro*; however, the unfavourable PK/PD profile of this drug results in low efficacy and high toxicity rates. Two large randomized controlled studies have shown the addition of high-dose meropenem to colistin does not result in clinical benefit [155,156]. Nebulised polymyxins are not currently recommended in view of preferential distribution to the unaffected areas of the lung, absence of benefit in randomized trials and potential for bronchospasm [157–159]. The role of cefiderocol is debated [160,161]. This drug shows high rates of *in vitro* activity and, despite it was associated with higher mortality compared with standard treatment (mostly consisting of colistin-based regimens) in patients with CR-Ab infections in the phase III CREDIBLE-CR trial [161], it has been shown to be more or equally effective than older regimens, with a significantly lower toxicity, in several real-word observational studies [162].

CONCLUSION

To conclude, to draw the global burden of MDROs in SOT recipients is difficult due to the lack of standardization in screening and reporting colonization and/or infections with such pathogens; and the access to diagnostic and therapeutic resources could be variable across countries. To improve outcomes associated with MDRO colonization and/or infections in SOT recipients, new rapid advanced diagnostics could be supportive, as well as the prompt availability of phenotypic susceptibility to old and new drugs. Use of these tests should be guided by local epidemiology and patient risk factors, their impact on outcome should be investigated.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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ORIGINAL RESEARCH
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Infection-Related Hospitalizations After Simultaneous Pancreas-Kidney Transplantation Compared to Kidney Transplantation Alone

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The total burden of infections after transplantation has not been compared in detail between recipients of simultaneous pancreas-kidney transplantation (SPK) and kidney transplantation alone (KTA). We compared infection-related hospitalizations and bacteremias after transplantation during 1- and 5-year follow-up among 162 patients undergoing SPK. The control group consisted of 153 type 1 diabetics undergoing KTA with the inclusion criteria of donor and recipient age < 60, and BMI < 30. During the first year, SPK patients had more infection-related hospitalizations (0.54 vs. 0.31 PPY, IRR 1.76, p = <0.001) and bacteremias (0.11 vs. 0.01 PPY, IRR 17.12, p = <0.001) compared to KTA patients. The first infection-related hospitalizations and bacteremias occurred later during follow-up in KTA patients. SPK was an independent risk factor for infection-related hospitalization and bacteremia during the first year after transplantation, but not during the 5-year follow-up. Patient survival did not differ between groups, however, KTA patients had inferior kidney graft survival. SPK patients are at greater risk for infection-related hospitalizations and bacteremias during the first year after transplantation compared to KTA patients, however, at the end of the follow-up the risk of infection was similar between groups.

Keywords: kidney transplantation, pancreas transplantation, infection, bacteremia, infection-related hospitalization, complication, survival

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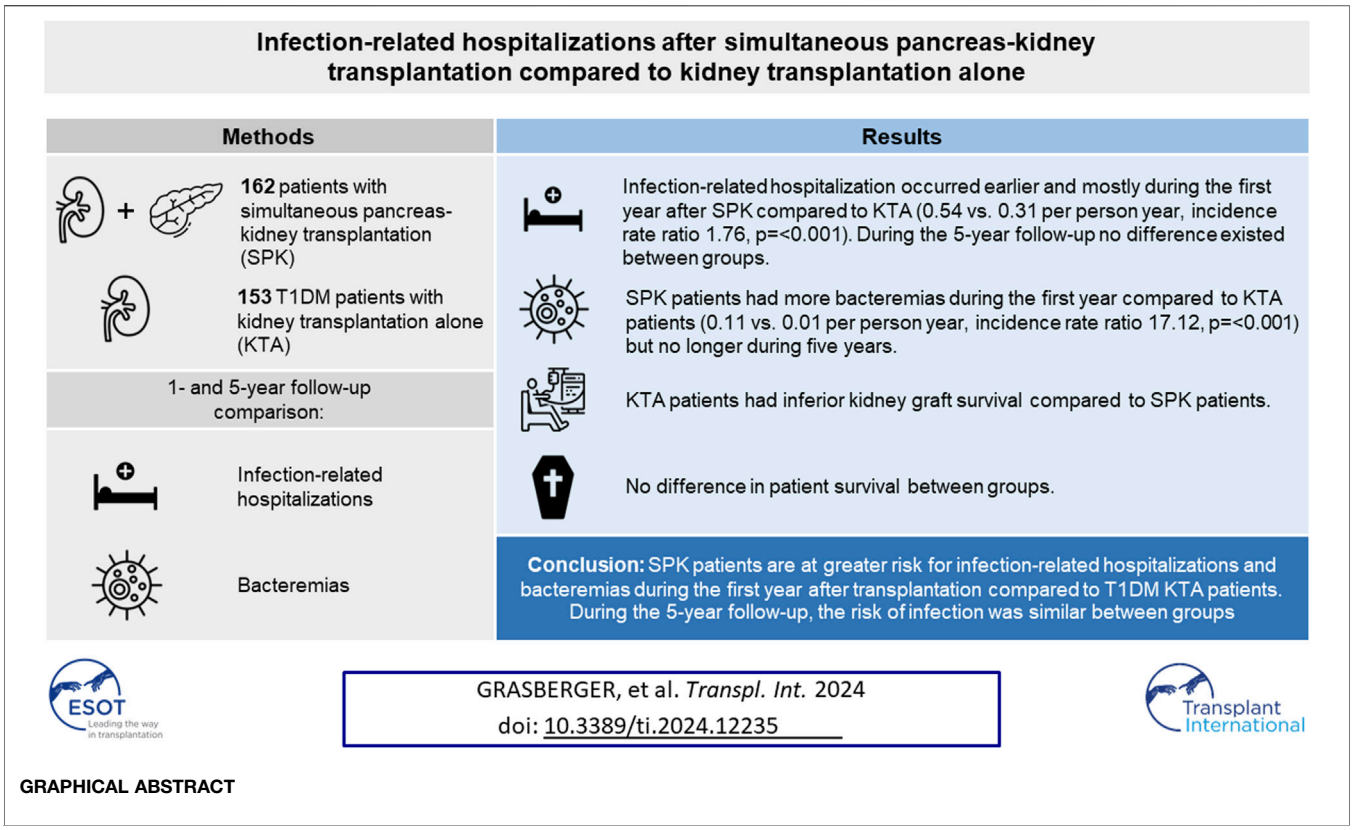
INTRODUCTION

The results of simultaneous pancreas-kidney transplantation (SPK) have improved during the last decades due to advanced surgical techniques and immunosuppressive therapies [1, 2]. Many studies have shown superior patient and kidney graft survival in SPK patients compared to kidney transplantation alone (KTA) [3–8], as well as the reduction of micro- and macrovascular

Abbreviations: CMV, cytomegalovirus; D+/R−, donor cytomegalovirus positive, recipient negative; DGF, delayed graft function; GI, gastrointestinal; KTA, kidney transplantation alone; MMF, mycophenolate mofetil; SOT, solid organ transplantation; SPK, simultaneous pancreas-kidney transplantation; UTI, urinary tract infection.



GRAPHICAL ABSTRACT

complications of diabetes [9–12]. However, postoperative complications are common in SPK patients with relaparotomy rates reported to range from 23% to as much as 44% [13–15], and the incidence of surgical site infections is among the highest in solid organ transplant (SOT) recipients [16]. Surgical complications cause significant morbidity and may adversely affect the pancreas graft survival [14]. In addition, more intensive immunosuppression, and especially the use of lymphocyte-depleting agents, may predispose SPK patients to increased infections compared to KTA patients.

On the other hand, KTA patients continue to be exposed to the hyperglycemic conditions and studies have shown increased risk of infections [17] and infection-related mortality [18] among patients with diabetes compared to the general population. Also, in a large study comparing infections among kidney transplant recipients, the infection-related mortality was higher for diabetics compared to non-diabetics [19]. Therefore, the ongoing diabetes and hyperglycemia may continue to act as a risk factor for infections in diabetic KTA patients compared to SPK patients who usually achieve normoglycemia after a functional pancreas transplant.

Data about the long-term infectious complications in SPK patients compared to KTA patients are limited and studies comparing the infection burden of specifically diabetic KTA patients with SPK patients do not exist to our knowledge. The primary aim of this study is to compare infection-related hospitalizations and bacteremias between SPK and type 1 diabetic KTA patients after transplantation during 1-year and 5-year follow-up time. Our aim is also to characterize the site of infections, the risk factors for infection-related hospitalizations and bacteremias, as well as the impact of infection-related hospitalization and bacteremia on patient and graft survival in both groups. In addition, we compare overall patient and graft survival between SPK and KTA patients.

MATERIALS AND METHODS

We analyzed retrospectively all patients undergoing SPK for type 1 diabetes since the program was launched in Finland from March 2010 to December 2019. All transplantations were done in Helsinki University Hospital, the only transplant center in Finland. The control group consisted of patients with end-stage kidney disease secondary to type 1 diabetes who received KTA from a deceased donor in our institution during 2004–2013, which was before the routine implementation of the SPK program. The inclusion criteria for the controls were donor and recipient age < 60 and BMI < 30, the same age and weight limit used for SPK. This study had the approval of the Helsinki University Hospital institutional review board, and the Finnish Institute for Health and Welfare regarding the use of their administrative health data on hospitalizations in this study (THL/1877/5.05.00/2019).

All transplantations were ABO compatible and cytotoxic cross-match negative. For the SPK group, immunosuppression comprised tacrolimus, mycophenolate mofetil (MMF) and

steroid. All SPK patients received induction with single-dose antithymocyte globulin (8 mg/kg) pre-transplantation. The post-transplantation trough level target for tacrolimus was 12–15 ug/L the first 14 days and 10–12 ug/L for days 15–90 after transplantation. From three to 12 months post-transplantation, the trough level target was 9–11 ug/L, from 12 to 24 months 8–10 ug/L, and thereafter 7–9 ug/L. Steroid was discontinued after 6 months unless donor-specified-antibodies existed, in which case methylprednisolone 2–4 mg remained as part of the immunosuppression. All transplantations were performed using enteric proximal jejunal exocrine drainage. For the KTA patients, baseline immunosuppression comprised primarily of cyclosporine combined with MMF and steroid. The cyclosporine trough level target was 170–200 ug/L for the first 3 months, from three to 6 months 160–190 ug/L, six to 12 months 100–120 ug/L, 12–24 months 80–120 ug/L, and thereafter 60–100 ug/L. Immunologically high-risk KTA patients received tacrolimus (trough level target 6–8 ug/mL for the first 3 months) and in selected cases induction therapy with basiliximab was administered. Steroid was usually discontinued after 1-year post-transplantation in KTA patients.

All SPK patients received perioperative antibiotic prophylaxis with piperacillin-tazobactam and ciprofloxacin in addition to anti-fungal prophylaxis with fluconazole or anidulafungin. These prophylaxis regimens were continued for three to 5 days postoperatively intravenously. In KTA patients, a single-dose of cefuroxime was administered during operation and another dose after operation. All patients received a 6-month prophylaxis for *Pneumocystis jirovecii* pneumonia with trimethoprim/sulfamethoxazole. Ureteral stent was removed 3–4 weeks after transplantation in both groups.

Six-month CMV prophylaxis with valganciclovir (900 mg once daily, or dose adjusted to renal function) was intended for all patients with CMV D+/R− constellation in both groups. This 6-month CMV prophylaxis protocol has been used since 2004 in our institution for these high-risk patients. Also, SPK patients with CMV R+ status received a 3-month valganciclovir prophylaxis since 2019, regardless of donor CMV status. KTA patients with other constellation besides D+/R− did not receive any prophylaxis. Patients without prophylaxis were monitored preemptively during their routine follow-up visits for DNAemia and antiviral treatment was initiated if the viral load exceeded 1,000 IU/mL. In viral loads lower than that, viremia was usually only monitored. In the case of treatment for acute rejection, CMV prophylaxis was given for one-to-three months depending on the used rejection treatment.

We analyzed all infections requiring hospital admission during 5 years after transplantation. Infections during the admission for transplantation were excluded due to higher risk of infections related to surgical complications in SPK. All SPK patients were followed at our institution and the hospitalizations gathered from the national transplant register and patient electronic medical records. In KTA patients, the infection related hospitalizations were gathered from the Finnish Care Register for Healthcare, which is a national administrative health registry maintained by the Finnish Institute for Health and Welfare, using ICD-10 codes A00–B99, J00–J99 and R50–R50.9 for primary diagnosis or as a secondary diagnosis when primary diagnosis was type 1 diabetes or diabetic nephropathy (N039*E10). Reporting of hospitalizations to the registry is mandatory by law. Additionally, in KTA patients, the follow-up data was also obtained from the national transplant register. The data were collected until 5 years from transplantation or until January 2022 in SPK patients who did not fulfil the 5-year follow-up time. Bacteremia was defined as presence of bacteria in the blood. Due to the lack of clinical information considering KTA patients, no further categorization was made.

The interval from transplantation to the first infection-related hospitalization was compared between SPK and KTA patients. The localizations of the infections were categorized as skin and soft tissue, gastrointestinal, pulmonary, pyelonephritis, unspecified, bacteremia, and CMV disease.

Statistical tests were performed using SPSS Version 28. For the comparison of study groups, 2-sided Mann-Whitney U-Test was used for continuous variables and chi-squared test for categorical variables. For the comparison of first infection-related hospitalizations or bacteremias between groups, Kaplan-Meier estimates were applied and censored for death or kidney graft loss which was defined as return to dialysis or death with functioning graft. Survival probabilities were also executed using Kaplan-Meier estimates. The SPK patients with initially functioning pancreas graft were included in the analysis. SPK patients who lost their pancreas graft, were still included in the SPK group after graft loss as they were exposed to the surgical procedure and the immunosuppression used in SPK patients. Pancreas graft failure was defined according to the definitions implemented in 2018 by the Organ Procurement and Transplantation Network (OPTN) including any of the following: recipient's transplanted pancreas is removed, recipient reregisters for a pancreas transplant, recipient registers for an islet transplant after undergoing a pancreas transplant, recipient dies or recipient's total insulin use is greater than or equal to 0.5 units/kg/day for 90 consecutive days. Cox regression models were used to study SPK as a risk factor for the first infection-related hospitalization and bacteremia after transplantation compared to KTA using only variables present at the time of transplantation. In the multivariable analysis SPK was adjusted with only recipient age and recipient sex since many of the other baseline characteristics are associated to SPK itself. Variables with $p < 0.05$ were considered statistically significant. All the infection-related hospitalizations and bacteremias during the follow-up was compared with incidence rate ratio since not all SPK patients fulfilled the 5-year follow-up. The effect of infection-related hospitalization or bacteremia on patient and kidney graft survival were studied with Cox's regression using the first infection-related hospitalization or bacteremia as time-dependent variables, adjusted with patient's age and sex.

RESULTS

Altogether 163 pancreas transplantations were performed between March 2010 and December 2019 in our institution. In

TABLE 1 | Baseline characteristics of all the patients included in the study (n = 315).

Patient characteristics	SPK (n = 162)	KTA (n = 153)	p-value
Recipient age (years)	42.6 ± 8.1	45.3 ± 8.5	0.004
Recipient male sex (%)	108/163 (67)	101/153 (66)	0.91
Recipient BMI	24.2 ± 3.2	24.5 ± 3.1	0.39
Donor age (years)	38.5 ± 13.6	44.4 ± 13.1	<0.001
Donor male sex (%)	83/162 (51)	80/153 (52)	0.91
Donor BMI	23.6 ± 2.9	24.1 ± 2.9	0.09
Kidney cold ischemia time (min)	573 ± 124	1,298 ± 222	<0.001
Time in dialysis (months)	15.0 ± 11.3	29.5 ± 18.2	<0.001
Diabetes duration (years)	33.1 ± 8.2	33 ± 8.4	0.88
HLA-AB-mismatch	2.65 ± 0.9	1.65 ± 0.9	<0.001
HLA-DR-mismatch	1.49 ± 0.6	0.62 ± 0.5	<0.001
CMV D+/R– (%)	40/162 (25)	28/153 (18)	0.17
Hemodialysis before tx (%)	68/162 (42)	66/153 (43)	0.91
Peritoneal dialysis before tx (%)	88/162 (54)	85/153 (56)	0.91
Preemptive (%)	6/162 (4)	2/153 (1)	0.28
Kidney DGF (%)	18/162 (11)	40/153 (26)	<0.001
Rejection treatment (%)	53/162 (33)	26/153 (17)	0.002
Relaparotomy (%)	37/162 (23)	2/153 (1)	<0.001
Creatinine 1 year (mg/dL)[a]	1.3 ± 0.8	1.2 ± 0.4	0.48
Creatinine 5 years (mg/dL)[b]	1.2 ± 0.5	1.43 ± 0.63	0.04

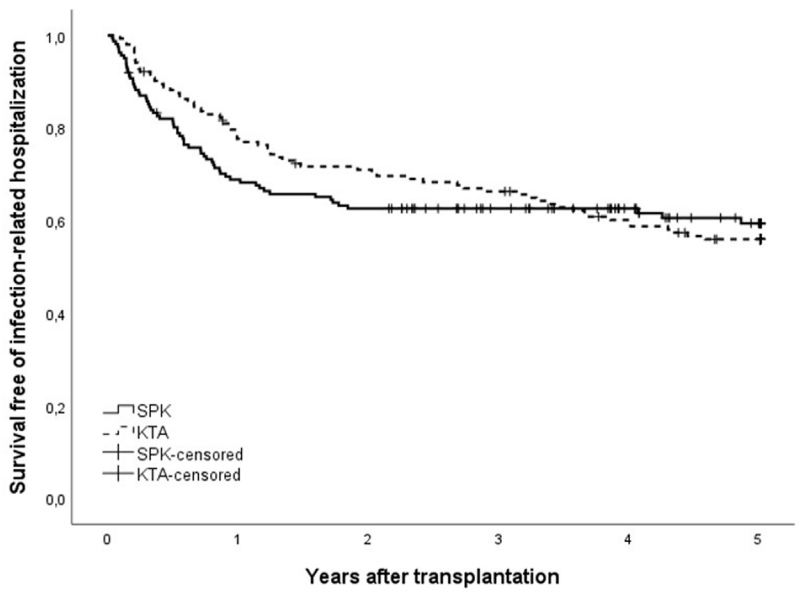
All values presented as mean ± standard deviation unless otherwise noted. BMI, body max index; CMV, cytomegalovirus; D+/R–, pre-transplant donor seropositive/recipient seronegative to CMV; DGF, delayed graft function.

[a]*Data available in 156/162 SPK patients and 129/153 KTA patients.*

[b]*Data available in 73/162 SPK patients and 122/153 KTA patients.*

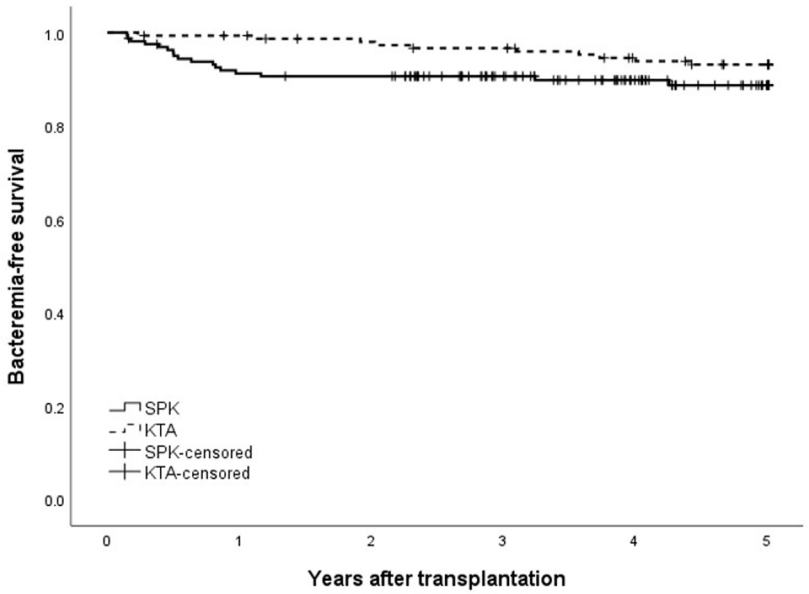
total, 161 were SPK patients and two patients received pancreas after kidney transplantation. One patient with hyperacute pancreas graft rejection and immediate removal of the graft was excluded from the analyses resulting in 162 SPK patients included in the study. For the control group, 153 patients with end-stage kidney disease (ESKD) due to diabetic nephropathy who underwent KTA, met the inclusion criteria (recipient and donor BMI < 30 and age < 60) and were included in the study. The baseline characteristics of patients are shown in **Table 1**. The median follow-up time for SPK patients was 4.7 years (range 0.2–5.0, IQR 3.1–5.0) and for KTA patients 5.0 years (range 0.3–5.0, IQR 5.0–5.0). Altogether 84 patients of the SPK patients fulfilled the 5-year follow-up (unless died or lost their kidney graft) and 78 patients had a follow-up time varying from two-to-five years.

All SPK patients received tacrolimus-based immunosuppression and ATG induction. Among KTA patients, 128 (84%) were initially on cyclosporine and 25 (16%) on tacrolimus. Altogether 6 (4%) KTA patients received induction therapy with basiliximab and 147 (96%) did not receive any induction therapy. In KTA patients on cyclosporine, the mean trough level at three and 12 months was 169 ± SD 42 ug/L and 120 ± SD 32 ug/L, respectively. In SPK patients, mean tacrolimus trough level was 11.6 ± SD 3.4 ug/L at 3 months and 9.3 ± SD 2.4 ug/L at 12 months post-transplantation.



SPK	162	110	100	82	66	49	Number of subjects at risk
KTA	153	117	105	98	86	76	
SPK	0	50	60	60	60	63	Number of events
KTA	0	34	45	51	61	66	

FIGURE 1 | First infection-related hospitalization during 5 years after transplantation between SPK (simultaneous pancreas-kidney transplantation) and KTA (kidney transplantation alone) patients, p = 0.87.



SPK	162	146	143	116	90	65	Number of subjects at risk
KTA	153	150	144	141	133	127	
SPK	0	14	15	15	16	17	Number of events
KTA	0	1	4	5	9	10	

FIGURE 2 | First bacteremia during 5 years after transplantation between SPK (simultaneous pancreas-kidney transplantation) and KTA (kidney transplantation alone) patients, $p = 0.12$.

TABLE 2 | Site of all the infection-related hospitalizations in SPK (simultaneous pancreas-kidney transplantation) and KTA (kidney transplantation alone) patients during 5 years after transplantation.

	SPK 120 episodes	KTA 143 episodes
Skin and soft tissue (%)	17/120 (14)	24/143 (17)
GI (%)	24/120 (20)	29/143 (20)
Pulmonary (%)	10/120 (8)	37/143 (26)
UTI (%)	18/120 (15)	9/143 (6)
Unspecified (%)	19/120 (16)	16/143 (11)
Bacteremia (%)	22/120 (18)	15/143 (11)
CMV (%)	10/120 (8)	13/143 (9)

GI, gastrointestinal; UTI, urinary tract infection; CMV, cytomegalovirus.

TABLE 3 | All pathogens for bacteremia in SPK and KTA patients during the 5-year follow-up.

SPK (22 episodes)	KTA (15 episodes)
Escherichia Coli 8	*Escherichia Coli 5*
Staphylococcus Aureus 6	*Staphylococcus Aureus 4*
Enterococcus Cloacae	*Pseudomonas 2*
Klebsiella Pneumoniae	*Klebsiella Pneumoniae 2*
Staphylococcus heamolyticus	*Unspecified pathogen 2*
Pseudomonas	
Candida Albicans	
Enterobacter species	
Enterococcus feacium	
Candica Glabrata	

Infection-Related Hospitalizations and Bacteremias After Transplantation

The first infection-related hospitalization during 5-year follow-up time occurred earlier and mostly during the first year in SPK patients, whereas in KTA patients the first infection-related hospitalizations occurred later during follow-up (**Figure 1**). During the first year after transplantation, SPK patients had 0.54 infection-related hospitalizations/person year and KTA patients 0.31 infection-related hospitalizations/person year with an incidence rate ratio of 1.76 (95% CI 1.2211–2.5672, $p = <0.001$). During 5 years after transplantation, SPK patients and KTA patients had both 0.18 infection-related hospitalizations/person year, with an incidence rate ratio of 1.00 (95% CI 0.7971–1.3348, $p = 0.81$).

Figure 2 depicts the first bacteremia during 5 years after transplantation between the groups. In SPK patients, the majority of bacteremias occurred during the first year while in KTA patients the first bacteremias occurred mainly after the first year and were divided more constantly for the following years. During the first year after transplantation, SPK patients had altogether 0.11 bacteremias/person year and KTA patients 0.01 bacteremias/person year with an incidence rate ratio of 17.12 (95% CI 2.704–713.40, $p = <0.001$). During 5 years after transplantation SPK patients had 0.034 bacteremias/person year

TABLE 4 | Hazard Ratios (HR) with 95% confidence intervals by Cox's regression of the risk factors for infection-related hospitalization during the first year after transplantation.

	Univariable (95 % CI)	Multivariable (95 % CI)
SPK vs. KTA	1.5 (1.0–2.4), $p = 0.06$	1.6 (1.0–2.5), $p = 0.04$
Recipient age	1.0 (1.0–1.0), $p = 0.34$	1.0 (1.0–1.0), $p = 0.2$
Recipient male sex	1.0 (0.6–1.5), $p = 0.90$	0.9 (0.6–1.5), $p = 0.77$
Recipient BMI	1.0 (0.9–1.1), $p = 0.61$	
Donor age	1.0 (1.0–1.0), $p = 0.28$	
Donor male sex	0.9 (0.6–1.3), $p = 0.47$	
Time in dialysis	1.0 (1.0–1.0), $p = 0.14$	
Diabetes duration	1.0 (1.0–1.0), $p = 0.98$	
DGF (kidney)	1.6 (1.0–2.7), $p = 0.06$	

BMI, body max index; DGF, delayed graft function; SPK simultaneous pancreas-kidney transplantation; KTA, kidney transplantation alone.

TABLE 5 | Hazard Ratios (HR) with 95% confidence intervals by Cox's regression of the risk factors for bacteremia during the first year after transplantation.

	Univariable (95 % CI)	Multivariable (95 % CI)
SPK vs. KTA	13.8 (1.8–104.7), $p = 0.01$	16.3 (2.1–125.1), $p = 0.01$
Recipient age	1.0 (1.0–1.1), $p = 0.32$	1.1 (1.0–1.1), $p = 0.1$
Recipient male sex	0.6 (0.2–1.6), $p = 0.27$	0.5 (0.2–1.4), $p = 0.2$
Recipient BMI	1.0 (0.8–1.2), $p = 0.92$	
Donor age	1.0 (1.0–1.1), $p = 0.18$	
Donor male sex	1.1 (0.4–2.9), $p = 0.91$	
Time in dialysis	1.0 (0.9–1.0), $p = 0.09$	
Diabetes duration	1.1 (1.0–1.1), $p = 0.11$	
DGF (kidney)	1.1 (0.3–3.9), $p = 0.90$	

BMI, body max index; DGF, delayed graft function; SPK simultaneous pancreas-kidney transplantation; KTA, kidney transplantation alone.

and KTA patients 0.017 bacteremias/person year with an incidence rate ratio of 1.89 (95% CI 0.9052–4.059, $p = 0.07$).

Site of Infections

The site of all the infections during the 5-year follow-up, including patients with multiple infection episodes, are shown in **Table 2**. In the SPK group, the most frequent cause of infection-related hospitalization were gastrointestinal infections (24 episodes, 20%) and bacteremias (22 episodes, 18%). From the gastrointestinal infections, the most common cause was *Clostridioides difficile* infection (nine episodes, 38%). One patient had persistent *Clostridioides difficile* enteritis and was admitted four times and finally treated with bezlotoxumab. Norovirus gastroenteritis accounted for 25% of the cases (six episodes). Three patients suffered from prolonged norovirus gastroenteritis and two of these patients received treatment with nitazoxanide. Altogether 25% of the gastrointestinal infections (six episodes) were of unknown etiology. Pulmonary infection in SPK (10 episodes, 8%) were mainly bacterial pneumonias with unknown pathogen. Urinary tract infections (UTI) in SPK patients (18 episodes, 15%) were mainly caused by *Escherichia Coli* and *Klebsiella pnemoniae*.

In the KTA group, pulmonary infections (37 episodes, 26%) were the most common cause for hospitalization and the majority were bacterial pneumonias and unspecified bronchitises. Gastrointestinal infections were the second most common site of infection (29 episodes, 20%) with the majority of unknown etiology. Hospitalization due to UTI was only 6% (9 episodes), with *Escherichia Coli* the main pathogen.

All the pathogens causing bacteremia are listed in **Table 3**, in both groups, the most common pathogens causing bacteremia were *Staphylococcus aureus* and *Escherichia coli*.

The Outcome in SPK and KTA With Infection Related Hospitalization or Bacteremia

Infection-related hospitalization was not related to worse patient or kidney graft survival compared to patients without infection-related hospitalization in 5-year follow-up in either group (**Supplementary Figures S1A–D**). However, in both groups, bacteremia was associated with both inferior kidney graft and patient survival (**Supplementary Figures S2A–D**).

Risk Factor Analysis

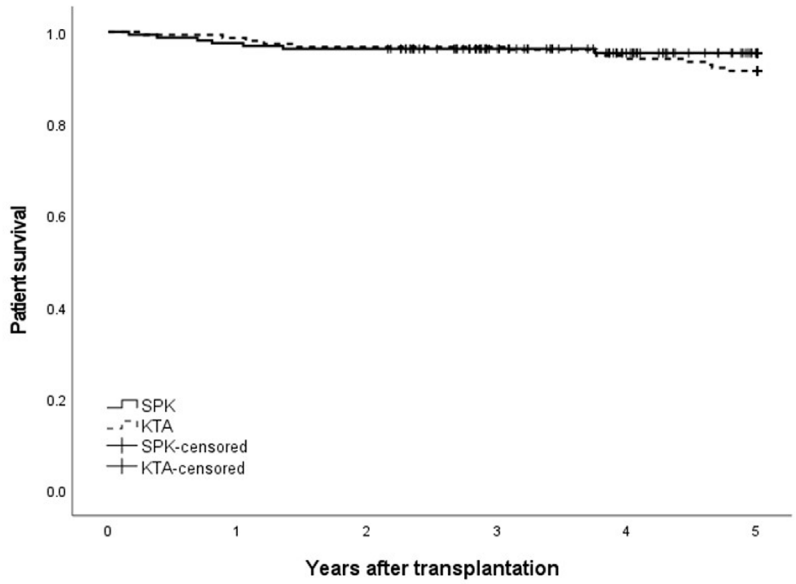
The results of univariable and multivariable analyses of risk factors associated with infection-hospitalization and bacteremia during the first year after transplantation are shown in **Tables 4**, **5**, respectively. In the univariable analysis for infection-related hospitalization, no significant risk factors were found. When adjusted with recipient age and sex in the multivariable model, SPK was identified as a risk factor for infection-related hospitalization during the first year after transplantation. In addition, SPK was a risk factor for bacteremia in both univariable and multivariable models during the first year after transplantation.

In the 5-year risk analysis for infection-related hospitalization and bacteremia, SPK was not a risk factor in the univariable analysis or when adjusted with recipient age and sex. Donor age was found to be a risk factor for bacteremia in the univariable analysis (**Supplementary Tables S1, S2**).

Mortality and Graft Survival

Altogether 7/162 (3.7%) SPK patients died during follow-up with functioning grafts. Three of these deaths were considered infection-related, one patient died from pulmonary embolism 8 months post-transplantation after being treated for bacteremia, one patient died from complicated atypical mycobacterial infection combined with pancreatitis of the patient's native pancreas 4 months after transplantation, and one patient died due to Fournier's gangrene and septic shock 10 months after transplantation.

In addition, altogether six patients experienced pancreas graft failure during follow-up and the death-censored 5-year pancreas graft survival was 96.3% Five pancreas grafts were removed during follow-up and four of these were removed during the first 3 months due to persistent intra-abdominal fungal infections. One patient with severe leukopenia had recurrent infections and was diagnosed with necrotic ulcer in the bowel. This progressed into septic fungal infection and pancreas graft had to be removed 9 months after transplantation. In addition, one patient had pancreas graft failure without known reason 32 months after transplantation and returned to full-dose insulin treatment.



SPK	162	158	156	124	98	70	Number of subjects at risk
KTA	153	151	148	148	144	140	
SPK	0	4	6	6	7	7	Number of events
KTA	0	2	5	5	9	13	

FIGURE 3 | Patient survival during 5 years after transplantation between SPK (simultaneous pancreas-kidney transplantation) and KTA (kidney transplantation alone) patients, $p = 0.32$.

Furthermore, four patients had deteriorated pancreas function and required insulin treatment despite detectable C-peptide concentration. Also, 13 patients developed insulin-resistance during follow-up and required oral hypoglycemic therapy. In patients with SPK, all kidney grafts were functioning at the end of the follow-up.

In the KTA group, 12/153 (8.5%) patients died during the 5-year follow-up. Only 1/13 of the deaths was considered as infection-related, a patient who died from urosepsis 44 months after transplantation. In addition, seven patients returned to dialysis during follow-up. The earliest return to dialysis occurred 2 years 4 months after transplantation.

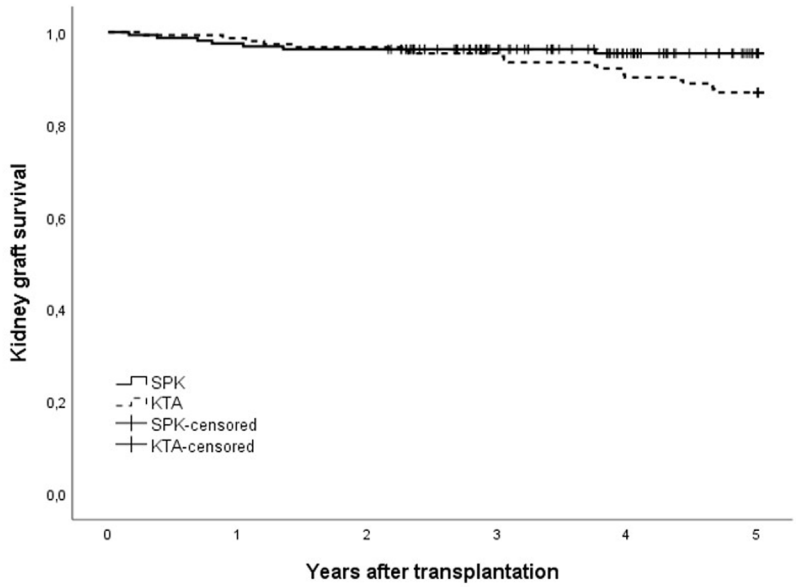
No differences were observed in patient survival between groups during 1- or 5-year follow-up between SPK and KTA patients (**Figure 3**). However, at the end of the 5-year follow-up, kidney graft survival was lower in KTA patients compared to SPK patients (**Figure 4**).

DISCUSSION

Our study showed that the risk of infection-related hospitalizations and bacteremias concentrates especially to the first post-transplant year after SPK and is higher compared to KTA patients with type 1 diabetes. However, during longer follow-up the risk of infections declines in SPK patients whereas in KTA patients, the infection-related hospitalizations, mainly due to community acquired infections, become increasingly common.

Previous studies have indicated that the incidence of infections has been high during the early post-transplant phase in SPK patients, but the risk of infections seems to decline in the long run [20, 21]. Similarly, our study showed that majority of first infections requiring hospitalization occurred during the first year after transplantation in SPK patients. In a study comparing the rate of sepsis in SPK and KTA patients, SPK patients showed higher incidence and an earlier onset of sepsis compared to KTA patients [22], which also is in line with our results even though we excluded early infections during the primary admission and focused on the later posttransplant course. Of note, in our study we specifically compared SPK patients only with KTA patients with type 1 diabetes, whereas previous studies have used KTA patients from all ESKD etiologies as controls.

When assessing the site of infections, gastrointestinal infections were the most common reasons for hospitalization in SPK patients, and the second most common reason in the KTA group. In SPK patients, the majority of identified pathogens were *Clostridioides difficile* and norovirus. Overall, the high risk of gastrointestinal infections in SPK patients may be related to surgery involving the bowel, and *Clostridioides difficile* infections to ATG induction therapy and longer prophylactic antibiotic treatment. In previous study, age older than 55 years, transplant other than kidney transplantation alone, and ATG



SPK	162	158	156	124	98	70	Number of subjects at risk
KTA	153	151	148	146	138	133	
SPK	0	4	6	6	7	7	Number of events
KTA	0	2	5	7	15	20	

FIGURE 4 | Kidney graft survival during 5 years after transplantation between SPK (simultaneous pancreas-kidney transplantation) and KTA (kidney transplantation alone) patients, $p = 0.04$.

induction were associated with higher risk of *Clostridioides difficile* associated diarrhea in SOT patients [23]. Pneumonia or infection of the upper respiratory tract was the most common reason for hospitalization in KTA patients accounting for 26% of all hospitalizations. In a large multicenter study in SOT recipients, pneumonia was similarly a frequent complication after transplantation, and among renal transplant recipients over half of the cases occurred later (>6 months) after transplantation [24]. The low incidence of infection-related hospitalizations due to UTIs in our study is probably due to the fact that bacteremias that were derived from the urinary tract were classified as bacteremias not as UTIs. In addition, as this study focused only on the infection-related hospitalizations, it does not provide information about the overall risk of UTIs after transplantation.

In risk factor analysis, SPK was found to be a risk factor for infection-related hospitalizations and bacteremia during the first year after transplantation but no longer during the 5-year follow-up compared to KTA patients. This suggests that stronger immunosuppression and the use of lymphocyte-depleting agents predisposes SPK patients to infections especially during the first year after transplantation. In addition, the higher rate of relaparotomy and rejection after SPK is a possible explanation for the higher infection risk. Female sex was a near-significant risk factor for bacteremia, the association of recipient female sex and bacteremia has been shown in a previous large cohort study in kidney transplant recipients and is most likely relates to the increased risk for urinary tract infections [25].

According to the U.S. Renal Data System Annual Data Report, sepsis was one of the most commonly known cause of mortality among kidney transplant recipients, in addition to cardiovascular causes and malignancies [26]. In our study, bacteremia was associated with inferior kidney graft and patient survival in both groups.

When comparing overall patient and kidney graft survival between groups, no difference was detected in patient survival. However, kidney graft survival was inferior in KTA group during 5-year follow-up, as none of the SPK patients alive at the end of the follow-up lost their kidney transplant. These excellent results of kidney graft outcome in SPK patients were also demonstrated by the recent OPTN/SRTR Annual Data Report on pancreas transplantation [27]. In our patients, five pancreas grafts had to be removed and four of these graft removals were due to persistent intra-abdominal fungal infections, emphasizing the high risk of graft loss related to fungal infections in SOT patients [28].

Our study had some limitations of note and the most important limitation to our study is the difference in immunosuppression between the groups. All SPK patients received lymphocyte-depleting induction and tacrolimus-based immunosuppression which probably explains the higher risk of infections during the first post-transplant year. Despite this, the risk of infections seems to be similar during the first 5 years suggesting that improved glycemic control in SPK patients could

protect SPK patients from infectious risks. Second, this was a single center study as our center is the only transplant center in Finland, and results may not be comparable to other populations. Third, KTA patients were selected by the recipient and donor BMI and age criteria, similar to the criteria used for SPK patients in our center, from a time period of 2004–2009 when SPK was not performed in Finland, or during the early years of SPK transplantation in 2010–2013, when the activity was very low. Our baseline assumption was that during later years, these patients could have been considered for SPK. Baseline characteristics were relatively similar between the groups regarding diabetes duration and BMI, although SPK patients were slightly younger and had shorter waiting time to transplantation, and therefore shorter exposure to pretransplant dialysis treatment. There were also differences in HLA mismatch, cold ischemia time, and prophylactic antibiotic regimens between the groups, resulting in possible bias in our findings. We acknowledge that there might be also other unmeasured factors, associated with either the type of transplantation, or the era of transplantation, that could confound our findings. Also, the extension of the CMV prophylaxis criteria in SPK patients in 2019 that may have decreased the hospitalizations caused by CMV. In addition, not all the SPK patients fulfilled the 5-year follow-up, limiting our possibilities to compare infection-related hospitalizations during the whole study period.

In conclusion, simultaneous pancreas-kidney transplantation (SPK) patients are at greater risk for infection-related hospitalizations and bacteremias compared to kidney transplantation alone (KTA) patients with type 1 diabetes during the first year after transplantation, which may be associated with the use of stronger immunosuppression and lymphocyte-depleting induction in simultaneous pancreas-kidney transplantation, and this should be taken account during pretransplant evaluation for candidacy. However, during longer follow-up, the risk of infection-related hospitalizations was similar between SPK patients and KTA patients, suggesting that the relative risk of infections after the first posttransplant year is lower among SPK patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by the Helsinki University Hospital institutional review board, and the Finnish Institute for Health and Welfare regarding the use of their administrative health data on hospitalizations in this study (THL/1877/5.05.00/2019). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG, IH, and ML participated in research design. JG and IH performed the research. JG, IH, PF, and MG participated in data collection and analysis. JG, FO, AE, VS, KA, PF, MG, ML, and IH participated in the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

IH reports receiving consulting fees from Novartis, Hansa Biopharma, MSD, and Takeda, and research funding from MSD and Hansa Biopharma outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12235/full#supplementary-material

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Isavuconazole for Treating Invasive Mould Disease in Solid Organ Transplant Recipients

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Solid organ transplant (SOT) recipients have a higher risk of developing invasive mould diseases (IMD). Isavuconazole is a novel broad-spectrum azole active against *Aspergillus* spp. and Mucor, well tolerated, with an excellent bioavailability and predictable pharmacokinetics, that penetrates in most tissues rapidly, and has few serious adverse effects, including hepatic toxicity. Contrary to other broad-spectrum azoles, such as voriconazole and posaconazole, isavuconazole appears to show significant smaller drug-drug interactions with anticalcineurin drugs. We have performed an extensive literature review of the experience with the use of isavuconazole in SOT, which included the SOTIS and the ISASOT studies, and published case reports. More than 140 SOT recipients treated with isavuconazole for IMD were included. Most patients were lung and kidney recipients treated for an *Aspergillus* infection. Isavuconazole was well tolerated (less than 10% of patients required treatment discontinuation). The clinical responses appeared comparable to that found in other high-risk patient populations. Drug-drug interactions with immunosuppressive agents were manageable after the reduction of tacrolimus and the adjustment of mTOR inhibitors at the beginning of treatment. In conclusion, isavuconazole appears to be a reasonable option for the treatment of IMD in SOT. More clinical studies are warranted.

Keywords: isavuconazole, solid organ transplantation, invasive mould disease, invasive fungal infections, invasive aspergillosis

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INTRODUCTION

Solid organ transplant (SOT) recipients have a significant high risk of developing invasive mould diseases (IMD) due to the impact of the immunosuppressive drugs on the patient's immune response [1]. IMD in SOT are mainly caused by *Aspergillus* spp., followed by mucormycosis (zygomycosis), *Fusarium*, *Scedosporium*, and by dematiaceous fungi (dark molds) [2]. Lung transplant recipients have a higher risk for developing invasive aspergillosis (IA) (tracheobronchitis and pulmonary aspergillosis [IPA]) due to specific characteristics related to this transplant: higher rate of pre-transplant colonization, airway ischemia, impaired ciliary function, blunted cough reflex, and denervation injury [3]. Other known risk factors for IMD are post-transplantation renal replacement treatment, cytomegalovirus infection, treatment for acute rejection, mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and liver re-transplantation or transplantation due to fulminant hepatic failure [4, 5]. The morbidity and mortality associated with these infections is extremely high. In most cases, diagnosis is made

after invasive procedures, and treatment usually requires a prompt and multidisciplinary treatment, requiring surgical resection of the infection site in some cases [6].

The treatment of choice for IA is voriconazole [7, 8], but the potential hepatotoxicity associated to the drug, as well as its inhibition of cytochrome CYP3A4 and the consequent elevation of serum levels of immunosuppressive drugs (tacrolimus, cyclosporine, and sirolimus/everolimus), makes its use problematic in SOT recipients [9]. Liposomal amphotericin B is the antifungal of choice for the treatment of mucormycosis, while posaconazole is used as a second-line drug [10]. However, the increased risk of nephrotoxicity associated with amphotericin B [11] and the interactions between posaconazole and immunosuppressive drugs [12], entails that the administration of these antifungals in SOT is not without risk.

Isavuconazole (Cresemba®; Pfizer, New York City, United States) is the drug most recently incorporated into the azoles. The drug shows predictable pharmacokinetics, good tolerance and few adverse effects (a low incidence of gastrointestinal symptoms, headache, peripheral edema, and dose-dependent shortening of the QT interval have been described), excellent oral bioavailability and good diffusion to tissues, including the central nervous system [13]. Moreover, the intravenous formulation of isavuconazole does not contain the excipient sulfobutyl ether β-cyclodextrin sodium (SBECD), which would facilitate its use in patients with moderate or severe renal insufficiency. Experimental animal studies have also confirmed the synergistic action between isavuconazole and micafungin in the treatment of IPA [14].

We have performed an extensive literature review concerning the use of isavuconazole in SOT, and described the most frequent side-effects, clinical response and mortality when isavuconazole was prescribed for the treatment of an IMD.

PATIENTS AND METHODS

We conducted a computer-based PubMed (Medline) search with the MeSH (Medical Subject Headings) terms "Isavuconazole," "Solid Organ Transplantation," "Infection Fungal Infection" or "Invasive Mould Disease" to identify published literature between March 2015 and June 2023 pertaining the clinical use of isavuconazole in SOT for the treatment of IMD. We searched for articles written in English language.

We have especially focused on the adjustments made on the maintenance immunosuppressive regimen during isavuconazole treatment, the rate of adverse events associated to the antifungal drug, and the clinical response of the IMD to the treatment with isavuconazole.

Case reports, and prospective or retrospective clinical studies which included SOT recipients treated with isavuconazole for an IMD were considered. Articles for which data could not be extracted from the published results were not considered.

We have defined "end of follow-up period" as the last follow-up visit described in the revised articles. "IMD-related mortality" was defined as all demise which resulted of the IFI for which the patient was being treated. For prospective or retrospective clinical studies, IMD-related mortality was determined based on the rates presented by the authors of the articles. For case reports, we have carefully reviewed all the clinical cases, and determine, in case of the patient's demise, if this was related to the IMD for which the patient was being treated with isavuconazole.

Statistical Analysis

Quantitative variables are shown as mean (or median) ± standard deviation (or interquartile range [IQR]), whereas qualitative variables are depicted as absolute and relative frequencies. The statistical analysis was carried out using SPSS v. 23.0 (IBM Corp, Armonk, NY).

RESULTS

Clinical Characteristics of the Study Population

We identified 20 studies which included at least one SOT recipient who received isavuconazole as treatment for an IMD (**Figure 1**).

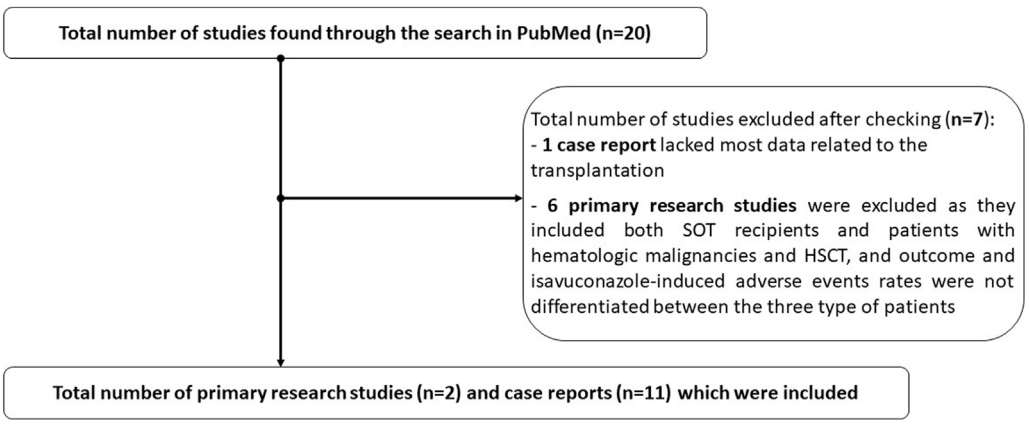

FIGURE 1 | Flowchart of the study.

TABLE 1 | Baseline and clinical characteristics of the 145 SOT recipients included.

	Recipients included (*n* = 145)
Age at diagnosis of IMD, mean ± SD, y	58.3 ± 2.9
Female gender, n (%)	53 (36.6)
Type of transplant, n (%)[a]	
Lung transplant	70 (48.3)
Kidney transplant	36 (24.8)
Liver transplant	20 (13.8)
Combined liver-kidney	1 (0.7)
Sequential pancreas after kidney	1 (0.7)
Heart transplant	14 (9.6)
Small bowel/multivisceral	4 (2.8)
Maintenance immunosuppressive regimen, n (%)	
Corticosteroids	137 (94.5)
Tacrolimus	132 (91.0)
Cyclosporine	4 (2.8)
MMF/MPS	114 (78.6)
Azathioprine	5 (3.4)
Everolimus	13 (9.0)
Sirolimus	7 (4.8)
Posttransplant complications, n (%)	
ECMO	9 (6.2)
COVID-19 infection	13 (9.0)
Use of prophylaxis previous diagnosis, n (%)	58 (40.0)
Echinocandin	8 (5.5)
Nebulized amphotericin B	50 (34.5)

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; MMF/MPS, mycophenolate mofetil/mycophenolate sodium.
[a]*One recipient received a combined single sequential lung and liver transplantation.*

TABLE 2 | Clinical characteristics of the fungal invasive infections.

	Recipients included (*n* = 145)
Time from transplantation to IFI, median (IQR), d	174 (122–174)
Moulds isolated, n (%)[a]	
Aspergillus	119 (82.1)
Mucormycosis	14 (9.7)
Alternaria	3 (2.1)
Lomentospora prolificans	1 (0.7)
Cladophialophora bantiana	1 (0.7)
Diaporthe spp.	1 (0.7)
Purpureocillium lilacinus	1 (0.7)
Type of fungal infection[b]	
Tracheobronchitis	32 (22.1)
Fungal pneumonia	65 (44.8)
Bronchial anastomotic infection	2 (1.4)
Mycetoma	6 (4.1)
Cutaneous infection	3 (2.1)
Disseminated fungal infection	12 (8.3)
Osteomyelitis	2 (1.4)
Chronic otitis media	1 (0.7)
Rhino-sinusal-cerebral mould infection	3 (2.1)
Primary gastric	2 (1.4)
Primary colonic mucormycosis	1 (0.7)
Primary hepatic IA	1 (0.7)
Primary mediastinal IA	2 (1.4)
Skin and deep soft tissues infection	5 (3.4)
Isolation in donor	2 (1.4)
Post-traumatic wound	1 (0.7)
No proven or probable FI	6 (4.1)
First line-therapy with isavuconazole, n (%)	98 (67.6)
Previous antifungal treatment, n (%)[c]	47 (32.4)
Reasons to stop previous treatment, n (%)	
IV-to-oral switch and avoiding interactions	14 (9.6)
No previous clinical response	11 (7.6)
Switch according to antifungal susceptibility	4 (2.8)
Adverse events with previous treatment	17 (11.7)
Clinical response at last clinic follow-up visit[d]	80 (55.2)
All-cause mortality at last clinic follow-up visit[d]	52 (35.9)
IFI-related mortality[e]	23 (15.9)

IA, invasive aspergilosis; IFI, infection fungal infection; IQR, interquartile range.
[a]*Four SOT, recipients received isavuconazole for an IFI, which was produced by a yeast, whereas in one case, isavuconazole was prescribed for an unidentified new mould species.*
[b]*One patient in the ISASOT study was treated for a fungal tracheobronchitis and a subcutaneous infection at the same time.*
[c]*Isavuconazole was added to an ongoing lipid complex amphotericin therapy in 1 recipient.*
[d]*In the ISASOT study the last follow-up visit was performed 90 days after the end of treatment, whereas in the SOTIS, study the clinical response was evaluated 12 weeks after the initiation of isavuconazole. In the case reports, follow-up spanned from 45 days to 12 months.*
[e]*2 patients died from a fungal pneumonia, 1 from a disseminated aspergillosis, 1 from a disseminated mucormycosis and 1 from a disseminated* C. bantiana *infection, with central nervous system involvement. Detailed data of the 18 cases of IFI-related mortality included in the SOTIS study was not available.*

Overall, 13 studies met the inclusion criteria, including one prospective observational study which described 53 SOT recipients treated with isavuconazole for fungal infections [15], one multicenter retrospective study with 81 SOT recipients with proven or probable IMD treated with isavuconazole for ≥24 h as first-line or salvage therapy [16], and eleven case reports [17–27]. One case report was not included as it lacked most data related to the transplantation and six studies were excluded as they included both SOT and patients with hematologic malignancies and stem cell transplantation. The key features of the included studies are available in the **Supplementary Table S1**.

A total of 145 SOT recipients were included (**Table 1**). Mean age at diagnosis of IMD was 58.3 ± 2.9 years, and 36.6% of recipients were female. Lung transplant accounted for 48.3% of recipients, followed by kidney transplant (24.8%) and liver transplant (13.8%). Median time from the transplantation and diagnosis of IMD was 174 days (IQR 122–174). The majority of recipients were receiving corticosteroids (94.5%), tacrolimus (91.0%) and mycophenolate mofetil/mycophenolate sodium (78.6%) as maintenance immunosuppressive regimen. Interestingly, 13.8% of patients were receiving an mTOR inhibitor. Also noteworthy, 40.0% of patients were receiving anti-mould prophylaxis previous the diagnosis of IFI, especially nebulized amphotericin B (34.5%) (**Table 1**).

Clinical Characteristics of the Invasive Fungal Infections and Efficacy of Isavuconazole Therapy

The most common IFI in our review was produced by *Aspergillus* spp. (82.1%), followed by mucormycosis (9.7%), *Alternaria* (2.1%), *Lomentospora prolificans* (0.7%), *Cladophialophora bantiana* (0.7%), *Diaporthe spp* (0.7%) and *Purpureocillium lilacinus* (0.7%) (**Table 2**). It's import to mention that up to four patients (2.8%), who were included in the ISASOT study [15] and that received treatment with isavuconazole, were diagnosed with an IFI which was not produced by a mould. The most common presentation was fungal pneumonia (44.8%) followed by tracheobronchitis (22.1%). Approximately 8.3% of the patients presented disseminated fungal infection.

TABLE 3 | Isavuconazole-related adverse events.

	Recipients included (n = 145)[a]
Total number of patients with TEAE, n (%)	43 (29.7)
Type of TEAE, n (%)	
Liver enzyme elevation	27 (18.6)
Myopathy	8 (5.5)
Nausea and vomiting	6 (4.1)
Neurologic or visual disturbances	4 (2.8)
Fatigue	3 (2.1)
Diarrhea	3 (2.1)
Electrolyte disturbance	1 (0.7)
Weight loss	1 (0.7)
Hyporexia	1 (0.7)
Acute renal failure	1 (0.7)
Sinus tachycardia	1 (0.7)
Tacrolimus overdose	1 (0.7)
TEAE requiring premature discontinuation of isavuconazole, n (%)[a]	13 (9.0)

TEAE, treatment-emergent adverse event.
[a]Isavuconazole was stopped due to hepatoxicity (4 recipients), gastrointestinal disturbances (3 patients), fatigue (2 cases), myopathy (2 patients), neurological adverse event (1 patient) and due to an isavuconazole-induced diarrhea, which promoted tacrolimus overdose and acute renal failure, followed by multiple episodes of sinus tachycardia (1 recipient).

Isavuconazole was prescribed as first line-therapy in 67.6% of recipients, whereas 32.4% of patients had already started an antifungal treatment. The most common reasons to perform a change to isavuconazole were adverse events associated with the first antifungal drug (11.7%), intravenous-to-oral switch and avoid interactions (9.6%), and absence of a clinical response (7.6%). In a specific patient, isavuconazole was added to liposomal amphotericin B as treatment for a mucormycosis.

At the last clinic follow-up visit, approximately 55.2% of patients presented a clinical response to the isavuconazole treatment (**Table 2**). All-cause mortality and IMD-related mortality was available in all of the 13 included studies. Overall, the all-cause mortality was of 35.9%, with an IFI-related mortality of 15.9%.

Safety Outcomes

Approximately 29.7% of patients were diagnosed with an isavuconazole-related adverse event (**Table 3**). The most common adverse events were liver enzyme elevation (18.6%), myopathy (5.5%) and nausea and vomiting (4.1%). No cases of QT shortening were diagnosed. Noteworthy, only 9.0% of patients required premature discontinuation of isavuconazole due to an adverse event (**Table 3**).

Dose Adjustment and TDM of Immunosuppressive Agents

Tacrolimus was adjusted in 99 of the 132 patients who were receiving the immunosuppressive drug (75.0%) (**Table 4**). mTOR inhibitors were adjusted in 60% of patients who were receiving these immunosuppressors (**Table 4**). A total of 14 recipients were able to concomitantly receive an mTOR inhibitor and isavuconazole.

TABLE 4 | Dose adjustments of tacrolimus and mTOR inhibitor agents after initiating isavuconazole.

	Recipients included (n = 145)
Tacrolimus, n (%)	
Any dose adjustment, n (%)	99/132 (75.0)
mTOR inhibitor	
Any dose adjustment, n (%)	12/20 (60.0)[a]

[a]In six patients, the mTOR inhibitor was withdrawn, whereas in six recipients the dose of the immunosuppressive drugs was decreased.

DISCUSSION

We have performed an extensive literature review which included a total of 145 SOT recipients treated with isavuconazole for an IMD. We observed that isavuconazole appeared to be well-tolerated, and that interactions between isavuconazole and the immunosuppressive drugs were manageable. Clinical responses were also similar to that found in other high-risk patient populations.

Isavuconazole was recently approved for the treatment of IA and mucormycosis based in two pivotal trials. In the SECURE trial, a phase 3, double-blind, global multicentre, comparative-group study, patients with suspected invasive mould disease were randomized to receive isavuconazole or voriconazole [28]. A total of 532 patients were enrolled, with 258 patients in each arm. The authors concluded that isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive mould disease, and that was better tolerated when compared with voriconazole, with fewer drug-related adverse events (42% vs. 60%, $p < 0.001$) [28]. In the VITAL trial, 37 patients diagnosed with mucormycosis were treated with isavuconazole for a median of 84 days [29]. Patients were matched with up to three contemporaneous FungiScope patients who had received a primary amphotericin B-based treatment for proven or probable mucormycosis. The authors concluded that isavuconazole was active as primary or secondary treatment (refractory or intolerant to other antifungals), with an overall end-of-treatment complete and partial response similar to those associated with liposomal amphotericin B [29]. Interestingly, isavuconazole showed a significantly fewer hepatobiliary adverse events than voriconazole in the SECURE trial (9% vs. 16%, $p = 0.016$), and in the VITAL study less than 10% of enrolled patients experienced an increase in the liver enzymes [28, 29]. Unfortunately, data was still extremely scarce in SOT, since SOT recipients were not included in the SECURE trial, and only one SOT recipient was included in the VITAL trial.

This review included more than 140 SOT patients who received isavuconazole as treatment for an IMD. We have especially addressed clinical response, adverse events and drug-drug interactions.

Although effectiveness was not the main objective of the reviewed studies, we have calculated a clinical response and an all-cause mortality at last clinic follow-up of 55.2% and 35.9%, respectively, and an IFI-related mortality of 15.9%. Our results are similar to other published studies in which SOT recipients were primarily treated with other antifungal drugs. A recently

published Spanish cohort study (Diaspersot study), which included 85 (67.4%) SOT recipients with IA mostly treated with voriconazole reported a clinical improvement of 54.6%, a global mortality of 34.1% and an attributed mortality of 24.6% at the third month of diagnosis [30]. The Swiss Transplantation Cohort Study, which included 70 patients diagnosed with probable and proven IA that were treated with antifungal drugs different than isavuconazole, described a mortality rate of 22.9% at the third month of IA diagnosis [31]. Finally, a multinational study which included 112 KT recipients diagnosed with pulmonary IA, who were also treated with antifungal drugs different than isavuconazole, reported that 39.3% of patients had died by the third month of diagnosis, a mortality rate similar to the found by us [32].

The rate of isavuconazole-related side effects and the rate of isavuconazole-emergent adverse events which required permanent discontinuation of treatment in our review was in line with the SECURE trial (29.7% vs. 42%, and 9.0% vs. 14%, respectively) [28]. Moreover, the Diaspersot study reported that of the 85 recipients treated with voriconazole, 30 (35.3%) presented some degree of toxicity and 13 (15.3%) required a premature discontinuation of the triazole [30]. These results indicate that isavuconazole could be associated with a lower rate of drug-induced toxicity in SOT recipients than voriconazole (29.7% vs 35.3% and 9.0% vs 15.3%, respectively). Finally, patients in the ISASOT study, who required discontinuation of voriconazole due to adverse events were able to continue treatment with isavuconazole [15]. Therefore, the rate of isavuconazole-related adverse events and the rate of permanent discontinuation of the drug seems to be considerably lower in SOT when compared to voriconazole.

In most patients, the daily dose of tacrolimus was lowered at the beginning of therapy and increased after isavuconazole discontinuation. Afterwards, tacrolimus was managed according to the plasmatic levels' during the treatment. Some patients receiving mTOR inhibitors at the beginning of isavuconazole were also able to maintain the immunosuppressive drug, with an overall good tolerance. Based on our review, drug–drug interactions between isavuconazole and immunosuppressive agents appear to be reasonably manageable in the daily clinical practice. These results are in line with previously published studies which concluded that the degree of interactions between isavuconazole and immunosuppressive agents is smaller than that reported for other triazole antifungal agents [33], and that, because of significant interpatient variability and between each type of SOT, therapeutic drug monitoring (TDM) of the immunosuppressive drugs is recommend in guiding the drug dosing [34].

There are some limitations of this study that have to be taken into account. As we have previously mentioned, both the SOTIS and the ISASOT studies did not include a parallel comparator group which was treated with a different antifungal drug. Moreover, the ISASOT study included a significant high number of lung transplant recipients (83.0%), who were treated with isavuconazole for a fungal tracheobronchitis (25/53 [47.1%]). It would also have been interesting to determine the rate of combined treatment used in these studies; unfortunately, these data were not fully available. The length of the follow-up was also different in both the studies and in the case reports, and the total duration of the isavuconazole treatment was not described in some of the case reports. Unfortunately, TDM of isavuconazole was only available in eight patients (5.5%). Interestingly, one patient, after a month of therapy, presented isavuconazole trough levels below the therapeutic range. It was decided to increase the daily dose of isavuconazole to 200 mg every 12 h. Isavuconazole blood levels arose to therapeutic range afterwards [16]. Another patient with isavuconazole trough levels of 7.2 mg/L, required the withdraw of the antifungal drug due to multiple side effects [19]. Two retrospective studies which included 55 and 26 SOT recipients that received isavuconazole as prophylaxis, and had TDM performed for both isavuconazole and tacrolimus, concluded that the interaction between these drugs was more significant after liver transplantation, that the impact of isavuconazole on tacrolimus levels varied between individuals and that a moderate interpatient variability in isavuconazole pharmacokinetic parameters could be observed [35, 36]. It should be remarked that, nowadays, isavuconazole TDM is especially recommended in patients who are unresponsive to treatment, who have unexpected toxicity or possible drug-drug interactions, or if the infection is produced by a mould with elevated minimum inhibitory concentration (MIC) or is located in sanctuary sites such as the central nervous system (CNS) [8]. The strength of our study lies in the fact that it describes the majority of published cases using isavuconazole in SOT for the treatment of IMD, including its use in patients with non-*Aspergillus* spp. fungal infections, such as *Alternaria*, *Lomentospora* and mucormycosis.

In conclusion, isavuconazole appears to be a well-tolerated drug in SOT recipients, with clinical responses comparable to that found in other high-risk patient populations, and manageable drug–drug interactions, even with calcineurin and mTOR inhibitors. We consider that isavuconazole could be also an acceptable option in non-*Aspergillus* infections in SOT recipients. More future prospective studies are warranted.

AUTHOR CONTRIBUTIONS

Study conception and design: JS and JA. Data collection: JS. Analysis and interpretation of results: JS, SH, and JA. Draft manuscript preparation: JS. Revision of the draft manuscript: SH and JA. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11845/full#supplementary-material

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REVIEW
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Non-Standard Risk Donors and Risk of Donor-Derived Infections: From Evaluation to Therapeutic Management

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Expected and unexpected donor-derived infections are a rare complication of solid organ transplantation, but can result in significant morbidity and mortality. Over the last years, the growing gap existing between patients on the waiting list and available organs has favored the use of organs from donors with suspected or confirmed infections, thanks to the improvement of risk mitigation strategies against transmission of well recognized and emerging infections. Given the recent developments, the particular interest of this review is to summarize data on how to maximize utilization of HIV+ donors in HIV+ recipients, the use of HCV-viremic donors and HBV positive donors. This article also covers the implications for recipient of organs from donors with bacteremia and the challenge of multidrug resistant (MDR) infections. Lastly this review describes emerging risks associated with recent Coronavirus Disease-2019 (COVID-19) pandemics.

Keywords: donor derived infections, emerging pathogens, HIV, hepatitis, SARS-CoV-2, bacteremia, multidrug resistant

INTRODUCTION

Expected and unexpected donor-derived infections (DDI) remain an inherent risk of solid organ transplant (SOT) and are associated with significant morbidity and mortality, especially in the setting of parasitic and fungal diseases [1, 2].

The mitigation risk process for DDIs is based on the prevention of the transmission of infections with SOT with adequate safety simultaneously decreasing organ discard [3]. This complex methodological approach needs to adapt continuously to the changing landscape of infectious disease and the emerging evidence of new therapeutic and preventive options [4, 5]. While it is not an exhaustive list of potential pathogens impacting donors, the conditions demonstrate different approach to donor-derived disease mitigation. The aim of this review is to provide an update on DDIs to maximize organ utilization.

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Abbreviations: AFP, alpha fetoprotein; COVID-19, Coronavirus Disease-2019; D, donor; DAA, direct-acting antiviral agents; DO, donor oriented; HCC ENT, entecavir, Hepatocellular carcinoma; LAM, lamivudine; MDR, multidrug resistant; NA, nucleos(t)ide analogue; NAT, nucleic acid testing; R, recipient; RO, recipient oriented; RR, reactivation risk; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus; SOT, solid organ transplant; TDF, tenofovir; TR, trasmissione risk (without propylaxis).

TABLE 1 | Behaviors at high risk of acquiring blood-born infections if present in the 30 days before organ procurement (10-11-12).

Non-standard risk donors
• Use of parenteral or inhaled drugs for non-medical reasons
• Exposure to blood from a person suspected of being infected with HIV either by inoculation or by contamination of skin or mucous wounds
• Incarceration (confinement in jail, prison, or juvenile correction facility) for ≥72 consecutive hours
• Infants breastfed by an HIV-infected mother
• Children born from mothers infected with HIV, HBV or HCV
• Unknown medical or social history
• Sexual habits that can increase the risk of transmission of diseases
o sexual relations with people affected or suspected of being affected by HIV, HCV, HBV
o habitual and repeated sexual behavior (promiscuousness, casualness, sexual relations with the exchange of money or drugs)
o sexual relations with people with a history of mercenary sex
o sexual relations with subjects who have used parenteral or inhaled drugs
o sex in exchange for money or drugs
o people who have been diagnosed or have been treated for syphilis, gonorrhea, *chlamydia* or genital ulcers

HEPATITIS B POSITIVE DONORS

The availability of effective antivirals with low risk of developing drug resistance and hepatitis B (HBV) vaccination have changed the epidemiology of HBV. All organ transplant candidates who are nonimmune to the virus, based on serologic testing, should be vaccinated against HBV infection. Active immunization against HBV in transplant candidates should be strongly encouraged not only because of the expected acquisition of protection against HBV, but also because it might allow the use of organs from HBV-positive donors [6]. Reducing the incidence of the disease has significantly reduced the carrier rates, HBV-related mortality (mainly due to cirrhosis and hepatocellular carcinoma) and the need for liver transplantation, allowing to expand the donor pool without impairing transplant outcomes [7–9].

Organ donors should be screened for serological evidence of HBV infection with chemiluminescence immunoassay (CLIA) techniques for HBV surface antigen (HBsAg) and core antigen antibodies (anti-HBc). In addition, nonstandard risk donors and donors with positive screening (HBsAg+ or anti-HBc+) should be screened for HBV infection by nucleic acid testing (NAT) (**Table 1**) (**Figure 1**) [10–12]. Of note that HBV antibody screening assays may not be reactive during the serologic window period (≈44 days), and NAT may also fail to detect the pathogen in the blood or plasma during the eclipse phase (≈20–22 days for HBV) [13].

All cases with potential risk of HBV transmission should be discussed with an expert [7, 14]. The most robust evidence on the risk of potential HBV transmission and related outcomes are with liver and kidney transplant, with very limited experience with thoracic transplant [7–9, 15, 16]. There is a lack of standardized antiviral prophylaxis and long term follow up.

The risk of transmission is well documented in donors with positive HBsAg (range 0.5%–7%) [17]. Transplantation from an HBsAg+ donor can be performed to an HBsAg+ recipient or with reactive surface antigen (anti-HBs) antibodies (HBsAb titer ≥10 IU/mL) as a result of immunization or natural infection [18]. Transplantation of organs from an HBsAg+ to naïve unvaccinated patients (HBsAg negative and anti-HBs-negative recipient) is usually not recommended except in the setting of emergency transplantation or in HBV hyperendemic geographical areas. However, transplanting organs from HBsAg+ donors to naïve vaccinated or unvaccinated patients, with human immunoglobulin against HBsAg (HBV-Ig) and antiviral prophylaxis is currently allowed by the Italian guidelines, based on positive preliminary experience [8, 10]. Transplant recipients of HBsAg+ organs should receive HBV-Ig, starting in the intraoperative phase, plus a high barrier nucleos(t)ide analogue (NA) regardless of the immune status, whose duration may significantly vary depending on local center protocols, the transplanted organ (with shorter duration for non-liver recipients), the presence of coinfections (HIV, HDV). **Figure 2** summarizes expert opinion recommendations. High barrier NAs have proven to be highly effective, with a successfully suppression of viral replication for the long term with minimal risk for drug

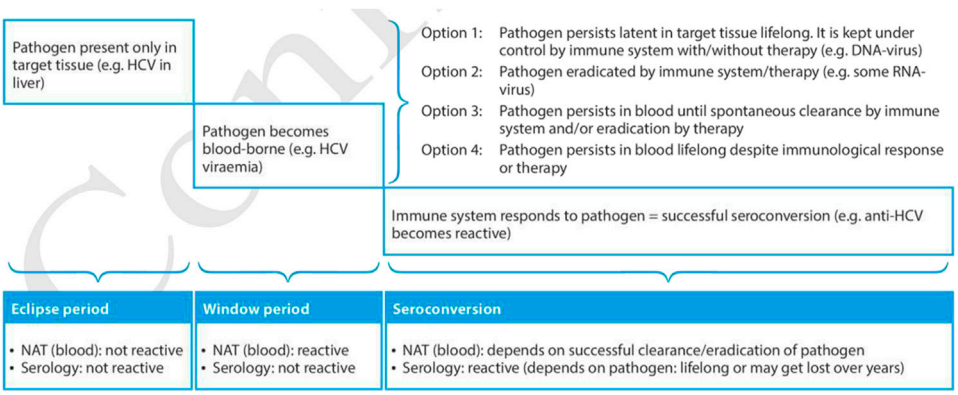

FIGURE 1 | Timeline from infection until final seroconversion, including the eclipse period and window period. (Reproduced from EDQM Guide on Quality and Safety of Organs for Transplantation 8th edition, [11]).

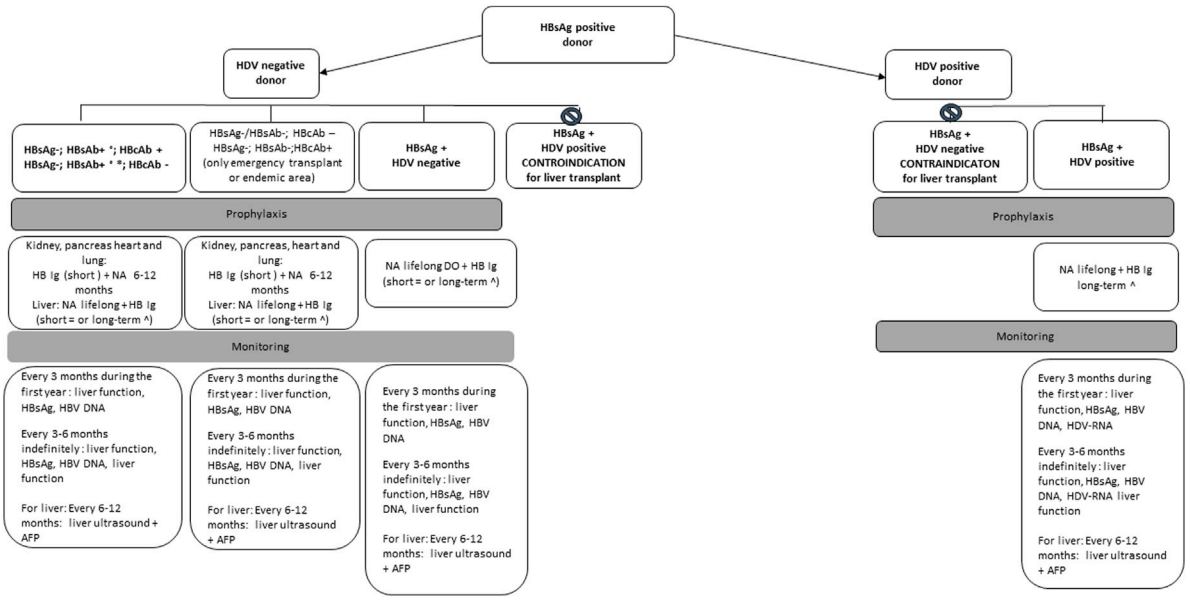

FIGURE 2 | Management of recipients of organs from HBs Ag positive donor based on expert opinion recommendations.

resistance, although prophylaxis does not prevent transmission of infection universally. Treatment using tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir is currently preferred over lamivudine [7]. Laboratory and radiological monitoring after transplantation is recommended to rule out potentially acquired HBV after transplant (**Figure 2**).

HBsAg+ donors need to be screened to rule out the presence of a Delta virus (HDV) coinfection. Of note that the presence of HBV-DNA in the absence of HBsAg + does not require HDV research. The HDV infection is documented by the positivity of the anti-HDV IgG or IgM. In case of positive anti-HDV-IgG or IgM the presence of an active infection should be ruled out by the determination of plasma HDV-RNA [19].

Liver transplantation from an HBsAg+ and anti-HDV positive donor, according to the Italian guidelines, can be perfumed only in HBsAg+ and anti-HDV positive recipients. On the contrary liver transplantation from an HBsAg+ and anti-HDV negative donor is contraindicated in recipients with HBV-HDV co-infection, because of the risk of HDV infection of the new graft and potential subsequent graft loss [10, 20]. Grafts from donors with isolated anti-HBcAb positivity can be safely used in HBsAg + and anti-HDV positive recipients [7]. Currently there is no approved treatment for HDV after transplant and most effective method for preventing HDV infection of transplanted liver in these patients is dependent on preventing HBV recurrence, with an indefinite combination of NAs with anti-HBV Ig [21]. Interferon remains an option for HDV infection, with poor efficacy and the risk of inducing liver rejection, whereas further studies are needed to determine the role of bulevirtide in the context of liver transplantation (LT) [21, 22] (**Figure 1**).

Isolated anti-HBc positive donors warrant specific consideration, since HBV may persist in the liver with covalently closed circular DNA (cccDNA), which currently cannot be cleared by the host immune response and by antiviral therapies [23]. The risk of transmission from donors with isolated anti-HBc will depend on the immunologic status of the recipient and the type of transplanted organ. Anti-HBc positivity may be seen as 1) false-positive result, especially if risk factors for HBV are absent 2) early hepatitis B infection 3) or resolved infection (HBcAb+, HBsAb-). The risk of transmission of infection from an HBcAb+, HBsAg negative, HBsAb ± donor to a susceptible non-liver recipient is low and recipients with HBV protective immunity do not need antiviral therapy post-transplantation, but careful monitoring and antiviral therapy at the earliest sign of HBV transmission is recommended for recipient management [24]. In contrast for liver recipients, it is recommended to start antiviral prophylaxis and to perform consecutive laboratory testing for HBV infection after transplantation [25] (**Figure 3**).

No studies have been performed to assess the optimal frequency and type of monitoring for the development of *de novo* hepatitis after transplantation. For recipients of anti-HBc+ livers, most of the studies have described initial monitoring every 1 ± 3 months for 1 year and every 3 ± 6 months after 1 year. For non-liver recipients, optimal monitoring intervals have not been established but we suggest monitoring of serological markers of HBV every 3 months for the first year (**Figures 2**, **3**).

HEPATITIS C POSITIVE DONORS

The introduction of direct-acting antiviral agents (DAA) has produced several consequences in SOT because the number of patients with HCV related cirrhosis and the number of anti-HCV+ viremic recipients in the waiting lists has significantly reduced, the number of HCV+ non viremic individuals in the

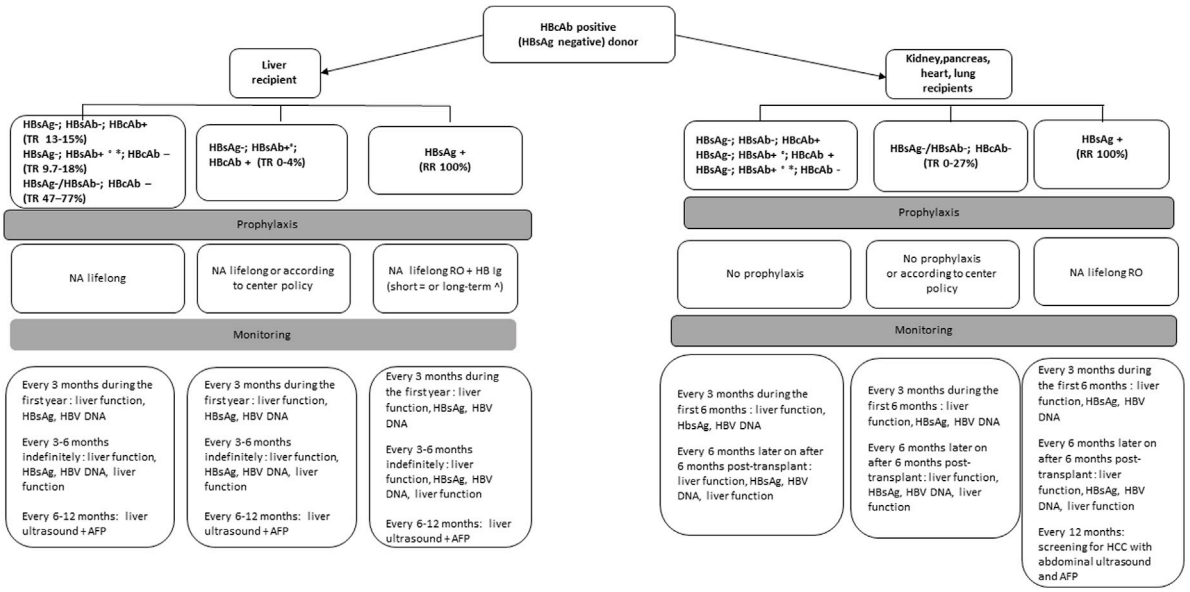

FIGURE 3 | Management of recipients of organs from HBcAb positive, HBsAg negative donors based on expert opinion recommendations.

general population has increased, and allowed the possibility to successfully treat HCV after transplantation [26]. Overall it has also open the option of the use of HCV viremic organs in HCV negative recipients expanding the donor pool without impairing short-term transplant outcomes [27–30].

HCV serological screening should be performed in all donors for the detection of HCV antibodies (anti-HCV) using CLIA techniques or third-generation enzyme immunoassay (EIA), with a sensitivity of at least 95%. HCV RNA screening should be performed to rule out viremia in all anti-HCV+ donors during the donation process and in non standard-risk donors (**Table 1**). For non standard-risk donors HCV-RNA detection is indicated to reduce the window period from ≈66 to 70 days (antibody detection) to ≈ 5–7 days (eclipse period using NAT) (**Figure 1**). In the United Sates, screening by NAT for HCV has been mandatory for all organ donors since 2017, regardless of the risk criteria identified during donor evaluation, to reduce the diagnostic window period [31].

The transmission of infection from an anti-HCV+ non-viremic (HCV RNA negative) donor is exceptional (with a low risk for heart, kidney, pancreas and lung and potentially higher risk for liver recipients) but anti-HCV+ viremic donors (HCV RNA positive) transmit HCV infection to almost all recipients, regardless of the transplanted organ [32, 33]. All anti-HCV positive liver donors (both HCV-RNA positive or negative) must be evaluated histologically to exclude the presence of fibrosis [34].

The organs of an anti-HCV+ non-viremic donor (after effective treatment or spontaneous clearance) may be used in anti-HCV positive recipients without restrictions or may be used in anti- HCV negative recipients that accept the risk after informed consent and with close monitoring and treatment in case of transmission [14, 29, 35].

Donation of organs from an anti-HCV+ viremic donor can be performed in HCV viremic recipients or in an anti-HCV negative recipient, if allowed by the national law, who agrees to take the risk after informed consent. In each case early treatment with DAA is strongly recommended [27, 35–38]. Use of liver allografts from HCV-viremic donors to previously treated HCV RNA-negative recipients has also been done with successful DAA retreatment after transplant [39].

It is advisable to determine the viral load and the HCV genotype of the donor, both relevant to recipient management after transplantation. HCV antiviral therapy may be started in the recipient at transplant or as soon as possible early post-transplant depending on the national rules for DAA reimbursement policies [10, 28, 35, 40, 41]. Standard DAA duration of treatment (12 weeks) is usually recommended but short courses (8 weeks) and ultrashort duration of treatment (≤8 days) may be efficacious in certain settings [35].

Drug interactions between immunosuppressive and DAA should be monitored after transplantation. Recipients of organs from anti-HCV positive donors (HCV-RNA positive or negative) should be monitored by quantitative HCV-RNA determination in peripheral blood at 1, 2, 4, 8 and 12 weeks after transplantation [14].

HIV POSITIVE DONORS

Management of human immunodeficiency virus (HIV) has come a long way since the harrowing days of the 1980s. Currently, life expectancy for a person living with HIV who engages with care shortly after diagnosis now approaches that for the general community. Transplantation is an accepted option for candidates who are themselves living with controlled HIV. It

is also expanding as an option for both living and deceased donors [26, 42].

Organ donation from HIV+ patients is available in the United States under the HIV Organ Policy Equity (HOPE) Act, and is now available in multiple other countries, depending on local laws [43]. Much of the early experience came out of South Africa, where using HIV+ kidney donors exclusively for HIV+ recipients has been an option for more than a decade [44]. Almost all global experience subsequently has been in HIV D+/R+ situations, with very rare exceptions (HIV D+/R−) that demand careful legal, ethical and medical caution [45].

For potential deceased donors, organ quality should be examined as per center standards. Patients dying of Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infections or cancer are not eligible for organ donation. On the basis of previous literature, in US setting, most (around 60%) of HIV D+ were AntiRetroviral Therapy (ART) experienced which contrasts the South African cohort with the majority (92%) of HIV D+ being ART-naïve. However, even with an ART experienced donor pool, there were no events of HIV breakthrough and no evidence of donor-derived superinfection [44, 46, 47]. Otherwise, assessment should be made regarding the risk of transmitting resistant virus to a recipient both for ART experienced and for ART naïve donors. When a clinician examines a potential donor and notes a clear history of antiretroviral compliance and viral suppression, they should be able to confirm that the antiretroviral treatment of the recipients will also maintain viral suppression of any donor virus. Generally, these are acceptable situations [48]. However, it is the donor with a protracted history of non-compliance or drug resistant virus who needs particular attention, and in some instances, good quality organs should be declined if post-transplant viral control cannot be ensured. Notably many people still do not know of their HIV status, perhaps only being tested when they become a potential organ donor. These individuals might be good donors, not having had an opportunity to acquire more drug resistance, however the possibility of a drug resistant virus should be considered [41, 49].

Centers should be aware that testing for donor evaluation are designed to be particularly sensitive, but consequently can lead to false positives, particularly antibody, or antibody/antigen tests. In recent US HIV transplant cohorts, up to 30% of donors testing positive for HIV were ultimately found to be false positives [50]. HIV-NAT screening is recommended in non-standard risk donors but HIV-NAT positive donors are much less common (**Table 1**). Donor viral load does not appear to negatively impact organ quality and graft survival, similarly donor CD4 count at terminal illness should be interpreted with caution, as the absolute value may fall significantly during terminal illness, and does not reflect ultimate graft and recipient outcome [51, 52].

For HIV-positive living donors, additional assessments are required, but the small number of outcomes so far have been reassuringly positive for both donors and their recipients [53]. Not only are organ quality characteristics important, but long-term donor renal health must be considered. Historic data would suggest a more rapid decline in living donor residual renal function, although contemporaneous data from an era where integrase inhibitors have dominated care is lacking. A living donor consent conversation should recognize these unknowns [54].

Early data from HIV D+/R+ is promising, however a few caveats are notable. Firstly, rejection rates in the recipients appeared higher when compared against HIV-positive recipients receiving HIV-negative organs. The reasons for this remain unknown. Additionally, in liver recipients, cancer-free survival appeared statistically worse, although numbers were small. These potential detrimental factors should be balanced against an expanded donor pool and shorter transplant waitlist when reviewing potential donor-recipient matches [46, 55].

COVID-19 POSITIVE DONORS

Since the emergence of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), there has been a significant impact on organ transplant numbers throughout the world. Especially during 2020, transplant rates fell, as centers tried to prevent spread not only to recipients, but also to healthcare workers. Well documented cases of donor-derived SARS-CoV-2 transmission exist, including transmission to transplant team members [56]. Concern regarding organ quality also led to many potential organs offers being turned down, given the inflammatory nature of Coronavirus Disease-2019 (COVID-19) [57].

Over the course of the pandemic, reassuringly a number of things have changed that allow for the preservation of the donor pool despite ongoing community transmission. Firstly, diagnostics that were so lacking in early 2020 are now widely available, including both point of care testing and molecular testing. Organ procurement policy in many jurisdictions has required testing of potential donors, including the lower respiratory tract if lung donation is considered. Most centers also test transplant candidates, especially those who are symptomatic at the time of organ offer.

Secondly, fear of inflammatory damage to a donated organ has fallen as community levels of immunity have risen. Good quality vaccines are now available across the globe, such that all recipients, and ideally all healthcare workers should be vaccinated. With so many potential donors also vaccinated and/or naturally infected, immunity is such that widespread tissue coagulation and now hyperinflammation are rarely seen. Consequently, even if a donor tests positive for SARS-CoV-2 at the time of donation, clinicians can proceed with confidence that graft organ function is unlikely impaired [58].

Third, treatment options are now widely available and well-studied in the immunosuppressed patient population. Intravenous remdesivir remains a first line treatment agent for acute COVID-19 in any transplant recipient who develops symptomatic disease. Treatment of recipients of non-lung organs is likely unnecessary as now good data suggests these are unlikely to be infectious.

Fourth transplantation of non-lung organs from donors with active SARS-CoV-2 infection is considered possible and well tolerated, without SARS-CoV-2 transmission. There are no documented donor-derived transmission events to liver,

kidney or heart recipients [59]. Lung donation from SARSCoV-2 NAT + donors is generally not recommended, outside two potential approaches [60]. The first is to recover lungs from SARS- CoV-2 NAT positive donors only when symptom onset or test positivity occurred >20 days prior. The second is to recover all organs from asymptomatic SARS-CoV-2 NAT positive donors, stratifying the risk of disease transmission using the Ct value. The former emphasizes safety while the latter maximizes organ utilization at the expense of a higher risk of disease transmission given limitation of Ct values to determine infectivity [59, 61, 62]. Finally the use of subgenomic RNA, a proposed surrogate marker of active virus replication, might help to guide organ utilization although this technique is not widely available [63]. There are no reports of using intestinal organ from COVID-19 donors. Given the intestinal tract can be a reservoir for SARS-CoV-2, and intestinal transplant is rarely if ever urgent, this is not routinely advised.

Healthcare worker protection should still be paramount for transplant teams. Generally speaking, any donor who tests positive for SARS-Cov-2 should be managed as potentially infectious. However, once the organ has been procured, this is likely no longer the case, and centers who use positive donors manage infection control at their hospital as per routine. Lung donors with positive SARS-CoV-2 tests should, however, be managed as if they are potentially infectious, as should their recipients after transplant, until suitable tests confirm no transmission [59].

On the basis of the current experience, transplantation of non-lung organs from donors with active SARS-CoV-2 infection has been associated with good short-term outcomes, in terms of 30-day graft loss and mortality. However, studies with longer follow up (6–12-month) found significantly higher rates of hepatic artery thrombosis among recipients of liver and kidney grafts and higher mortality among recipients of hearts obtained from donors with active SARS-CoV-2 [60, 64, 65]. Further studies are needed to assess the long-term outcomes of recipients of organs from donors with active SARS-CoV-2 infection.

BACTEREMIC AND CANDIDEMIC DONORS

Blood donor cultures should be obtained routinely at the time of organ donation and prompt transmission of information on blood culture positivity to the recipients' centers should be done in the shortest time possible and with the highest quality [66, 67]. It has been estimated that 5%–7% of organ donors have bacteremia at the time of organ procurement, but the transmission of the infection to the recipient is low and it has been mainly described in donors with bacteremia due to microorganisms resistant to perioperative antibiotic prophylaxis used in transplantation [68, 69]. In general, liver recipients may be at higher risk of donor transmitted bacteremia compared with recipients of non-hepatic organs and Gram-negative bacilli (GNB) appear to pose a greater risk for transmission and are associated with poorer outcomes compared with Gram-positive bacteria (GPB), except for *S. aureus*, which is a potentially more virulent GPB [70–72].

Transmission of bacterial infections from a donor with bacteremia has been associated with serious consequences for the recipient including overwhelming infection, vascular anastomosis dehiscence in the graft resulting in transplantectomy and death. Additionally, there is controversial information on the relationship between bacteremia in the donor and worsening of graft function [73]. In the same way, there is evidence that demonstrates that the administration of effective antimicrobial therapy in both donor and recipient at the time of the donation process, decreases dramatically (but not eliminates) the risk of transmission, making this practice reasonably safe.

In general organs from donors with positive blood cultures may be safely used if they have received an appropriate antimicrobial for at least 24–48 h, ideally with some degree of clinical response (improved white blood cell count, improved hemodynamics, defervescence of fever), since in clinical practice documented clearance of donor bacteremia is often not achievable before transplantation.

In addition, a complete course of therapy (range 7–14 days) depending on the presence of virulent microorganism (such as *S. aureus* and *P. aeruginosa* in particular) should be given to the recipient post-transplant with targeted antimicrobial treatment. Donors with documented bacteremia should be used with informed consent, after evaluation of the transplant infectious diseases team, and recipients should undergo systematic surveillance cultures after transplantation.

Endocarditis does not constitute a contraindication for transplantation, except for heart. The use of organs from donors with infective endocarditis remains controversial for the risk of metastatic infections but can still be used based on individual decision [74]. Ideally patients with endocarditis can be accepted as donors of non-heart organs if they have received proper antibiotic treatment prior to donation (preferably a minimum of 24–48 h), if they have cleared blood cultures and there is no evidence of peripheric emboli that have damaged the organs to be transplanted. The recipient must continue treatment for at least 10–14 days with active drugs, whose choice and duration must be modulated according to the results of the blood cultures of the donor at the time of organs procurement.

Non-bacteremic localized infections from other sites only require antibiotic treatment if transmission in the transplanted organ is plausible (positive urine cultures for kidney recipients; respiratory cultures for lung recipients) but it is not recommended for the other organs recipients. The donor with localized bacterial infection must have received adequate treatment prior to donation (preferably a minimum of 24–48 h). Targeted antibiotic treatment should be continued in the recipient of the infected organ.

Most cases of donor-derived candidiasis have occurred in kidney transplant recipients and rarely in liver transplant recipients in whom contaminated preservation fluid is a commonly proposed source, but also donor candidemia without effective antifungal therapy can be infection source [75, 76]. In this setting DDI fungal infection can result in life-threatening complications like arteritis and vascular aneurysms. On the basis of our national protocol, transplant of donors with

untreated candidemia is not recommended and donors with positive blood cultures for *Candida* spp. can be accepted only after 24–48 h of effective antifungal therapy prior to organ procurement and recipients should receive at least a 14-day course of antifungals (echinocandins are the preferred antifungal therapy) targeting the donor *Candida* spp. isolate [10].

MULTIDRUG RESISTANT BACTERIA AND FUNGI

Transmission of most bacterial infections may be prevented by the use of surgical prophylaxis at time of transplant surgery, but due to the emergence of multidrug resistant (MDR) bacteria, routine prophylaxis might fail to prevent transmission of bacteria from the donor organ at the time of procurement [77, 78]. Gram-positive MDR bacteria (vancomycin-resistant *Enterococcus* species, methicillin-resistant *Staphylococcus aureus*) do not appear to have a significant impact on organ utilization [79]. On the contrary MDR Gram-negative bacteria (MDR GNB), which include, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, *Klebsiella pneumoniae* and other carbapenem-resistant Enterobacterales, has been observed to reduce organ procurement and transplantation [79, 80]. There is no evidence to suggest that organs from donors infected or colonized with Extended-spectrum β- lactamase—producing Enterobacterales (ESBL) be excluded from transplantation [81, 82].

Transmission with organ transplantation of MDR-GNB organisms has been associated with serious consequences for the recipients in terms of morbidity and mortality [71, 83, 84]. There is limited experience on risk mitigation strategies related to MDR-GNB bacteria that have been successfully implemented to minimize the impact of MDR-GNB donor-transmitted bacteria following organ transplantation. Indeed, limited reports showed that recipients of organs from donors with MDR-GNB infection may have a favorable outcome with early microbiological diagnosis, peri-transplant targeted antibiotic therapy due to successful intra- and inter-institutional communication and prolonged treatment after transplantation [67, 85–87]. These results underline that active surveillance system should be implemented to avoid communication gaps that might be associated with infection transmission and could allow the policies on the use of organs from MDR-GNB positive donors to be reconsidered [87]. Rapid and effective interagency and interinstitutional communication regarding donor cultures are imperative to optimize recipient management [81].

In addition, the current availability of new drugs with activity against some MDR-GNB pathogens and new possible decontamination techniques performed after organ procurement might allow in the future a more liberal use of these organs [85, 88]. However further work is needed to understand how to prospectively identify donors that may harbor MDR subclinical infection, and how to best manage recipients at risk for MDR-GNB donor-derived infections following transplantation [89].

In general, the confirmed presence of MDR-GNB bacteremia constitute an exclusion criterion from the donation, because outcomes in such circumstances are still unknown, but individual donor evaluation is required with careful discussion with the transplant infectious diseases team. The efficacy of appropriate antimicrobial treatment of the donor before organ procurement on the basis of *in vitro* susceptibility data, in preventing recipient infection, is not known. Risk-benefit assessment is needed to drive decisions to accept the organ but a clear plan for effective peri- and post-transplant antibiotics for the recipient should be outlined prior to the use of such organs [78, 89]. As regards as localized infections (pneumonia, infections of the urinary tract), in the absence of associated bacteremia, the exclusion applies only to the infected organ [90].

There is insufficient data to determine the risk of transmission of infection from a donor colonized by MDR-GNB to a recipient. The isolated positivity of the rectal swab for MDR-GNB should not be considered a criterion of exclusion from donation, except for bowel and pancreas donation and requests the highest respect for surgical aseptic procedures in order to avoid contamination of the procured organs [78, 90].

It seems prudent to exclude organs colonized or infected by MDR GNB (lungs, kidney) although in specific situations the organs colonized with MDR bacteria may be safely used when the recipients receive prompt tailored antibiotic treatment [91]. It is not currently recommended administration of modified antibiotic prophylaxis to recipients of organs from donors that are colonized but it is important to have the microbiological donor history recorded in order to adjust the empirical antibiotic treatment in case of suspected infection immediately after the transplantation [78, 90].

Candida auris is an emerging pathogen capable of drug resistance and persistence in the environment with important public health implications and has several implications for organ transplantation. The possibility of donor-derived transmission of *C. auris* has been described [92]. Isolation from an organ donor warrants careful consideration before transplantation. At present, there are few data to guide such decisions.

CONCLUSION

Donor-derived infections continue to be a challenge. Awareness of epidemiological changes and emerging pathogens alongside the improvement of rapid and reliable microbiological screening are basic tools to improve organ safety and quality of organs allocation. It is vital to develop prospective and high-quality research to improve a more tailored approach and knowledge on short- and long-term outcomes of DDIs. Moreveor new frontiers need to be explored to expand the donor pool demanding careful legal, ethical and medical caution.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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