An Update in Antimicrobial Therapies and Infection Prevention in Pediatric Lung Transplant Recipients

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Abstract

Lung transplantation can offer life-prolonging therapy to children with otherwise terminal end-stage lung disease. However, infectious complications, like those experienced by their adult counterparts, are a significant cause of morbidity and mortality. These include bacteria, viruses, and fungi that infect the patient pretransplant and those that may be acquired from the donor or by the recipient in the months to years posttransplant. An understanding of the approach to the management of each potential infecting organism is required to ensure optimal outcomes. In particular, emphasis on aggressive preoperative management of infections in pediatric patients with cystic fibrosis is important. These include multidrug-resistant Gram-negative bacteria, fungi, and *Mycobacterium abscessus*, the posttransplant outcome of which depends on optimal pretransplant management, including vaccination and other preventive, antibiotic-sparing strategies. Similarly, increasing the transplant donor pool to meet rising transplant demands is an issue of critical importance. Expanded-criteria donors—those at increased risk of blood-borne viruses in particular—are increasingly being considered and transplants undertaken to meet the rising demand. There is growing evidence in the adult pool that these transplants are safe and associated with comparable outcomes. Pediatric transplanters are therefore likely to be presented with increased-risk donors for their patients. Finally, numerous novel antibiotic-sparing therapeutic approaches are on the horizon to help combat infections that currently compromise transplant outcomes.

Key Points

Despite advances in surgical techniques and optimization of non-infectious complications after lung transplant, infectious morbidity and mortality rates remain high.

Novel antibacterial/antiviral-sparing approaches to the management of infection are likely to become an increasingly important component of therapy in the future in light of rising rates of bacterial and viral resistance.

Expansion of the lung donor pool to include donors with potential or actual blood-borne viral infections is increasingly likely.

1 Introduction

Lung transplantation (LTx) offers life-prolonging therapy to children with end-stage lung diseases [1]. According to the International Society for Heart and Lung Transplant data registry, upwards of 961 pediatric recipients underwent LTx between 2008 and 2016 [2]. The majority (>70%) of these recipients were aged between 11 and 17 years, and >50% received a deceased organ from an adult donor, making them as vulnerable to donor-derived infections as their adult counterparts [2]. The most frequent indication for LTx in this setting is cystic fibrosis (CF), which accounts for >66% of cases [2]. These children are often unwell, with complicated infections associated with multidrug-resistant organisms at the time of transplant. After LTx, these children are at risk of dissemination of existing commensals and infecting agents as well as the acquisition of new infections. Notably, all infections are difficult to treat in the post-LTx setting because of the combination of immune-suppressing agents and complex drug–drug interactions.

Aggressive peri-transplant infection-management strategies are a critical part of successful clinical LTx outcomes.

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Timely planning is required to target peri-LTx eradication with a combination of surgical debridement and directed antimicrobial and antiviral therapies. Such approaches must be based on knowledge of both donor and recipient pathogens—previous, current, and predicted. Antimicrobial-sparing strategies, including vaccination and novel adjunctive therapies, are also increasingly recognized as important components of effective models of care, a discussion of which is included in this review.

There are numerous organisms and therapies considered of particular interest to pediatric LTx recipients as well as recent novel insights into the management of specific pathogens. This review summarizes the recent literature on these topics.

2 Bacterial Infections

2.1 *Mycoplasma* and *Ureaplasma* Species

Mycoplasma hominis and *Ureaplasma* spp. make up part of the genitourinary commensal flora in up to 80% of young, sexually active adults [3, 4]. While not recognized as part of the normal lower respiratory tract flora, up to 8% of adults with chronic respiratory disease and 14% of young adult LTx donors have been found to harbor these organisms in the lower respiratory tract [5]. In children, *Ureaplasma* spp. have been associated with wheezing and pertussis-like syndromes, urinary tract infections, various arthritides, and fatal pneumonitis, whereas *M. hominis* is associated with urinary tract, surgical site, skin, and soft tissue infections and dissemination with overwhelming infection in the immunocompromised host [6–12]. The number of reports of these organisms causing disease after LTx is increasing and, because they are difficult to diagnose, it is likely these cases are under recognized in both adult and pediatric transplant populations [13, 14]. In addition, posttransplant hyperammonemia syndrome, an increasingly recognized cause of morbidity and mortality early posttransplant appears to be closely associated with infection with these organisms [5].

The genital mycoplasma, as they are often referred to, are the smallest self-replicating organisms [15]. They lack a cell wall, which means they do not take up conventional bacterial stains in the laboratory and will not be detected by Gram stain [15]. Many are uncultivable on conventional agar, but those that are form microscopic pinpoint colonies, often obscured by competing bacterial flora so may be overlooked and missed by laboratory staff. Infection should be considered when microbiological samples demonstrate purulence but no organism is identified on Gram stain in the setting of a clinically compatible syndrome. These organisms are extremely sensitive and often will not survive the collection of clinical specimens [13]. Specimens should be

inoculated at the bedside whenever possible, ideally using liquid media, and transported to the laboratory for inoculation within 60 min to improve diagnostic yield [13]. Cotton swabs should be avoided for sampling areas suspicious for infection as they can inhibit growth of the organism [15]. Real-time polymerase chain reaction (PCR)-based tests provide highly accurate and rapid results, and numerous platforms are commercially available [16]. Molecular testing is typically only available at reference or specialized laboratories. The advantage of molecular diagnostics is detection of nonviable organisms missed with culture methods [15, 17]. Notwithstanding all this, no validated data exist to link PCR results to disseminated disease.

The lack of cell wall in these organisms has not only diagnostic implications but also therapeutic consequences. The bacteria are non-susceptible to cell wall-active antibiotics and are considered inherently resistant to beta-lactams, glycopeptides, sulphonamides, trimethoprim, and rifampin [15]. Therefore, the antibiotics routinely administered by most institutions to their unwell and undifferentiated LTx recipients, typically beta-lactam/beta-lactamase combinations or carbapenems, will be ineffective against these bacteria. Infection should therefore also be considered in patients who do not respond to these empiric regimens. Resistance to macrolides and lincosamides varies according to species [13]. Tetracycline resistance has been well documented in *M. hominis* and *Ureaplasma* spp., with rates approaching 40–50%, mediated by the tetM determinant [18]. Rates of high-level macrolide resistance are increasing [19]. Fluoroquinolones such as moxifloxacin and levofloxacin are usually active against all the genital mycoplasma species [15]. Reports describing emergence of resistance with single-agent therapy in overwhelming infection leads the authors to recommend empirical dual-agent therapy in LTx recipients with disseminated infection while awaiting either in vitro or molecular evidence to support directed therapy [20].

Infection typically occurs within the first 1–2 weeks post-LTx [5, 13, 14, 21, 22]. The most frequent presentations are pleuro-pericardial and sternal or wound infections, with bacteremia occurring less frequently [14, 21–23]. While only a single case has been reported in the pediatric LTx literature, it is likely that cases go unrecognized. Dixit et al. [10] described a bilateral LTx recipient with a history of stem cell transplant who developed fevers, pleural effusions, and respiratory distress requiring reintubation day 5 post-LTx after a favorable early post-LTx course. This case closely resembles those reported in the adult population.

The origin of infection in these patients remains unclear, with debate surrounding whether infection represents translocation of recipient flora versus donor-derived infection. There is increasing evidence to support donor-derived transmission as the primary route of acquisition. Fernandez et al. [5] undertook screening urine and bronchoalveolar lavage

(BAL) in a cohort of 29 consecutive LTx recipients and their 28 donors and found that 14% of donor BALs were positive for either *Ureaplasma* spp. or *M. hominis*, whereas only a single recipient had a positive baseline test with isolation from urine. Importantly, all recipients who received lungs with a BAL detecting a genital mycoplasma went on to develop pulmonary infiltrates [5]. Furthermore, there was a positive association between donor isolation of genital mycoplasma and younger donor age, a greater number of donor sexual partners, and donor male sex. The authors of this review used whole genome sequencing to demonstrate that *M. hominis* was the cause of donor-derived infection in an adult LTx recipient, and various other reports have demonstrated donor colonization with subsequent recipient infection [13, 14].

Hyperammonemia has historically been a poorly understood and potentially fatal complication post-LTx. Calcineurin inhibitors (CNIs) have long been implicated as a contributor to the development of hyperammonemia, as all case reports have involved cyclosporine- or tacrolimus-based regimens [24]. Understanding of this entity has recently progressed, with reports proposing a causal relationship between *Ureaplasma* spp. infection and hyperammonemia [20, 25]. Previous approaches to treatment included aggressive ammonia-lowering therapies and cessation of the CNI. However, administration of antimicrobials directed at *Ureaplasma* spp. infection has recently been shown to result in complete clinical resolution and should be part of therapy in all patients [20]. Although understanding has progressed, the etiology is again largely unknown, and understanding has been limited to case reports and small series [24, 26, 27]. Chen et al. [28] recently published the largest case series to date and developed a treatment protocol from their experience, recommending empirical genital mycoplasma-directed antibacterials pending microbiological study results. Until further evidence regarding the pathophysiology of hyperammonemia is provided, we recommend dual empirical genital mycoplasma-directed therapy while awaiting genital mycoplasma antimicrobial susceptibility testing, in addition to the protocol outlined by Chen et al. [28].

In summary, disseminated infection with genital mycoplasmas post-LTx likely occurs more frequently than currently recognized. A high index of suspicion is required because these organisms are difficult to isolate with conventional methods. These organisms are capable of causing sternal wound, pleuro-pericardial, and disseminated infections in addition to the often fatal hyperammonemia syndrome.

2.2 *Mycobacterium abscessus* Complex

Mycobacterium abscessus complex (MA) has emerged as one of the most problematic infections post-LTx, mainly because of its refractoriness to treatment [29–31]. While

pretransplant infection is largely confined to the respiratory tract, post-LTx infection is more likely to be extrapulmonary and disseminated and very difficult to treat [32, 33]. While MA was historically thought to be an absolute contraindication to LTx, increasing evidence from institutional cohorts indicates that outcomes in recipients with pre-LTx MA are comparable to those of their uninfected counterparts, particularly those with aggressive pre-LTx management [34–36]. The incidence and prevalence of nontuberculous mycobacteria, including MA, continues to rise in children with CF, the foremost indication for pediatric LTx, so both transplant physicians and CF physicians must work together to optimize the pre- and peri-LTx management of these infections to optimize post-LTx outcomes [37–39].

Since its elevation to species level, MA has been further divided into three subspecies using 16S ribosomal RNA gene sequencing: *M. abscessus* subsp. *abscessus* (MAA), *M. abscessus* subsp. *bolletii* (MAB), and *M. abscessus* subsp. *massiliense* (MAM). Based on sequencing of the *erm*(41) gene, suggestions have been made that further subdivision is necessary [40, 41]. Identification to subspecies is now a critical component of evaluating any patient with an MA, as significant therapeutic and prognostic predictions can be made based on identification of subspecies alone [41–47].

MA is ubiquitous in the environment, particularly in water sources, and outbreaks have been traced to environmental sources and devices contaminated with tap water [48]. MA has been shown to persist in the environment after exposure to numerous hospital biocides, and concern has arisen that transmission between patients may occur via contaminated fomites [49]. However, investigations of single-institution outbreaks have failed to demonstrate environmental sources beyond contaminated water reservoirs [29, 50, 51]. Guidelines from the American Thoracic Society/Infectious Diseases Society of America suggest avoiding contamination of indwelling intravenous catheters with tap water and the use of tap water in fiberoptic endoscopic cleaning processes to avoid contamination with nontuberculous mycobacteria, but there remain no clear guidelines regarding the utility of patient isolation or other infection-prevention measures. Recently, MA has been demonstrated to survive in respirable-size aerosol droplets that can travel up to 4 m, thus providing proof of concept for risk of patient-to-patient transmission [52]. However, the investigation of outbreaks using molecular diagnostics have yielded contradictory results with regards to transmissibility between patients, with evidence both in favor of and against cross-transmission. There is some suggestion that transmission risk may be subspecies dependent, with MAM a greater risk than MAA or MAB [29, 53]. In the absence of definitive data documenting patient-to-patient spread, isolation practices are CF and transplant center dependent [54]. Further evidence is required to direct infection-control policies, but

the authors suggest that centers have some form of infection-control/separation policies in place for patients with MA, particularly those with smear-positive respiratory disease.

MA is an intrinsically multidrug-resistant organism. The most data exist for clarithromycin resistance, which may be intrinsic or acquired, mediated by the *erm*(41) gene and *rhl* gene, respectively. The patterns of resistance can be somewhat predicted based on subspecies. MAB have a complete *erm*(41) gene associated with clarithromycin resistance, whereas nearly all MAM harbor non-functional *erm*(41) genes that render them intrinsically susceptible to clarithromycin, and MAA have a complete *erm*(41) gene and sequevars associated with both clarithromycin susceptibility or resistance [40, 42]. There is increasing evidence that an even more complex overlapping network of resistance mechanisms are at play that includes, among others, amikacin resistance mediated by the *rrs* gene [55]. Most recently, identification of *whiB7*, a transcriptional activator, induced by exposure to antibiotics and conserved across all species of mycobacteria, has been described [56, 57]. The induction of *whiB7*-mediated resistance induced by one antibiotic inducer can promote cross-resistance to additional antibiotics [56, 57]. This implies that one group of antibiotics may antagonize the effects of another, for example that clarithromycin can antagonize the efficacy of amikacin. The practical implications of this finding are unclear but suggest that sequential antibiotic therapy based on inducers and antagonizers of this pathway may theoretically present a viable alternative to the existing approach that consists of multiple antibiotics administered concurrently.

Because there is poor correlation between in vitro antibiotic susceptibility testing and in vivo efficacy, increasing hope had been placed on the development of commercial molecular assays to identify these molecular markers of resistance [56]. Unfortunately, however, reports of the positive correlation between genotypic and phenotypic testing for resistance have been conflicting [55, 58, 59]. Furthermore, significant variations in genotypic and phenotypic resistance patterns have been observed based on geography [55]. For this reason, the authors recommend that all centers continue to routinely undertake MA antibiotic susceptibility testing and utilize local data regarding resistance patterns in addition to any available molecular diagnostics.

Current guidelines for treatment of MA emphasize the need for combination therapy, typically with a macrolide backbone in addition to amikacin and cefoxitin/imipenem for an extended treatment course, typically months to years in duration [60]. Unfortunately, treatment in the immunocompromized, including LTx recipients, can be even more complicated, required for longer durations (occasionally indefinitely), and associated with significant toxicity and development of resistance. Given the average rate of eradication is only 45% for these infections, focus has been

directed at identifying novel approaches to improve outcomes. In two cases recently described by Scott et al. [61], two patients with CF (including a child aged 10 years) with smear-positive lower respiratory tract infection were treated with aerosolized granulocyte-macrophage colony-stimulating factor (GM-CSF), one as sole therapy and the other as an adjunctive therapy in the setting of a failing multidrug regimen. Both patients experienced sputum conversion without toxicity [61]. The authors hypothesized that abnormally low levels of GM-CSF in the airways of patients with CF predispose them to persistent infection. This therapy may be most useful in the pre-LTx setting to improve the chance of sputum smear and culture conversion, which has been associated with better post-LTx outcomes [31].

An Ambler class A β -lactamase (Bla_{Mab}) was recently identified in MA, with hope that a β -lactam/ β -lactamase inhibitor combination might provide an additional antimycobacterial to add to the current armamentarium [62]. While Bla_{Mab} is not inhibited by clavulanate, sulbactam, or tazobactam, a combination of avibactam with carbapenems and ceftaroline has improved efficacy in vivo [62–65]. Human data are currently lacking, but this discovery provides hope for clinicians treating these recalcitrant infections.

An interesting observation was made during in vitro studies of antimycobacterial effectiveness when synergism between different classes of antibiotics was identified. Zhang et al. [66] showed that the combination of clarithromycin and moxifloxacin or clarithromycin and tigecycline demonstrated greater synergism in MAM than in MAA. The same group went on to demonstrate that the combination of linezolid + amikacin and of linezolid + tigecycline also demonstrated synergism, in contrast to linezolid + cefoxitin or moxifloxacin, which demonstrated antagonism [67]. The future approach to therapy for MA may well consist of a combination of these recent observations to include sequential antimycobacterials to capitalize on synergism and avoid antagonisms between classes, in addition to adjunctive nonantibacterial-based therapies such as inhaled GM-CSF.

Despite recent advances, MA remains an extremely challenging organism to treat, presenting a particular problem in those with CF and leading into the post-LTx setting. Emphasis must be placed on a carefully constructed peri-LTx diagnostic and therapeutic management plan to ensure successful post-LTx outcomes. Extended sensitivity testing and aggressive antimycobacterial therapies (including intra- and post-LTx surgical strategies, reduced immunosuppression, and long-term MA surveillance) must be part of a multidisciplinary and long-term approach to treatment for this recalcitrant organism.

2.3 Resistant Gram-Negative Bacteria

Multidrug-resistant Gram-negative (MDR GN) infections and colonization present a particular challenge in patients with CF, the most frequent indication for pediatric LTx, and remain problematic post-LTx [68–71], with a negative impact on survival [68, 72, 73]. Children pediatric recipients are increasingly likely to be offered otherwise viable lungs from donors with MDR GN infections, particularly in the pool of donors recently hospitalized or even simply living in the countries with very high rates of drug resistance [74]. Recipient outcomes in this setting appear to be related to appropriate peri-transplant management with targeted antimicrobials, highlighting the need for communication between transplant coordinators, the microbiology laboratory, transplant clinicians, and infectious diseases clinicians [68, 75]. Numerous newer β -lactam- and carbapenem- β -lactamase inhibitor combinations have recently become available, with emerging evidence in the adult population that these agents will be safe, well-tolerated, and efficacious. The combination of ceftazidime/avibactam has been shown to improve the inhibitory activity of ceftazidime towards Gram negatives producing class A, C, and some class D β -lactamases, with a particular affinity for difficult-to-treat *Klebsiella pneumoniae* carbapenemase (KPC)-producing Gram negatives [76–79]. Emerging data suggest this combination therapy is effective in adult transplant recipients; however, the experience is limited in the pediatric setting, although phase I data have shown this agent was safe and well-tolerated in children [80–82]. Ceftolozane, a novel fifth-generation oxy-imino cephalosporin closely resembling ceftazidime, has been combined with the β -lactamase inhibitor tazobactam, with broad activity against chromosomal ampC β -lactamases in addition to potent antipseudomonal activity [83–85]. While only case reports describe its use in the pediatric setting, the potent activity towards pseudomonal isolates is likely to be of significant value in the LTx setting [86]. Imipenem/cilastatin/relebactam and meropenem/vaborbactam are novel carbapenem/ β -lactamase inhibitor combinations with a growing body of evidence to demonstrate potent activity towards carbapenem-resistant but non-metallo- β -lactamase (MBL) producing Enterobacteriaceae and *Pseudomonas* spp. [87–90]. While phase III data are lacking, imipenem/cilastatin/relebactam is likely to be an important antipseudomonal antibiotic with significant activity towards pseudomonal isolates with reduced oprD expression and ampC overexpression, two of the more prevalent mechanisms of high-level carbapenem resistance, in addition to high penetration into pulmonary tissues [87, 91–93]. Finally, the combination of ceftazidime/avibactam with aztreonam has demonstrated synergy in vitro towards MBL-producing Enterobacteriaceae, including those expressing *bla*_{IMP} and *bla*_{NMD} [94]. In a recent description

of an outbreak in ten patients, four of whom were adult solid organ transplant (SOT) recipients, with extensively drug-resistant New Delhi MBL (NDM)-1-producing *K. pneumoniae* infection, clinical success rates of 60% were observed without adverse effects. Although data to support the use of these newer agents in the pediatric setting are limited, adult data provides reason to hope these agents will prove to be safe and efficacious in the pediatric population, as they are proving to be in adults.

3 Viral Pathogens

3.1 Hepatitis C Virus

Lung donation from hepatitis C virus (HCV)-positive donors has historically been associated with high rates of viral transmission and subsequent inferior outcomes when compared with donation from HCV-negative donors [95–97]. Until recently, however, only hepatitis C serological testing was readily available to screen donors, leaving clinicians unable to differentiate those who were viremic (with high risk of transmission) from those who were non-viremic (or aviremic) (with negligible risk of transmission). With only serological testing available, this collective group of HCV-positive donors were generally declined by transplant services. However, in recent times, attitudes to HCV-positive donors have begun to change, including those who are viremic and aviremic [97]. This reflects an increasing demand for organs, the changing epidemiology of HCV in the adult donor pool, ready access to nucleic acid tests (NATs) to determine viremic or aviremic status, and ready access to safe and effective direct-acting antivirals (DAAs). The increasing prevalence of HCV in the donor population, particularly in the USA, where up to 30% of the donor pool is HCV positive, has forced centers to consider HCV-positive expanded-criteria donors [97–100]. Pediatric recipients are not immune to this changing epidemiology, as the adolescent and adult population are accounting for an increasing percentage of the pediatric donor population [101–103].

The prevalence of HCV in the pediatric population is far below that in their adult counterparts and estimated to be between 0.05 and 0.36% in the USA and Europe [104]. However, there are concerns that this is likely an underestimation given the low prevalence of testing in this population [105]. The major route of transmission in children is vertical, from mother to child, and 60% of these cases will go on to develop chronic HCV, usually by age 2 [106]. Children are rarely symptomatic, so potential pediatric donors also require HCV screening prior to donation like their adult counterparts [107]. The same testing sequence used for screening adults, consisting of a HCV antibody assay followed by NAT testing if serology is positive, is recommended for the

investigation of pediatric donors aged > 18 months. Children aged < 18 months should be screened with NAT only, as they are likely to have detectable maternal immunoglobulin [106].

The absolute number of pediatric LTx is increasing over time; as outcomes improve, more children are put on the waitlist. Waitlist mortality is greater in pediatric patients than in adults, so identifying suitable donors is often time critical [101, 103]. Donors aged ≥ 17 years are increasingly represented among the donors for pediatric LTx, and, while the epidemiology of HCV in the pediatric pool is relatively static, the same cannot be said for the adult donor pool [97]. Therefore, pediatric transplant physicians are increasingly likely to be presented with either seropositive/NAT-negative or NAT-positive potential donor candidates for consideration. To meet the increasing organ demands, adult transplant centers are beginning to utilize both viremic and aviremic donors. The safety and efficacy of the interferon-sparing DAAs have allowed the treatment of HCV in transplant recipients without the predictably increased risk of rejection that complicated interferon-containing regimens. DAAs have successfully treated HCV in recipients of LTx and non-lung transplants [108, 109].

Unfortunately, evidence for the use of DAAs in the pediatric population lags behind that in their adult counterparts [110]. Until recently, evidence for the use of interferon-free regimens in pediatric patients was limited, but the body of evidence that these therapies are safe and highly effective in children is growing [111, 112]. Further work will need to be undertaken to establish whether these therapies are safe for use in pediatric LTx recipients.

Pediatric transplant centers are also likely to be offered seropositive/aviremic HCV donors for consideration. The authors encourage strong consideration be given to accepting these organs in the absence of other contraindications. There is no evidence that these donors have transmitted virus to adult recipients [97]. Interestingly, the authors and others have observed a phenomenon of persistent HCV seropositivity in the absence of detectable viremia in a subset of adult recipients of HCV-seropositive/aviremic donor grafts [113–115]. The mechanisms for this seropositivity are unclear but do not appear to represent transmission of virus. They may represent a form of passenger lymphocyte syndrome, with memory B cells transplanted among allograft-associated lymphoid tissue. As published experience with these donor/recipient pairs is absent, we strongly suggest protocolized follow-up that includes both HCV serology and NAT testing within the first 7 days of transplant and regularly thereafter.

There is currently no evidence to support donation from the lungs of HCV viremic donors into pediatric recipients. While we await more robust evidence to support the efficacy and safety of DAA use in children, these donors should

continue to be declined. However, the authors suggest that strong consideration be given to accepting donor lungs from seropositive/aviremic donors as they do not appear to represent a risk for viral transmission.

3.2 Human Immunodeficiency Virus

Outcomes for HIV-positive recipients who receive organs from HIV-positive or -negative donors appear favorable [116, 117]. Evidence from inadvertent transplant of HIV-positive donors to HIV-negative recipients has shown good patient and graft survival [118]. Modern antiretroviral therapies can be safely administered post-LTx without major problematic drug–drug interactions. The risk of donor-derived HIV from pediatric donors to pediatric recipients is extremely low, but the risk is greater from adult donors, which are increasingly represented as pediatric donors [119]. With growing interest in expanding the donor pool to address expanding waitlists, the need to consider otherwise viable organs from HIV-positive donors may become necessary [120].

3.3 Cytomegalovirus

Cytomegalovirus (CMV) continues to contribute to significant morbidity and mortality following LTx, and this is no different in the pediatric population. A member of the herpesvirus family, CMV demonstrates latency and, in the immunosuppressed CMV-seropositive LTx patient, an ever-present risk of reactivation [121]. Given that CMV seropositivity increases with age, the proportion of CMV-naïve LTx recipients is higher in the pediatric population than in adults. Depending on their size, pediatric LTx recipients may receive donor organs from both the pediatric and the adult organ donor pool, with the latter being much more commonly CMV seropositive. These epidemiological factors peculiar to the pediatric population mean that the incidence of CMV mismatches, whereby a CMV-naïve recipient (R-) is transplanted with lungs from a CMV-seropositive donor (D+), is higher in pediatric patients. Importantly, the subsequent risk of CMV infection and disease is higher in the CMV R-D+ mismatched LTx recipient. Primary CMV infection in the R-D- child is also higher as a result of exposure in the community, especially around school attendance [122].

In the adult LTx population, CMV reactivation can be associated with direct end-organ disease and also indirect disease, including an association with secondary microbial infections and chronic lung allograft dysfunction (CLAD) [123, 124]. However, while CMV disease is associated with an increased 1-year mortality in pediatric LTx recipients, an association with opportunistic infections or CLAD has not been demonstrated [122].

Before the introduction of antiviral prophylaxis, viremia was seen in over 60% of LTx recipients, with almost half of these developing end-organ CMV disease [125]. With routine antiviral prophylaxis, CMV viremia and CMV pneumonitis is still seen in approximately 30% and 20% of pediatric LTx recipients, respectively [126]. Most centers advocate routine antiviral prophylaxis for all those at risk (R+D+, R+D–, or R–/D+), with a recent consensus statement advocating at least 3–6 months of antiviral prophylaxis using a combination of early intravenous ganciclovir followed by oral valganciclovir [127]. Prolonged 12-week courses of intravenous ganciclovir have been shown to be safe and efficacious in pediatric LTx recipients [128]. There are limited studies on the efficacy and safety of prolonged valganciclovir use in the pediatric transplant population for prophylaxis. Valganciclovir dosing algorithms that adjust for body surface area and renal function need to be used to ensure safe and effective dosing. In a retrospective review of pediatric LTx recipients from 14 sites, hyperimmune CMV immunoglobulin preparations decreased the risk of CMV infection, but not disease, after pediatric LTx [129].

Following cessation of antiviral prophylaxis, late CMV reactivation is common and associated with serious long-term consequences. Therefore, monitoring for viremia should continue for at least 3–6 months beyond the prophylaxis period. Weekly monitoring is recommended, but this can be logistically challenging to achieve. Data are starting to emerge on assays that determine the presence of host immunity to CMV, and these are likely in the future to be incorporated into decisions regarding duration of antiviral prophylaxis in the individual patient [130, 131]. Recommendations on treatment of actual CMV disease in pediatric LTx recipients are largely extrapolated from data in the adult population and include the initial use of intravenous ganciclovir (5 mg/kg every 12 h), adjusted to renal function. In severe disease, hyperimmune CMV immunoglobulin can be added. Where clinical or proven CMV resistance is apparent, foscarnet may be an appropriate substitute for ganciclovir. Secondary antiviral prophylaxis should be considered in children with recurrent CMV viremia.

4 Immunization and Pediatric Lung Transplant (LTx)

Pediatric LTx recipients are at increased risk of morbidity and mortality as a consequence of vaccine-preventable disease. Given that vaccines are less efficacious in the setting of immunosuppression, and that live attenuated vaccines (LAV) should be avoided, it is essential to ensure all children who may be considered for LTx are fully immunized.

The LTx assessment should be regarded as an opportunity to take a vaccine history and assess for humoral immunity to

common vaccine-preventable disease. Many centers screen for immunity to hepatitis B, measles, mumps, rubella, and varicella to assist in tailoring individual immunization recommendations. Despite many countries having national childhood immunization programs, children with chronic illness may not be fully vaccinated [132]. It is important to note that those who have missed primary vaccination may need a more extensive catch-up schedule. As protective antibody titers can decrease over time [133, 134], levels should be periodically assessed following LTx and revaccination undertaken if required. It is recommended that family members, household contacts, and healthcare workers are assessed and vaccinated to provide additional protection to the transplant recipient.

4.1 The Live Attenuated Vaccines

Following LTx, LAVs should be avoided because of the risk of developing vaccine strain-disseminated disease. Special care should be taken to ensure LAVs are administered pre-LTx if required. While studies have examined the use of LAV following other SOT in children [133, 135–137], these trials were in carefully selected patients with reduced immunosuppression. These trials were predominantly undertaken in liver and kidney recipients, and such protocols are unlikely to ever be suitable for LTx recipients.

4.1.1 Varicella Zoster Virus

There is significant risk of disseminated disease and significant complications if primary VZV is contracted following LTx [138]. Immunization prior to LTx is recommended. In children aged >9 months, two doses 4 weeks apart are required, and humoral immunity should be assessed to ensure seroconversion. As the VZV vaccine is a LAV, transplant should be delayed until 4 weeks after vaccination [139].

Following LTx, VZV vaccination should be avoided in those without evidence of detectable immunity. Exposure in this group should be treated with varicella immunoglobulin if available, and the antiviral acyclovir should be considered [138].

4.1.2 Measles, Mumps, Rubella Viruses

Measles has been previously regarded as an epidemic affecting predominantly children uncommonly seen in the developed world. However, with declining herd immunity as a result of vaccine avoidance, measles is becoming increasingly common [140]. Measles can cause significant morbidity and mortality in both immunocompetent and immunosuppressed individuals. As there is no antiviral treatment, immunization is the only defense available.

The measles, mumps, rubella (MMR) vaccine is an LAV and can be used in children aged ≥ 6 months. Two doses administered 4 weeks apart are required. MMR is a safe vaccine with high rates of seroconversion. Antibody titers should be checked following administration, and, as it is a LAV, transplant should be delayed until 4 weeks after vaccination [139].

4.1.3 Rotavirus

The rotavirus vaccine is a live oral vaccine usually given to infants on a 2- to 3-dose schedule from approximately 6 weeks of age [141]. It is not suitable after LTx due to the risk of significant infection. However, unlike other LAVs, it should be avoided in those awaiting LTx because of prolonged viral shedding. In immunocompetent children, viral shedding is seen for at least 28 days after first vaccination and can continue for up to 8 months [142].

4.2 Inactivated Vaccines

Inactivated vaccines are generally safe after LTx but should be delayed until the patient is on stable low-level immunosuppression [139]. This is generally approximately beyond 6 months post-LTx.

4.2.1 Influenza Virus

Seasonal influenza can cause significant morbidity and mortality following LTx [143]. Despite effectiveness varying from year to year, annual influenza vaccination remains one of the most effective ways to prevent disease. This inactivated vaccine is made up of A and B strains of influenza as recommended by the World Health Organization [144]. Seroconversion rates are reduced after SOT and are lowest in LTx recipients and those receiving mycophenolate mofetil [145, 146]. Given lower rates of seroconversion, some transplant centers recommend two doses at least 4 weeks apart [147].

4.2.2 Streptococcus Pneumoniae

Streptococcus pneumoniae can cause catastrophic invasive disease in immunosuppressed children [148]. The inclusion of pneumococcal vaccination in national vaccination programs has significantly reduced the incidence of invasive disease in immunocompetent children [149] and, as such, the vaccination of all pediatric LTx candidates and recipients is essential.

Two vaccines are available: the 23-valent polysaccharide vaccine (23PPV) and the 13-valent conjugate vaccine (13PCV). The 13PCV is used for primary vaccination as it has better immunogenicity than the 23PPV. However, a

booster of 23PPV at least 8 weeks after 13PCV is recommended to provide protection against a broader range of serotypes [147].

4.2.3 Hepatitis B Virus

Hepatitis B virus (HBV) vaccination is now on most childhood immunization schedules. It is recommended for LTx candidates to provide both general protection against HBV and to decrease the risk of transmission if a HBV-positive donor is used [150]. If time is limited pre-LTx, an accelerated schedule can be used. HBV vaccination is safe following LTx, and any individual without detectable immunity should be offered vaccination. Seroconversion following transplantation has been reported at between 40 and 70% [151].

4.2.4 Human Papilloma Virus

The human papilloma virus (HPV) vaccine is the most recent vaccine to become available. The quadrivalent vaccine, which offers protection against HPV16 and HPV18, the major strains implicated in cervical cancer, and HPV 6 and 11, the strains responsible for 90% of genital warts, is most commonly used. A nine-valent vaccine has been approved for use in the USA but is not available in all jurisdictions. HPV disease in the form of warts causes significant morbidity after SOT [152]. As such, all transplant recipients between the ages of 11 and 26 years should be offered vaccination.

5 Novel Approaches to LTx Infectious Disease

5.1 Nitric Oxide

Inhaled nitric oxide (NO) is emerging as an antibiotic-sparing antimicrobial agent that may have a role as adjunctive therapy for treatment of MA and a range of other chronic infective pulmonary infections, including bacteria and fungi [153–155]. NO is a hydrophobic gas with broad reactivity, is rapidly diffusible, and has been demonstrated as safe when administered via multiple doses of 160 parts per million [153, 154, 156, 157]. Administration is preferably intermittent to avoid accumulation of toxic NO₂, methemoglobin, and unacceptable hypoxemia [153, 158]. While various experimental platforms have been evaluated to deliver NO, including gaseous from a tank and generation from nanoparticles, no standardized or commercially available platforms are currently available for routine use [159].

Inhaled NO has demonstrated activity against bacterial and mycobacterial biofilms [154]. This may be of particular

value when treating MA infections that have biofilm or biofilm-like aggregation as a recognized virulence factor [160]. Deppisch et al. [153] demonstrated in a phase I trial that eight patients with CF previously treated for chronic lung infection with prolonged antimycobacterials experienced a further reduction in colony-forming units of all bacteria and fungi, with an improvement in forced expiratory volume in 1 s (FEV₁) when treated with inhaled NO alone [153]. Yaacoby-Bianu et al. [155] treated two patients with CF (aged 13 and 19 years) with intractable MA infection despite multidrug therapy and observed a reduction in the quantitative PCR load of MA; one patient experienced improved lung function. Further work is required before this therapy can be widely recommended, but it potentially provides a safe, adjunctive therapy against a range of infecting organisms in the peri-LTx setting.

5.2 Microbiome Insights

The microbiome is the term used to collectively describe the community of microorganisms that inhabit the body surfaces exposed to the outside world [161, 162]. Attempts to more clearly define the relationship between the microbiome, health, and health-related outcomes have seen an explosive outpouring of scientific literature. Investigation of the microbiomes in the lower respiratory tract of pediatric patients with CF has revealed that the microbiome changes over time. Infants have a relatively sterile lower airway and develop more complex bacterial communities in early childhood, dominated with species of organisms usually found in the mouth [163, 164]. As these children age, the microbiome shifts to a pathogen-dominated microbiome with a progressive decrease in microbiome complexity that parallels a decline in lung function [163–165]. These longitudinal studies show significant negative correlations between patient age and microbiome community richness and diversity, and between age and pulmonary function [163, 166].

Adult and pediatric patients with CF also have a disruption of the gut microbiome when compared with healthy controls, with a trend to lower species richness and temporal stability suggesting fecal dysbiosis [167, 168]. Furthermore, recurrent courses of antibiotics to treat pulmonary exacerbations have a dramatic effect on the commensal microbiota of these patients [169].

Much less is known about the microbiome of the transplanted lung. Infectious complications are the single greatest cause of morbidity and mortality in the first year post-LTx, highlighting the importance of the organisms that make up the microbiome post-LTx. There is also a strong observed link between infection and the risk of rejection, with further work beginning to delineate the role of the microbiome and immunological outcomes [170]. Charlson et al. [171] demonstrated that the microbiome in an LTx recipient's BAL

differs in structure and composition from that of healthy controls. Willner et al. [172] demonstrated that recolonization of allograft by pre-LTx microbiome seems to have a protective effect against CLAD [172]. Work to establish the precise dynamics of the lung microbiome over time in LTx recipients and the relationship with immunomodulation and outcome is needed before any meaningful conclusions can be drawn. The microbiome of both the airway and other mucosal surfaces, particularly the gut, is likely to be a significant target for antibiotic-sparing immunomodulatory therapy in the future.

6 Conclusion

Numerous infectious issues challenge pediatric LTx recipients and their clinicians. Expanding interest in ways to broaden the donor pool has led to consideration of donation from blood-borne virus-positive recipients, particularly those with HCV and those considered at risk of blood-borne viruses at the time of donation. Recent positive experiences in adult LTx recipients will see these approaches eventually attempted in pediatric LTx. A better understanding of the peri-LTx management of mycoplasma, ureoplasma, and MA LTx infections is translating to novel strategies to tackle previously difficult clinical situations. CMV strategies are also evolving, with the promise of further gains as host immune monitoring is explored. However, the increasing emergence of resistant Gram-negative bacteria reminds us to continue to respect the complexity and effects of all our agents on our transplanted patient's microbiomes.

It is apparent that much has been learnt in recent years about infections in pediatric LTx patients, but many issues remain to be explored and translated. Watch this space.

Compliance with Ethical Standards

Conflicts of interest O. C. Smibert, M. A. Paraskeva, G. Westall and G. Snell report on conflicts of interest.

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