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REVIEW

Management of Multidrug Resistant Infections in Lung Transplant Recipients with Cystic Fibrosis

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Abstract: Cystic fibrosis (CF) is an inherited multisystem disease characterised by bronchiectasis and chronic respiratory infections which eventually cause end stage lung disease. Lung transplantation (LTx) is a well-established treatment option for patients with CF-associated lung disease, improving survival and quality of life. Navigating recurrent infections in the setting of LTx is often difficult, where immune suppression must be balanced against the constant threat of infection. Sepsis/infections are one of the major contributors to post-LTx mortality and multiresistant organisms (eg, *Burkholderia cepacia* complex, *Mycobacterium abscessus* complex, *Scedosporium* spp. and *Lomentospora* spp.) pose a significant threat to survival. This review will summarize current and novel therapies to assist with the management of multiresistant bacterial, mycobacterial, viral and fungal infections which threaten the CF LTx cohort.

Keywords: lung transplant, cystic fibrosis, multidrug resistant infection

Introduction

Cystic fibrosis (CF) is the most common lethal autosomal recessive disorder of the Caucasian population, causing multisystem failure through defects in a single protein (CF transmembrane conductance regulator, CFTR).[1] CFTR is highly expressed in respiratory epithelial cells, and its impaired function leads to airway dehydration, progressive inflammation and reduced mucociliary clearance. A diverse and pathogenic microbiome, repeated pulmonary infection and a large cumulative exposure to antimicrobial agents are the hallmarks of CF.[2] Median life expectancy for CF patients in the contemporary age of multidisciplinary management and CFTR directed therapy is 32–46 years.[3,4]

Lung transplantation (LTx) is a well-established treatment option for patients with CF-associated end-stage lung disease, improving survival and quality of life.[5] Globally, from 1995–2016, 8484 CF patients underwent LTx. CF is the third most common indication for adult LTx, and the most common reason for pediatric LTx.[6] Survival following LTx is highest for CF compared to other indications (chronic obstructive pulmonary disease, interstitial lung disease, etc), with the latest international registry data demonstrating a median five-year survival of >50%. The leading cause of death amongst adults with CF who have had a LTx is pulmonary infection.[7]

Improved management and survival amongst pre-LTx CF patients have been reflected in the gradually increasing median age of the CF LTx recipient.[7] Although post-LTx survival is thought to improve when recipients are past adolescence at

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time of LTx,[8] an older cohort brings new challenges. Over time, the evolving microbiome within the CF lung acquires increasing resistance, reflecting cumulative exposure to antimicrobial agents.[9] There is increasing concern regarding the re-emergence of multiresistant infections following LTx, with a limited antimicrobial armamentarium at hand.

Over the past decade, advances in culture-independent sequence-based analysis of microbial genomes has highlighted the richness and complexity of the CF microbiome, beyond the pathogens classically linked to CF (eg, *Staphylococcus aureus, Pseudomonas aeruginosa*, *Burkholderia cepacia*)[10] Although LTx replaces both native and heavily infected CF-lungs, many microbiome studies demonstrate preservation of the pre-LTx lower airway microbiome post-LTx.[11] This review will summarize the emerging multiresistant bacterial, mycobacterial, viral and fungal infections which threaten the CF LTx cohort, together with some novel therapies to assist with management of these infections.

Bacterial Infections

Gram-negative Bacteria

Gram-negative bacteria represent the vast majority of pathogens featured in a recent World Health Organization (WHO) list of "priority pathogens" which pose the greatest threat to humans.[12] Major adversaries featuring on this list, include *Stenotrophomonas maltophilia, Acinetobacter baumannii* and *Enterobacteriaceae*, and are commonly found within the CF microbiome.[13,14] Traditionally, post-LTx bacterial infections caused by known pre-LTx colonizers within the host have been considered manageable.[15] Particularly, the presence of pre-LTx multiresistant *P. aeruginosa* which has been linked to increased frequency of post-LTx pneumonia, but importantly is not linked to a decreased survival.[16,17] Microbiome studies, specifically examining resistance patterns of gram-negative bacteria amongst CF-LTx patients are scarce; however, treating post-LTx re-emergent gram negatives in the current climate of growing antibacterial resistance is increasingly problematic.

Amongst gram-negative pathogens, resistance to β-lactam antibiotics is largely mediated by β-lactamases. Carbapenems will overcome β-lactamases; however, are themselves neutralized by metallo-β-lactamases (MBL).[18] MBL expression by *P. aeruginosa* represents one of the recent and most challenging resistance patterns clinicians have to manage. MBL-producing *P. aeruginosa* has been described in a postoperative CF-LTx patient, who ultimately needed a lung lobectomy eight months following LTx due to atelectasis with suppuration.[19] Similarly, a further case report of fatal empyema caused by MBL-producing *P. aeruginosa* in a CF-LTx patient was associated with failure of all antimicrobial therapy and required a right pneumonectomy.[20]

Ceftolozane-tazobactam was the first amongst the second-generation β-lactams with β-lactamase activity. There is growing experience with using it against extended spectrum β-lactamase (ESBL) producing *Enterobacteriaceae*, and it has demonstrated activity against multidrug resistant *P. aeruginosa*.[21] The chemical structure of ceftolozane is similar to ceftazidime, with the exception of a modified side chain which potentiates antipseudomonal activity.[22] Successful use in LTx recipients with ventilator-acquired pneumonia and complicated intra-abdominal infections have been reported.[23,24] Ceftolozane-tazobactam, however, lacks activity against carbapenemase-producing organisms.

Novel agents with activity against carbapenamase-producing gram-negative bacteria (including carbapenamase-resistant *Enterobacteriaceae,* CRE) such as ceftazidime/avibactam and meropenem/vaborbactam, have changed the management of invasive CRE, with increased cure rates, decreased mortality and decreased acute kidney injury when compared to colistin-based therapies.[25] In addition, the use of aztreonam together with ceftazidime/avibactam has been suggested as a strategy against ESBL with MBL expression, to avoid acquired resistance.[26]

Infections with *B. cepacia* complex (BCC) in the CF-lower airway have been associated with significantly increased early post-LTx mortality relating to overwhelming chest sepsis (pneumonia, mediastinitis, and empyema).[27] Many centers still consider isolation of BCC an absolute contraindication to LTx. Smaller studies attribute the increased mortality seen with BCC to the subspecies *B. cenocepacia* specifically.[28] Newer metagenomic tools have identified specific strains of *B. cenocepacia* (eg, those with ET12) which appear to have increased pathogenicity. The treatment of BCC is notoriously difficult, and no standard guidelines for management exists. Prolonged multidrug regimens are usually prescribed using local institution expertise and sensitivity testing. A reasonable combination includes inhaled tobramycin, trimethoprim-sulfamethoxazole, minocycline and a β-lactam (usually meropenem or ceftazidime).[29] In

addition, some success with ceftazidime/avibactam and meropenam/varobactam has been reported against BCC in the CF-LTx cohort.

New strategies for management of gram-negative infections are under development. High-dose adjunct inhaled nitric oxide has recently been reported as safe, well tolerated and of clinical benefit in an adolescent with CF suffering from *B. multivorans* infection.[30] A Phase II placebo-controlled clinical trial of inhaled nitric oxide amongst CF-LTx patients is currently underway (NCT02498535). Primary outcomes include change in FEV_1 and sputum colony forming units after a seven-day course of inhaled nitric oxide. In addition, technology to facilitate phage therapy (ie, the therapeutic application of viruses that infect bacteria) has existed for decades,[31] and recent reports confirm success of phage/antibiotic synergy against gram-negative pathogens.[32] Clinical trials for phage therapy in CF are currently underway (NCT04684641). Topical disinfectant application at the time of CF-LTx has also been explored and demonstrates some degree of success. A single center recently reported reduced colonization with multidrug resistant pathogens (particularly *P. aeruginosa*) at one year post-LTx when a 2% taurolidine bronchial lavage was applied intra-op to recipient native bronchi and pleural cavities.[33]

Nontuberculous Mycobacteria (NTM)

NTM have an estimated annual prevalence of 12% amongst patients with CF. Recent United States CF patient registry data demonstrated 20% had isolated a pathogenic NTM species at least once over a 5-year period.[34] The literature on NTM infection in solid organ transplant recipients is very limited, apart from case reports and institutional experiences.[35] *M. abscessus* complex (MABC) is the second most common NTM (following *M. avium* complex, MAC) and is emerging as one of the most worrisome NTM amongst CF-LTx patients. Infection is often associated with accelerated lung function decline and complicated toxic multidrug therapy which may span years.[36] MABC most commonly infects the pleuropulmonary space; however, cutaneous sites, operative sites, and disseminated disease have been reported.[35] A recent case report describes prolonged multidrug therapy for recurrent MABC in a CF-LTx recipient with cutaneous and pulmonary infection complicated by drug toxicities causing multiorgan failure and loss in lung allograft function.[37]

An isolation of NTM does not always confer disease, and recent guidelines highlight the clinical and microbiological features for diagnosis.[38] Given the absence of randomized clinical trial data, treatment is based on expert opinion. Macrolides are the cornerstone of NTM treatment; however, treatment is limited by resistance.[39] Therapy is guided by local epidemiology and pathogen sensitivity, and usually involves an induction phase with multiple intravenous and oral agents (including macrolide/clofazimine, amikacin and β-lactam) and a suppressive phase with multiple oral/inhaled drugs (macrolide, fluoroquinolone, inhaled aminoglycoside ±clofazimine). In addition, surgical intervention may be required, hyperbaric oxygen therapy can be considered[40] and reduction in immune suppression should be considered.[37,41]

Several novel therapies for treatment of NTM have recently emerged. Amikacin liposome inhalation suspension (ALIS) is a formulation of the aminoglycoside designed to facilitate targeted drug delivery whilst minimizing systemic exposure.[42] The molecule is phagocytosed by respiratory macrophages and delivered directly to infected respiratory cells. A recent prospective open-label randomized study revealed that addition of ALIS to guideline-based therapy for treatment refractory MAC lung disease achieved greater culture conversion by six-months.[43] Recent studies report success of regimens involving combination clofazimine and amikacin inhalational therapy, with significant synergistic activity and ongoing culture negativity in 43% after 12-months in MABC airway infections.[39] Linezolid use against pulmonary MABC has been reported; however, treatment limiting side effects such as cytopenia and peripheral neuropathy are potential complications.[44] Tedizolid has reported greater in vitro activity than linezolid against MABC; however, a large single center study reports no significant safety benefit of tedizolid over linezolid for treatment of NTM amongst solid organ transplant recipients.[45]

Viral Infections

Cytomegalovirus

Cytomegalovirus (CMV) is a β-herpesvirus which is usually acquired via primary infection in childhood or early adulthood and thereafter establishes latency in monocytes, megakaryocytes, dendritic cells and myeloid progenitor cells.[46] It is a major cause of morbidity/mortality after LTx when immunosuppression facilitates viral reactivation, manifesting as asymptomatic viremia, viremia with nonspecific symptoms (fever and malaise) or

evidence of tissue invasion with end-organ damage (most commonly pneumonitis). Fifty percent of CF-LTx recipients are seronegative pre-LTx for CMV. CMV reactivation is associated with increased rates of acute cellular rejection and chronic lung allograft dysfunction.[47] Before universal prophylaxis with valganciclovir, 54–95% of lung transplant recipients developed viraemia and over half developed disease.[48] This has significantly improved with prophylaxis, but CMV remains a serious problem especially for the CF-LTx at highest risk, (ie, donor seropositive/recipient seronegative mismatch LTx).[49]

The development of viral resistance to ganciclovir/valganciclovir is one of the complications of prolonged antiviral exposure, affecting approximately 2% of lung transplant recipients and nearly 5% of serological mismatches with three-year mortality rates as high as 70%.[50] CF is also associated with an increased risk of CMV resistance.[51] Resistance testing should be performed when CMV does not respond to ganciclovir therapy (eg, CMV viral load increases on therapy or fails to fall by a log within seven days of commencement of therapy). Resistance is most often mediated by mutations in UL97, which encodes a viral enzyme necessary for the activation of ganciclovir. Mutations in *UL54* usually arise as a second step and additionally confer resistance to foscarnet.[52] Management of ganciclovir-resistant CMV includes a combination of cautious reduction in immunosuppression, CMV-immunoglobulin, and an alternative antiviral strategy such as foscarnet, cidofovir and sometimes high-dose ganciclovir depending on resistance phenotype.[53–55] Novel agents such as maribavir appear to have efficacy for the treatment of resistant CMV. Letermovir as treatment is poorly studied to date, but appears to have a low barrier to resistance and may have more utility as secondary prophylaxis once the CMV viral load is suppressed and undetectable adoptive T cell immunotherapy is an investigational modality which holds promise.[56] Data are limited in this area and there are no specific studies on the management of resistant CMV in post-transplant CF patients. Further studies are required.

Epstein–Barr Virus

Epstein–Barr virus (EBV) is a γ-herpesvirus which is even more prevalent than CMV, with approximately 85% of individuals seropositive by 25 years of age.[57] Latent infection persists in B cells. In solid organ and hematologic transplantation, there is strong evidence that immunosuppression permits EBV to exert an oncogenic effect on B cells to precipitate post-transplant lymphoproliferative disorder (PTLD).[58] PTLD is the most common non-skin malignancy after SOT and serological mismatch enormously increases this risk.[59] EBV-mismatched CF patients have an even higher risk of PTLD, with a registry study of over 30,000 lung transplant recipients demonstrating 31% will be affected.[60,61] Although there is a lack of strong data supporting this strategy, many centers attempt to prevent PTLD in serologically mismatched patients via lifelong antiviral prophylaxis.[62] Management of PTLD usually involves a stepwise combination of reduction in immunosuppression, rituximab, and chemotherapy/radiotherapy depending on extent and phenotype of disease.[63–66]

Polyomaviruses

Polyomaviruses are nonenveloped double-stranded DNA viruses. The commonest is BK virus (BKV) which persists as a latent infection in renal tubular and uroepithelial cells in approximately 80% of adults and reactivates in 25–30% of renal transplant recipients, with 1–10% developing BKV-associated nephropathy.[67] BKV-associated nephropathy and presumed BKV-driven urological malignancies have been reported after LTx, including in CF patients.[68,69] The only proven therapy is reduction in immunosuppression (often withholding the cell-cycle inhibitor and temporarily or permanently exchanging the calcineurin inhibitor for a mammalian target of rapamycin inhibitor), but intravenous immunoglobulin, leflunomide and cidofovir have also been employed.[70,71]

John Cunningham virus (JCV) is a neutrotropic polyomavirus that can cause progressive multifocal leukoencephalopathy in immunocompromised hosts.[72] Although it remains very rare after LTx, with only several cases reported and none in CF patients, this demyelinating disease of the central nervous system frequently causes severe morbidity or death and thus, a high index of clinical suspicion should be maintained.[73,74]

Fungal Infections

Fungal pathogens following CF-LTx are of particular importance, given fungi are commonly found in the native CF-airway.[75] Due to the higher strength of initial immune suppression, the first year following LTx represents significant vulnerability to invasive fungal disease, contributing to significant morbidity and mortality. Invasive disease with *Aspergillus fumigatus* has a significant mortality (41–51%),[76] followed by *Candida albicans* and *Cryptococcus* spp. (23%).[77] In addition, reported mortality from invasive

Scedosporium/Lomentospora spp. disease is close to 100%.[78] Respiratory manifestations of fungal disease post-LTx include fungal pneumonia, other manifestations of invasive disease or local infection of the anastomosis (ie, tracheobronchitis or bronchial anastomotic infection) or colonization.[75]

Aspergillus spp

Invasive *Aspergillus* spp. disease are typically treated with triazoles such as posaconazole or voriconazole, needing close therapeutic drug monitoring and consideration of interactions with calcineurin inhibitors given its moderate inhibition of the CYP3A4 enzyme.[75] Isavuconazole is the newest extended spectrum triazole antifungal, approved as an alternative to voriconazole for treatment against invasive aspergillosis and as an alternative treatment to liposomal amphotericin B for mucormycosis. Unlike most other azole-antifungals, isavuconazole has excellent oral bioavailability and predictable linear pharmacokinetics in adults, with reduced impact from genetic polymorphisms, and reduced inter-patient variability. Isavuconazole is a mild inhibitor of CYP3A4, and causes increased serum concentration of calcineurin inhibitors, but much less than with posaconazole and voriconazole; but, dose adjustments are still required. In addition, isavuconazole increases serum concentration of mycophenolate, and monitoring for mycophenolate toxicity is required.[79]

Candida spp

Retrospective analysis of over 25,000 respiratory samples from a national German registry reports up to 75% of patients with CF isolated yeast (mainly *Candida* spp.) and around 35% isolated *Aspergillus* spp.[80] *Candida albicans* is the most common *Candida* spp. isolated from the CF airway, followed by *C. dubliniensis, C. glabrata* complex and *C. parapsilosis* complex. Although the *Candida* spp. do not commonly cause pulmonary exacerbations in CF patients, a recent retrospective analysis over 16-years revealed that colonization (in particular *C. albicans* and *C. dubliniensis*) was associated with a decline in lung function.[81] In addition, colonized patients who require central venous access are at risk of *Candida* spp. fungemia/sepsis and endocarditis. In a survey of bloodstream infections post LTx, *Candida* spp. were the second most common.[82] Randomized trials support the treatment for invasive candidemia typically with echinocandin therapy (anidulafungin or caspofungin) over fluconazole amphotericin B.[83,84] Non-neutropenic patients who are not critically unwell and unlikely to have fluconazole resistant organisms (eg, *C. glabrata* or *C. krusei*) can be treated with fluconazole, particularly as step-down therapy.

Scedosporium spp. and *Lomentospora* spp

Filamentous fungi (*S. apiospermum/L. prolificans*—formerly known as *S. prolificans*) are reported in up to 4% of CF patients, and multiple single-center studies demonstrate similar rates in CF-LTx patients.[80,85] *S. apiospermum/L. prolificans* are intrinsically multiresistant pathogens that often require complex surgical debridement and prolonged multidrug regimens with significant morbidity/mortality.[85,86] Treatments for these fungi are based on expert opinion and retrospective data. *S. apiospermum* is treated either with voriconazole monotherapy, or in conjunction with terbinafine.[87,88] Based on a review of the literature from 2000–2018 and Fungiscope (an international rare invasive fungal registry), patients with voriconazole-based therapy had longer overall survival and reduced 42-day mortality compared to amphotericin-based regimens.[89] Infections with *L. prolificans* are aggressive and often fatal, and treatments must be tailored on a case-by-case basis. Surgical debridement and reduction in immune suppression are often considered. Although *L. prolificans* has greater intrinsic resistance to voriconazole, multidrug regimens involving either posaconazole/voriconazole and terbinafine have been reported with reduced mortality,[90] although limited data is available.

Fungal Prophylaxis

There is significant global discordance in the fungal prophylaxis strategy that should be used post-LTx, and available data are contradictory.[91] A review and meta-analysis of 748 LTx recipients suggested that universal prophylaxis (agents included were fluconazole, voriconazole, and inhaled amphotericin B) reduced pulmonary invasive aspergillosis; however, limitations such as single center data and nonrandomized protocols were acknowledged.[92] Subsequently, two recent meta-analyses reveal no difference in the odds of fungal infection with universal prophylaxis compared to no prophylaxis following LTx.[93,94] Long-term exposure to antifungal medication has been reported as the major risk factor in the emergence of multiresistant fungal infections post-LTx[85] and the question remains as to whether universal prophylaxis risks breeding increased resistance to first-line antifungal medication without a mortality benefit.

In place of universal fungal prophylaxis, pre-emptive strategies have been successfully applied by large LTx

units. This involves treatment with antimould agents after initial isolation on surveillance bronchoscopy/sputum culture or following positive galactomannan on bronchoalveolar lavage sample. This strategy has been reported to reduce antifungal exposure by 60% compared to universal prophylaxis, without affecting mortality at one year.[95] Head-to-head randomized trials are needed to confirm which approach is superior.

Novel Antifungals

Olorofim (formerly F901318) is a novel investigational antifungal agent. This mould-active antifungal targets dihydroorotate dehydrogenase and inhibits pyrimidine biosynthesis. It is the first member of the orotomide class and is currently being evaluated for use against resistant moulds, including species with intrinsic or acquired resistance to azoles and amphotericin B; however, it lacks activity against yeasts and the *Mucorales*.[96] Published experience is currently limited to case reports (abstracts) against resistant moulds causing persistent infections and is quite promising.[97–99] A Phase II clinical trial for patients with invasive fungal disease (*Scedosporium* spp., *Lomentospora* spp. and azole-resistant *Aspergillus* spp.) is currently recruiting (NCT03583164).

Azole-resistant *Aspergillus* spp. infections are increasingly prevalent in CF patients, and can reach high prevalence in CF patients who are chronically treated with azoles. A second mould-active antifungal agent, fosmanogepix (formerly APX001A), which blocks glycophosphatidylinositol biosynthesis is currently under development.[100]

Conclusions

CF the is one of the most common indications for LTx and a diverse airway microbiome with high exposure to antimicrobial agents are hallmarks of this disease state. Improving multidisciplinary care and evolving CFTR-directed therapies are successfully preserving native lung function and delaying LTx. However, this delay may come with further challenges such as increasing multidrug resistance. Although few infections are established contraindications to LTx, immune suppression and pathogen reservoirs encourage re-emergent infections and threaten early and late LTx outcomes. Antimicrobial prophylaxis strategies are varied across virus, bacterial, and fungal pathogens, with a wide variation in global practice. Short-term bacterial prophylaxis against donor-derived infections and extended viral prophylaxis are generally well accepted strategies (depending on individual risk profiles); however, the approach to antifungal prophylaxis is less clear. Resistance to antimicrobial agents is emerging at a rapid rate, and the armamentarium against these pathogens is only slowly growing. Cautious and directed use of antimicrobial agents against multiresistant pathogens as guided by local epidemiology and resistance profiles and for well-defined timeframes are likely to continue to support the increased survival and improved quality of life experienced by CF patients following LTx.

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