Respiratory infections in lung transplant recipients

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Purpose of review
Morbidity and mortality rates after lung transplantation still remain higher than after other forms of solid organ transplantation, primarily due to a higher risk of infections and the development of chronic lung allograft dysfunction. Thus, a tiered approach highlighting the most significant respiratory pathogens including common opportunistic infections along with diagnostic, treatment and prevention strategies, including vaccination and prophylaxis is needed.

Recent findings
The need for intense immunosuppressive therapy to prevent rejection, coupled with the transplanted lung's constant exposure to environment and impaired local defence mechanisms leads to frequent infections. Viral and bacterial infections are most frequent while fungal infections mainly involve the tracheobronchial tract but may be fatal in case of disseminated disease. Some infectious agents are known to trigger acute rejection or contribute to chronic allograft dysfunction. Invasive testing in the form of bronchoscopy with bronchoalveolar lavage is standard and increasing experience in point of care testing is gained to allow early preemptive therapy.

Summary
Timely diagnosis, treatment, and ongoing monitoring are essential, but this can be difficult due to the wide variety of potential pathogens.

Keywords
community-acquired respiratory viruses, chronic lung allograft dysfunction, lung transplantation, respiratory infection

INTRODUCTION

Respiratory infections are a major complication after lung transplantation (LTx). They are associated with a high burden of disease and potentially life threatening either through immediate graft damage and/or its association with the development of chronic lung allograft dysfunction (CLAD). Besides immunosuppression, susceptibility to respiratory infections is increased because of impaired mucociliary clearance and dampened cough reflex due to organ denervation, potential colonization of the graft and continued exposure to the environment [1–3]. Overall infections are the most prevalent adverse events following immunosuppressive drugs. Of those bacterial infections represent the majority, followed by viral and fungal infections during a 3-year observational period [4▪▪]. The spectrum of respiratory pathogens is significantly broader in lung transplant patients than in other solid organ recipients. In addition to known pathogens, pathogens such as Nocardia, nontuberculous mycobacteria (NTM), fungal infections (especially *Aspergillus* spp.), CMV, Pneumocystis jirovecii and a broad spectrum of respiratory viruses should also be included if a respiratory infection is suspected [5]. During the first month after transplantation, infections are primarily bacterial, including hospital-acquired, donor- and recipient-related or affecting the bronchial anastomosis. Afterwards, viral reactivations and opportunistic infections are common, while community-acquired pathogens become increasingly significant in late-onset infections [1,6].

VIRAL INFECTIONS

Community acquired respiratory viruses

Community acquired respiratory viruses (CARV) are a common threat in lung transplant recipients. Data

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KEY POINTS

- Respiratory infections following lung transplantation carry significant risks, including immediate graft damage and chronic lung allograft dysfunction (CLAD).
- Community-acquired respiratory viruses (CARV) often cause serious complications in lung transplant recipients, including prolonged cough and graft dysfunction.
- Diagnostic approaches, including PCR, bronchoalveolar lavage, and point-of-care testing, are essential for rapid and accurate identification of infections to initiate timely treatment.
- Preventive strategies such as vaccination, lifelong prophylactic drug therapy and early antiviral treatment aim to reduce infection-related risks and improve survival for lung transplant patients.

about infection incidence vary between 10 and 68 cases/100 patient years among CARV [7]. Subtypes include influenza A/B, SARS-CoV-2, seasonal coronaviruses, human metapneumovirus-hMPV, respiratory syncytial virus (RSV), parainfluenza, rhinovirus, enterovirus and adenovirus [8–11]. Seasonal occurrence in the period between October and April is observed except for adenovirus, rhinovirus and parainfluenza virus [11–13]. Viral infections after lung transplantation not only cause potentially life-threatening pneumonia with higher risk for bacterial and fungal superinfection, but are also associated with an increased incidence or progression of chronic lung allograft dysfunction (CLAD). CLAD is a difficult to treat complication after LTx and is associated with increased mortality [12,14,15].

Clinical presentation and diagnostic

Symptoms and disease severity differ considerably between patients. CARV infection may cause symptoms of upper respiratory tract infection (URTI) e.g. sore throat, rhinorrhea or lower respiratory tract infections (LRTI) e.g. cough, wheezing and graft dysfunction assessed by declining forced expiratory volume (FEV_1) and even signs of respiratory failure [16,17]. In such cases, a diagnostic workup consisting of clinical, radiological and laboratory tests should be performed (Fig. 1). Chest radiographic and computer tomography scans (CT) may reveal heterogeneous abnormalities including ground glass opacities and consolidations [18,19].

For diagnosis there are several multiplex PCR kits commercially available for nasopharyngeal swabs as well as for samples from the lower respiratory tract including bronchoalveolar lavage [20]. Upper and lower respiratory tract sampling are frequently used as diagnostic tools in daily clinical practice. Although bronchoscopy implicates invasiveness and potential periinterventional complications it represents a safe procedure even in the outpatient setting after LTx [21]. A high concordance between both sampling methods was detected depending on viral pathogen. Bronchoalveolar lavage provides additional information especially regarding bacterial and fungal co-infections and noninfectious cases of graft dysfunction [22–24,25▪] (Fig. 1). The emergence of point-of-care tests (POCT) offers the opportunity to significantly accelerate the diagnosis of viral respiratory tract infections to rapidly initiate specific therapy. The diagnostic power is slightly lower [26▪,27▪] but return time for results is shorter usually by one day. When using POCT patient profiles should be defined to identify those who might benefit from POCT, for example, patients at high risk for severe disease.

Bronchoscopy is considered the gold standard for diagnosis of infections after LTx. Pathogen isolation is expected to be successful in 60% of LTx patients with infection, 20% will have a noninfectious cause mimicking infection and 20% of the cases remain unclear even after bronchoscopic work-up.

Infection with SARS-CoV-2 still represents a severe complication for lung transplant patients and is still associated with an elevated mortality around 1-5% and severe course in up to 10% in the Omicron era [28▪,29▪]. In the early phase of the pandemic mortality was reported to be up to 30% after LTx [30]. Thus, it is crucial to provide early therapy as well as identifying patients at risk of severe disease progression (age >60 years, glomerular filtration rate below 30 ml/min/1.73 m^2). Among solid organ transplanted patients lung transplant recipients are most endangered [31,32▪].

Treatment

Despite advances during the last years therapeutic options for the treatment of CARV infections treatment is still challenging. Oseltamivir, an oral neuraminidase inhibitor is the main therapeutic option for lung transplant recipients to treat influenza A and B infection. Several studies have provided evidence that early therapy is associated with a reduction in mortality, ICU stays and severe pneumonia with no significant interactions and good tolerability [33–35]. Further drugs against influenza, for example, baloxavir (endonuclease inhibitor), Peramivir or Zanamivir (neuraminidase inhibitor) are

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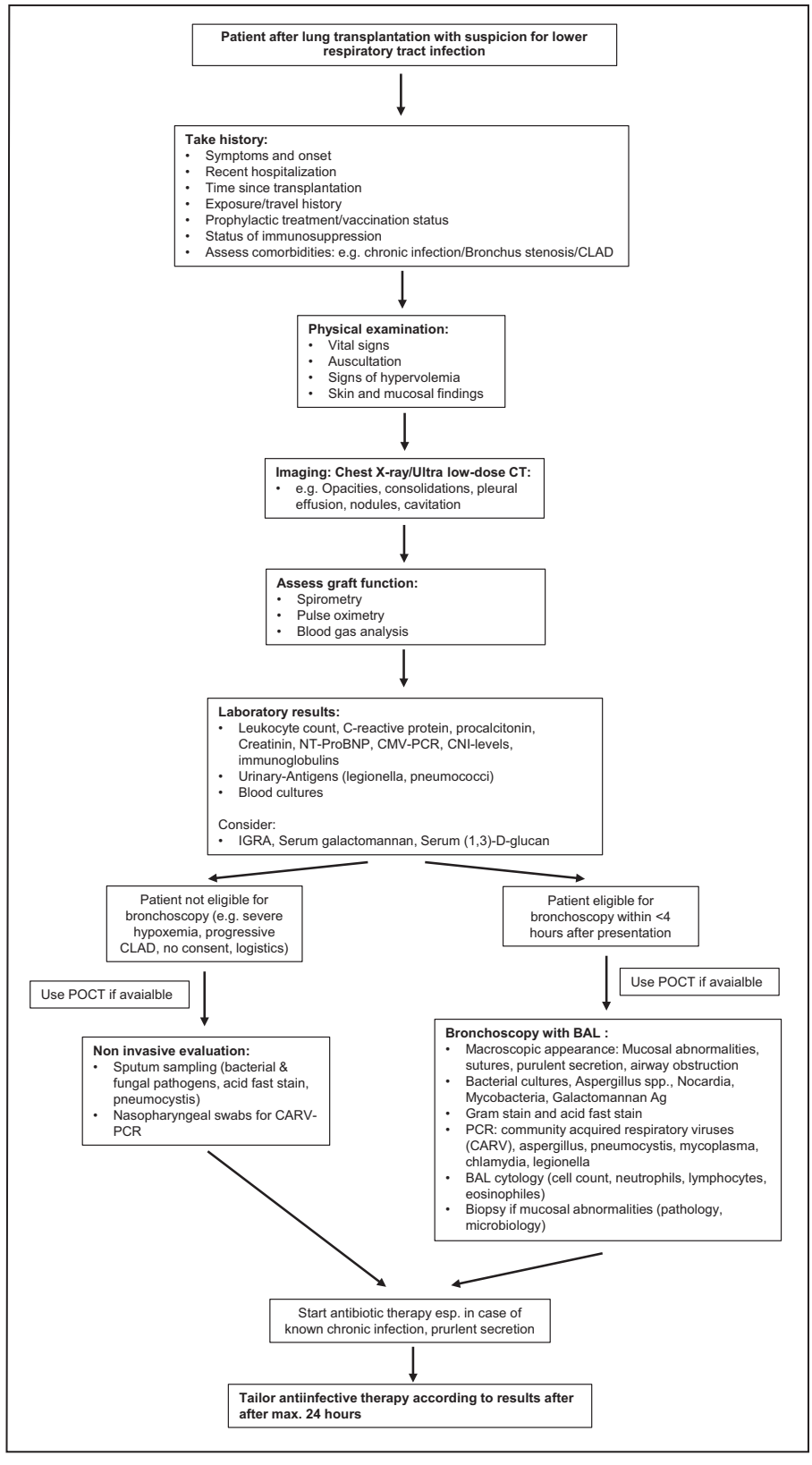

FIGURE 1. Diagnostic algorithm for lung transplanted patients with suspicion for lower respiratory tract infection. Ag, antigen; BAL, bronchoalveolar lavage; CARV, community acquired respiratory viruses; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CNI, calcineurin-Inhibitor; CT, computer tomography; HLA, human leukocyte antigen; IGRA, interferon-gamma release assay; NTproBNP, N-terminal pro-brain natriuretic peptide; PCP, *Pneumocystis jirovecii*; PCR, polymerase chain reaction; POCT, point-of-care test; TBB, transbronchial biopsy; TBC, *Mycobacterium tuberculosis*.

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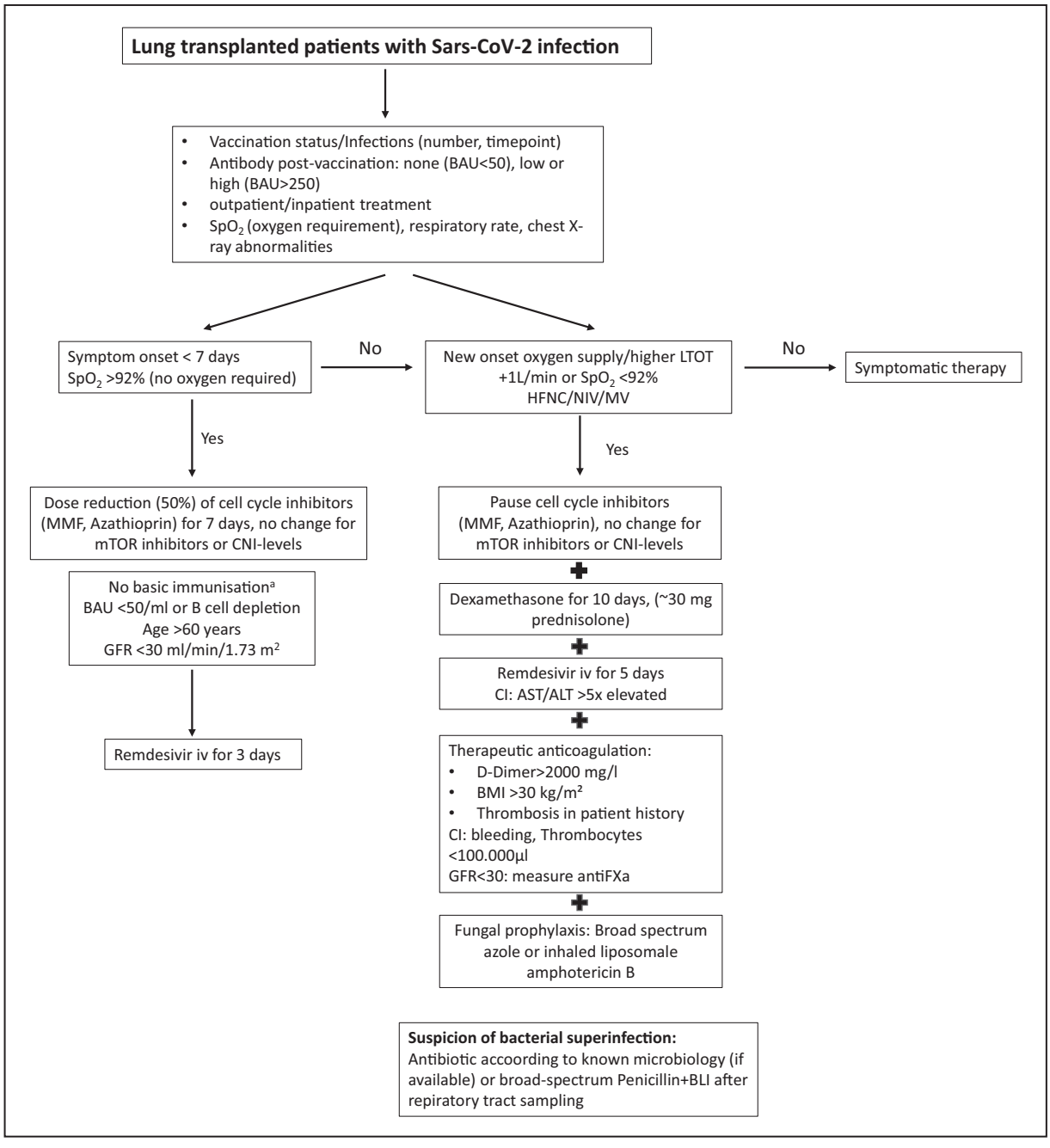

FIGURE 2. Therapeutic algorithm for Sars-CoV-2 infection after lung transplantation. (a) At least three antigen contacts consisting of at least two vaccines; ALT, alanin-aminotransferase; AST, aspartat-aminotransferase; BLI, betalactamase-inhibitor; CI, contraindication; CNI, calcineurin inhibitor; GFR, glomerulus filtration rate; HFNC, high flow nasal cannula; iv, intravenous; LTOT, long-term oxygen therapy; MMF, mycophenolate mofetil; mTOR, mechanistic target of rapamycin; MV, mechanical ventilation; NIV, noninvasive ventilation.

not approved for lung transplanted patients in all countries.

Cohort studies are pointing towards the direction that early therapy of intravenous Remdesivir is less frequently associated with progression to severe COVID-19 disease [31,32▪] (Fig. 2). Nirmatrelvir/ritonavir as an orally available drug is limited in use due to serious interactions with calcineurin inhibitors (CNI). There is no proven benefit and a high risk of CNI toxicity. If used close monitoring and extensive dose adjustments is needed [36].

Ribavirin is an antiviral agent against RSV and paramyxoviruses that may shorten lung function recovery after both RSV and paramyxoviruses and prevents development of bronchiolitis obliterans syndrome [12,37–39]. Oral administration appears

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to be more cost-effective and not inferior to intravenous administration due to the possibility of outpatient administration [40]. Unfortunately, there is no randomized controlled trial of ribavirin in paramyxoviruses to support its use. Other agents (Presatovir, ALN RSV01) have been studied in RCTs without proven benefit in RSV infected LTx recipients [41,42].

Cytomegalovirus

Cytomegalovirus (CMV) belongs to herpes virus family that can reactivate or infect primarily people with impaired immune systems. Since the lungs are a key reservoir for CMV, lung transplantation tends to involve a higher transfer of CMV compared to other organ transplants [43,44]. A diagnosis of CMV pneumonitis requires histopathological confirmation of inclusion bodies and is usually accompanied by CMV-DNemia. A Positive PCR in BAL alone is not sufficient for diagnosis. CMV pneumonitis is linked to a significant rise in mortality and morbidity whereas already reduced CMV replication within the lung is associated with CLAD [45,46]. Although CMV pneumonia is relatively uncommon because of preemptive therapy, CMV-infection is diagnosed by CMV-DNAema before organ manifestation occurs. Additional diagnostic criteria including imaging results and a high CMV load in bronchoalveolar lavage supports the diagnosis [47,48].

Therapy involves reduction of immunosuppression (usually cell cycle inhibitors) and antiviral treatment. Mild disease with low levels of DNemia may be treated with oral valgancyclovir, while severe cases require intravenous ganciclovir until symptoms and viremia resolve. In case of refractory disease, ganciclovir resistance or intolerance of ganciclovir, alternative treatments like foscarnet, maribavir, or adoptive CMV-specific T cell therapy may be considered [49].

Bacterial infections

Bacterial infections cause a high proportion of especially nosocomial complications early after transplantation, but are also a risk for the patient throughout the entire period after transplantation [50]. Tracheobronchitis must be differentiated from pneumonia with the latter being associated with severe disease and a higher incidence of respiratory failure [51]. Bacterial pathogens are responsible for 62–82% of cases of pneumonia in lung transplant recipients, most frequently caused by gram-negative species, especially Pseudomonas aeruginosa [50,52–54]. During ongoing follow-up after LTx, community-acquired pathogens like Streptococcus pneumoniae and Haemophilus influenzae gain importance. Pneumonia after LTx is associated with a risk of hospitalization, graft lost and death after LTx [55–57]. Patients become susceptible to these pathogens with increasing time after lung transplantation with considerably higher incidence than in the general population [56]. In general, LTx patients have more severe course of pneumonia and are frequently in need for prolonged treatment.

Opportunistic pathogens

Nocardia

Nocardia species are common environmental, opportunistic gram-positive bacteria that can cause both localized and widespread infections. Of all organ transplant recipients, lung transplants have the highest risk of infection affecting up to 3.5% of patients [58–60]. Risk factors include more intense steroids, advanced patient age and extended stays in the intensive care unit following transplantation [61]. Since the respiratory tract is the primary route of acquisition, the lungs are typically the first site of infection. Nocardiosis should be considered in LTx recipients who present with pneumonia, lung cavities or consolidations as well as pleural effusions visible on CT scans [1,62] (Fig. 3). If nocardiosis is diagnosed, brain imaging is recommended due to frequent disseminated (12.5-40% of cases), potentially asymptomatic disease to the central nervous system [58,61,62]. While surgical drainage may be required, antibiotic therapy remains the primary treatment for nocardiosis. First-line treatments typically involve carbapenems and cotrimoxazole. Alternative antibiotic regimens may be necessary if there is drug intolerance or resistance. After a prolonged intravenous therapy for several weeks oral therapy up to several months is usually initiated [63]. If the brain is infected, third-generation cephalosporins can be used due to good CNS access [63].

Mycobacteria

Non tuberculous mycobacteria (NTM) occur ubiquitously in the environment and cause opportunistic infections, mainly in the lung and pleura. Lung transplanted patients are at high risk of developing NTM disease due to the chronic lung damage, high immunosuppression and continuous environmental exposure [64]. Furthermore, patients with cystic fibrosis are infected before transplanted and NTM may harbor in the upper respiratory tract [65]. According to IDSA/ATS guidelines, the fulfillment of clinical, radiological and microbiological criteria is needed to establish a diagnosis of pulmonary NTM [64,66]. Among the many known subspecies, Mycobacterium avium complex, Mycobacterium

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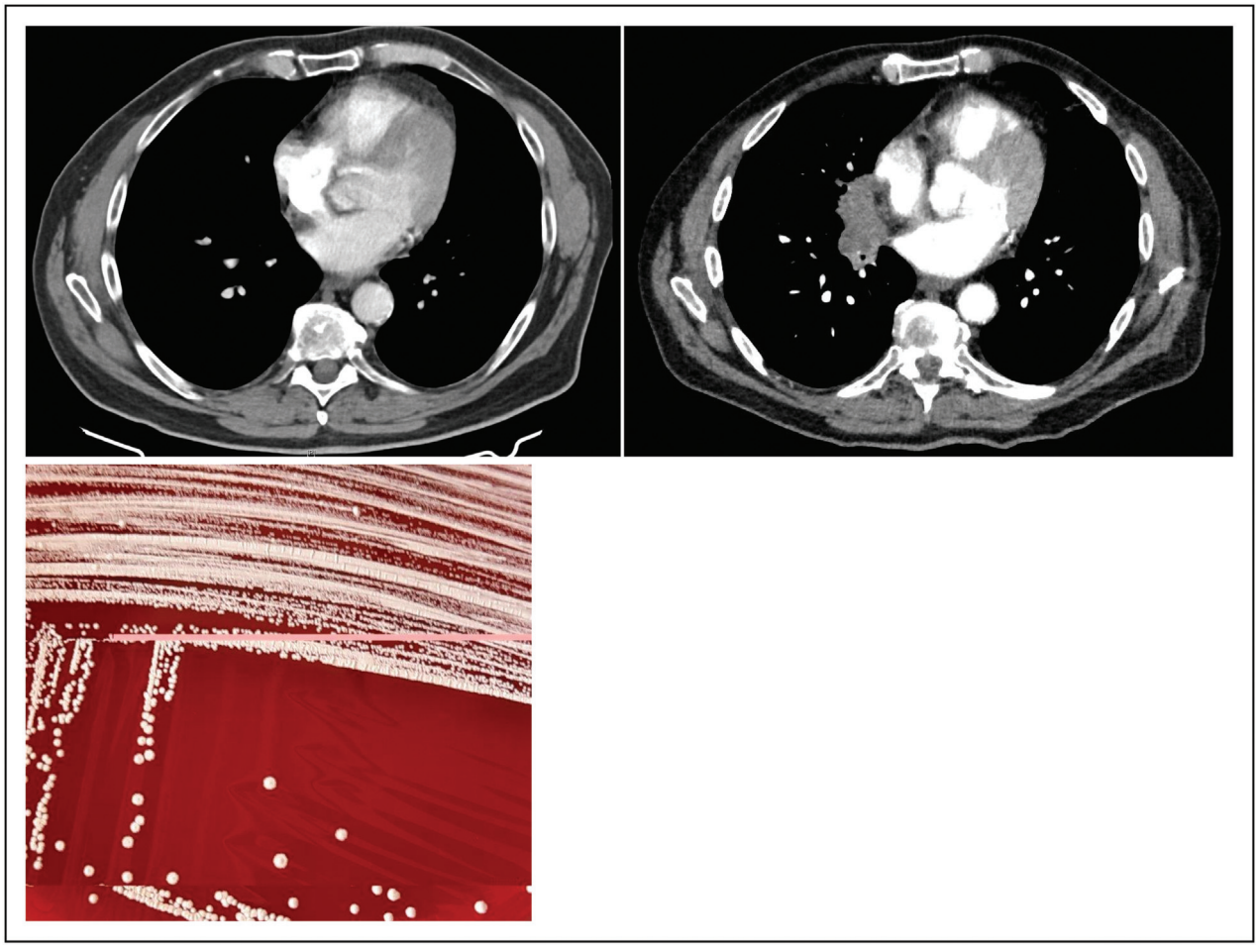

FIGURE 3. Nocardiosis in 66 years old male 10 month after transplantation. Upper CT-chest with new onset right mediastinal mass (upper right) within 6 weeks between scans (upper left and right). Lower left: culture plate with white colonies, typical of nocardia.

abscessus and Mycobacterium gordonae are most frequently detected in lung transplant patients. Although overall survival is not affected by NTM infection, morbidity is high and side effects of treatment relevant [67,68]. Depending on the species, treatment consists of a combination of usually three to four antibiotics with different mechanisms of action for usually more than 12 months. The use of rifampicin leads to severe interactions with CNI, which necessitates close monitoring of levels and dose adjustment [69].

FUNGAL INFECTIONS

Pneumocystis jirovecii

Pneumocystis jirovecii (Pj) is an opportunistic fungal pathogen leading to rapidly progressing pneumonia, which may result in respiratory failure and death (up to 23% 90 days after infection) in transplanted individuals, especially lung transplant recipients without prophylaxis [70–72]. Following the introduction of prophylaxis with sulfamethoxazole-trimethoprim, the infection rates among lung transplant recipients are rare [71,73]. Besides immunosuppression, increasing age, coincident CMV-infection and low total lymphocyte count were associated with a higher risk for severe Pj infection [73,74]. If symptoms like fever, cough and hypoxemia are present in a LTx patient without prophylaxis, Pj pneumonia (PjP) should be considered as a possible diagnosis. CT scans provide a higher sensitivity than a conventional X-ray chest [73,75]. Diagnosis of PjP relies on the direct detection of the microorganism in respiratory samples. PCR has become an increasingly valuable diagnostic tool due to its higher sensitivity compared to traditional microscopic methods [76]. Additionally, serum [1,3]-D-glucan as a component of the fungal cell wall, offers high sensitivity and specificity for Pj infection, serving as a useful complementary diagnostic tool [77,78]. The first-line treatment for Pj is

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high-dose intravenous sulfamethoxazole-trimethoprim and in patients with a high suspicion of the disease, treatment should begin without delay, even before diagnostic results are confirmed [73,79].

Aspergillus spp.

Infection with *Aspergillus* species impose serious threat for lung transplant recipients especially since they are ubiquitous in the environment and the respiratory tract is a major route of infection [80]. Aspergillus fumigatus accounted for the largest proportion of the pathogens detected [81,82]. Most centers worldwide are using universal prophylaxis with azoles or inhaled liposomal amphotericin B early after LTx [83]. Most aspergillus infections involve the tracheobronchial tree especially anastomoses and postanastomotic regions. Foreign bodies like stents and lose suture material are risk factors for chronic infection. This emphasizes the need for frequent endoscopic controls [84]. Disseminated disease is infrequent due to fungal prophylaxis; patients often suffer from systemic symptoms like fever and respiratory symptoms like cough, dyspnea, hemoptysis and in case of invasive growth chest/pleura pain [80]. In chest computer tomography, typical signs of invasive pulmonary aspergillosis include halo sign and macronodules [85]. Another manifestation of pulmonary aspergillosis is aspergilloma in preformed cavities in damaged transplant lungs (e.g. by CLAD) which is often accompanied by hemoptysis [86] (Fig. 4). Treatment of Aspergillus tracheobronchitis and anastomosis infection consists of topical antifungals (e.g. inhaled liposomal amphotericin B) and oral broad spectrum azole therapy in conjunction with endoscopic debridement of necrotic tissue and removal of foreign bodies. In case of severe tracheobronchitis accompanied by necrosis or in case of untreatable aspergilloma, surgical interventions need to be considered [80,86,87]. In general prognosis of tracheobronchial infections after LTx is excellent in contrast to disseminated disease. Prolonged use of voriconazole in LTx patients is associated with an increased risk of skin cancer and should be avoided [88].

PREVENTIVE STRATEGIES

Vaccination

For organ transplant recipients, there is limited information about the response to vaccinations against respiratory pathogens. Limited humoral responses and a higher rate of infections after vaccination have been reported in LTx patients. No measures to improve vaccination response are established [56]. As the vaccination rates of the recommended vaccinations vary greatly, even after transplantation, it is essential to update all vaccinations before transplantation [89,90]. It is important to note that vaccination recommendations differ between countries, so this review draws on recommendations for the depicted pathogens from the German authorities and societies (Table 1) [91–94].

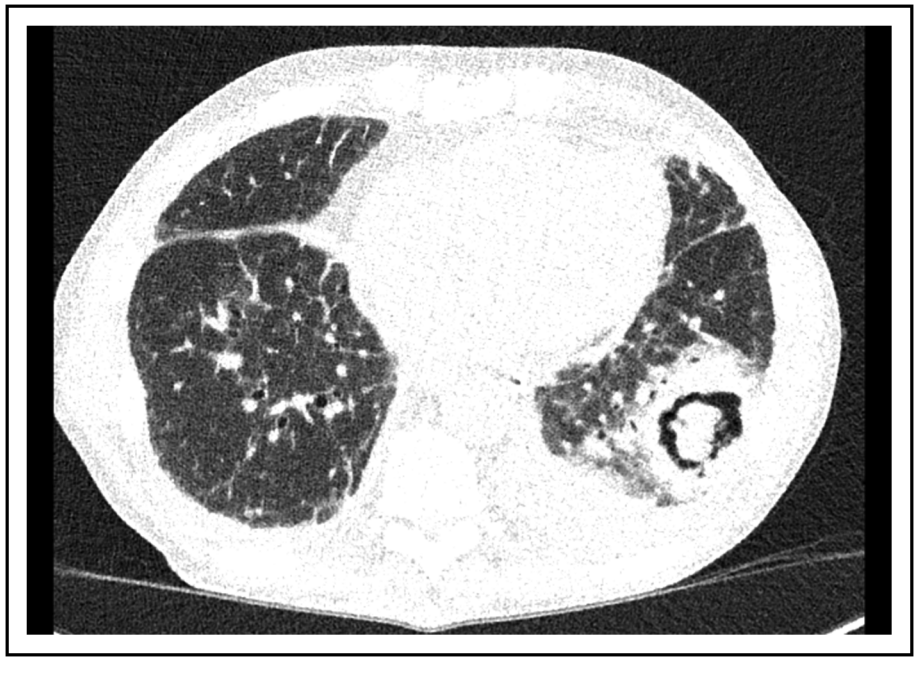

FIGURE 4. Pulmonary aspergilloma located in the left lower lobe in a lung transplant recipient.

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Table 1. Summary of key vaccines against major respiratory pathogens, including vaccine type, target groups, and recommended schedules according to Standing Committee on Vaccination (STIKO)

Pathogen	Type of vaccine	Vaccination schedule	Special considerations
Influenza	Inactivated virus	Annually before infection season	Elevated immunogenicity following HD vaccine
SARS-CoV-2	mRNA/vector	Booster depending on new variants	Basic immunization[a] prior to transplantation
Pneumococcus	20-valent conjugate (PCV20)	Depending on vaccination status with PCV13 and PPSV23	No sequential vaccination needed after PCV20
Respiratory syncytial virus	Adjuvanted protein-based, protein-based, mRNA	Single dose as soon as available	No data about immunogenicity nor about timepoint of booster vaccination

[a]At least three antigen contacts consisting of at least two vaccines.
HD, high-dose; mRNA, messenger RNA.

Results from a Dutch cohort revealed partial humoral immune response in lung transplanted patients after revaccination with polysaccharide vaccine PPSV23 [95]. In contrast, sequential vaccination with a 23-valent polysaccharide vaccines after a 13-valent conjugate vaccine did not improve antibody response [96]. Humoral immune response after vaccination against Sars-CoV-2 is generally low after transplantation but is increased after repetitive administration of mRNA vaccine in solid organ transplanted patients [97,98]. However, the percentage of patients with sufficient humoral immune response is lower than in immunocompetent individuals [97]. Some immunosuppressants, for example, mycophenolate mofetil in particular has a negative effect on the immune response [97,99]. Despite attenuated humoral immune response cellular-mediated immunity expected protection may co-exist [97].

Since 2023, there are vaccines available against RSV showing promising results to protect older adults 60+ [100,101], recently also a mRNA-based vaccine [102]. Despite pending approval for younger patients, several German specialist societies also recommend widespread use in patients with preexisting pulmonary diseases [103].

Prophylactic drug therapy against opportunistic pathogens

Lifelong or temporary oral prophylactic therapy has proven to be useful in preventing opportunistic infections, mainly due to cytomegalovirus, PjP and fungal infections.

Introduction of lifelong prophylaxis with trimethoprim–sulfamethoxazole ensured a dramatic drop of severe and potential life-threatening PjP [104]. In case of intolerance or severe side effects atovaquone or inhaled pentamidine can be considered as an alternative therapy [73].

Several options are available for the prophylaxis of invasive aspergillosis, including inhaled amphotericin B and systemic azoles. Liposomal amphotericin B is better tolerated than conventional amphotericin B formulation and can be applied 3-times weekly but is off-label. Azol therapy is convenient but may have side effects, interactions and is off-label in most countries for prophylaxis after lung transplantation. Due to direct application into the lung allograft, inhalative prophylaxis avoids systemic adverse effects and drug–drug interaction but possibly causes local effects like cough or bronchospasm. Additionally, prophylactic effects are limited to the lung allograft [105,106]. Among systemic azoles, data reveal a sufficient reduction of invasive fungal infection whereas itraconazole and posaconazole have a more favorable safety profile than voriconazole [107–109]. Results mainly based on small sample sizes in retrospective studies underlying the need for further exploration to establish an international standard [105].

The length of CMV prophylaxis depends on the individual risk profile, which is determined by the serostatus of the recipient and the donor. A positive donor (D+) and negative recipient (R−) are considered a high-risk profile with a recommendation for oral prophylaxis with valganciclovir for up to 12 months, whereas this can be shortened to 3–6 months if the recipient (R+) is positive [110–112].

CONCLUSION

Lung transplant recipients are particularly vulnerable to viral and bacterial infections due to their weakened immune systems. These infections can lead to severe complications, such as pneumonia, graft dysfunction, and increased mortality. Diagnosis is often complex and involves various tests, while treatment can be challenging due to interactions with the immunosuppressive drugs required to prevent organ rejection. Preventive strategies, such as vaccination and the use of prophylactic medications, are essential in reducing infection risks. Despite these measures, infections remain a significant cause of complications and can

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severely impact the long-term success of lung transplants.

Looking ahead, improving infection management in lung transplant patients will require advancements in diagnostic tools, more effective treatments with fewer side effects, and enhanced vaccination strategies that provide stronger protection. Further research is also needed to develop standardized protocols for preventing and treating infections, ensuring better outcomes and quality of life for transplant recipients.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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