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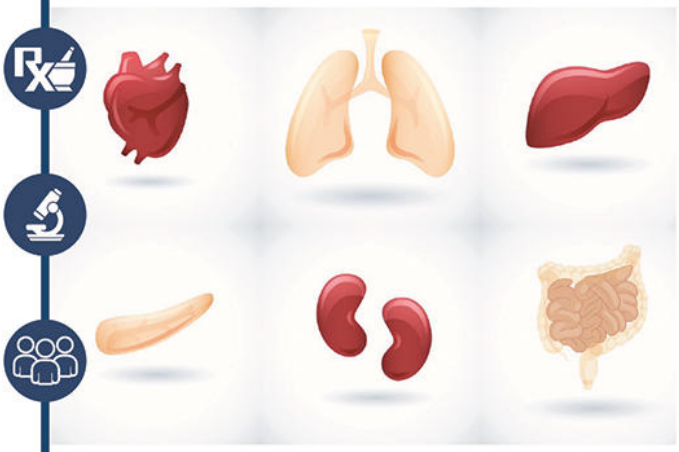

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Pneumonia in Solid Organ Transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract

These guidelines from the AST Infectious Diseases Community of Practice review the diagnosis and management of pneumonia in the post-transplant period. Clinical presentations and differential diagnosis for pneumonia in the solid organ transplant recipient are reviewed. A two-tier approach is proposed based on the net state of immunosuppression and the severity of presentation. With a lower risk of opportunistic, hospital acquired, or exposure-specific pathogens and a non-severe presentation, empirical therapy may be initiated under close clinical observation. In all other patients, or those not responding to the initial therapy, a more aggressive diagnostic approach including sampling of tissue for microbiological and pathological testing is warranted. Given the broad range of potential pathogens, a microbiological diagnosis is often key for optimal care. Given the limited literature comparatively evaluating diagnostic approaches to pneumonia in the solid organ transplant recipient, much of the proposed diagnostic algorithm reflects clinical experience rather than evidence-based data. It should serve as a template which may be modified according to local needs. The same holds true for the suggested empiric therapies,

which need to be adapted to the local resistance patterns. Further study is needed to comparatively evaluate diagnostic and empiric treatment strategies in SOT recipients.

Introduction

Pneumonia is a frequent infectious complication of solid organ transplantation (SOT). The occurrence of post-transplant pneumonia adversely impacts both graft and recipient survival, as well as the cost of care for SOT recipients [1]. Numerous micro-organisms can cause pneumonia in the SOT recipient with some etiologies resulting in self-limited infection and others causing significant morbidity and mortality. As a result of the varied clinical presentations and etiologies of pneumonia in SOT recipients, arriving at a specific microbiologic diagnosis can be challenging but is important for optimal care, especially with complicated or refractory pneumonias. In this section, the clinical presentation, differential diagnosis, diagnostic testing, and empiric antimicrobial treatment of pneumonia in SOT recipients is reviewed. Pathogen-specific sections within the AST ID Guidelines are referenced for further information regarding the diagnosis and treatment of specific pathogens that cause pneumonia in this vulnerable population.

Clinical Presentation

The clinical presentation of pneumonia in the SOT recipient is highly variable. The traditional presentation with cough, increased sputum production, and fever should always prompt evaluation for pneumonia. However, frequently more subtle symptoms predominate with the diagnosis of pneumonia being reached only after careful clinical evaluation. Clinical evolution can vary from very rapid, indicative of bacterial or viral pathogens, to the subacute or chronic presentation often seen with fungal or mycobacterial infections. A high index of suspicion for pneumonia is essential when any signs of infection are present in a solid organ

transplant recipient. Lung involvement should be evaluated in any transplant patient presenting with an unexplained fever, even in the absence of other lung-specific clinical findings.

Differential diagnosis

Considerations Impacting Differential Diagnosis

The differential diagnosis for pneumonia in SOT recipients includes infectious and noninfectious etiologies (Table 1). An understanding of infectious etiologies in these patients is driven by epidemiologic investigation of both transplanted [2-12] and otherwise healthy adult and pediatric patients [13, 14]. In earlier eras, studies of pneumonia in SOT recipients were focused on the high incidence of opportunistic infections such as invasive mold infections and cytomegalovirus (CMV) [12]. With improved infection prevention strategies, better diagnostic tools, and newer immunosuppressive strategies, the importance of community-acquired bacterial and viral infection in SOT-associated pneumonia has been increasingly appreciated [2].

The differential diagnosis of pneumonia in SOT recipients depends upon a multitude of non-specific factors including but not limited to age and timing post-transplant, net state of immunosuppression, specific organ transplanted, environmental exposures, site of pneumonia acquisition (community vs. healthcare/hospital acquired), and radiographic infiltrate pattern. The risk of pneumonia in SOT recipients is determined by the degree/depth of immunosuppression [15]. Healthcare and/or ventilator associated pneumonia are frequently diagnosed in the early-post transplant period. In two series, early onset pneumonia post-liver transplant was dominated by bacterial etiologies, the majority of which were Gram-negative bacilli [7, 8]. The majority of pneumonia episodes occur later post-transplant with 50% occurring >1 year post-transplant [9] in renal recipients and 70.4% of episodes occurring at >6 months post-transplant in a multicenter point prevalence study [2].

The type of organ transplanted influences the incidence, timing, and microbiologic spectrum of pneumonia in SOT recipients [16]. Lung transplantation poses unique challenges given the potential for donor-derived infection and recipient airway colonization to impact the occurrence and microbiology of pneumonia. In a prospective, multicenter study of pneumonia in lung transplant recipients, pneumonia incidence was 72 episodes per 100 lung transplants per year [3]. Though bacterial pneumonia was the most frequent etiology, fungal and viral pneumonia together accounted for 24.4% of episodes. The majority of

pneumonia episodes in this series occurred in the two months post-transplant [3]. In a large cohort of SOT recipients with invasive fungal infection, *Aspergillus* was the most common IFI in lung transplant recipients with presumably many of the invasive aspergillosis (IA) episodes presenting with primary lung involvement [17]. In other studies, over half of IA episodes occurred over 1 year post-transplant [18, 19].

In a retrospective study of 40 adult small bowel/multivisceral transplant (SmB/MV) recipients, 17% of recipients developed infection involving the lung(s) in the 30-day post-transplant period. Most of these were due to *Pseudomonas* aeruginosa [20]. In a prospective study of infections in SmB/MV recipients, 14% of patients developed pneumonia though no etiology-specific pneumonia data was provided [21].

Radiographic features can contribute to narrowing the differential diagnosis for pneumonia in SOT recipients though do not frequently lead to identification of a specific etiology. Diffuse, bilateral infiltrates suggest a range of etiologies including CMV, respiratory viruses, *Mycoplasma*, *Legionella*, and *Pneumocystis jirovecii* (PJP) [22]. Ground glass or mixed ground glass/micronodular infiltrate raises concern for PJP and CMV [23]. Single or multinodular lung involvement indicates potential for invasive mold infection, *Nocardia*, tuberculosis (TB) or non-tuberculous mycobacterial disease, endemic fungal infection, or malignancy [24]. Association of lung infiltrates with mediastinal or hilar adenopathy raises concern for TB and endemic fungal infection. The presence of pleural effusion or empyema suggests a range of etiologies including community acquired and hospital-acquired bacterial pneumonia, *Cryptococcus* and other fungal infections, or tuberculosis depending on the clinical presentation and exposure history [25, 26].

Epidemiology, environmental exposures, and seasonality also significantly influence pneumonia etiologies. Geographic location of the donor and recipient may impart risk for endemic fungal infections (*Histoplasma*, *Coccidioides*, *Blastomyces*, *Penicillium*), TB, or *Burkholderia pseudomallei* [26-29]. Zoonotic pneumonia can occur secondary to an array of pathogens following exposure to birds (*Chlamydia psittaci*), cats/dogs (*Pasteurella multocida*), rabbits and other wildlife (*Francisella tularensis*), horses (*Rhodococcus equi*), as well as farm animals (*Coxiella burnetti*) [30-33]. Environmental exposures to contaminated water (*Legionella pneumophila* and *Pseudomonas aeruginosa)* as well as soil (*Cryptococcus*, *Nocardia*, *Penicillium*, endemic fungi, molds) can also indicate potential etiology for pneumonia [34]. Seasonality and community contacts contribute to relative risk of respiratory viral infections such as influenza, parainfluenza, enteroviruses, and rhinoviruses [35, 36].

Potential pathogens

Potential pathogens causing pneumonia in the SOT recipient include bacteria, viruses, fungi, and parasites (Table1). Though specific etiologies are discussed in greater detail in pathogen-specific sections of this guideline series, broad categories of microbiologic etiologies that cause pneumonia in SOT recipients merit attention.

Bacterial pneumonia in the solid organ transplant recipient can be caused by community- or hospital-acquired organisms as well as by donor-derived pathogens in the setting of lung transplantation. Hospital acquisition, including ventilator-associated pneumonia, occurs predominantly early post-transplantation while community acquired pneumonia becomes relatively more frequent later post-transplant [2]. Community acquired bacterial pneumonia pathogens include *Streptococcus pneumoniae* [37, 38], *Haemophilus influenzae*, *Mycoplasma* spp.*, Legionella* spp.*, and Chlamydia spp.* Nosocomial/opportunistic bacterial etiologies include *Pseudomonas* spp., enteric Gram-negative bacilli, as well as *Stenotrophomonas* spp., and others. Additionally, bacteria such as *Nocardia*, tuberculous and non-tuberculous mycobacteria can be significant pathogens in SOT recipients [26, 39-41].

Fungal pulmonary infection in SOT recipients can be due to PJP*, Aspergillus* spp. and other invasive molds, *Cryptococcus*, and endemic/dimorphic fungi such as *Histoplasma*, *Blastomyces*, and *Coccidioides* [42, 43]. Though prophylaxis strategies have markedly decreased the occurrence of PJP in SOT recipients, late-onset [44] and outbreak associated [45, 46] infections remain a problem. In *Histoplasma* infection in SOT recipients, 81% of cases have pulmonary involvement and 34% of infections occur in the first year post-transplant[47]. Cryptococcal infection may present with pneumonia alone, or with dissemination, including to the central nervous system, in SOT recipients [25, 48-51]. Notably, CMV infection can predispose to invasive aspergillosis in SOT recipients [19].

Viral etiologies of pneumonia in SOT recipients include DNA viruses such as adenovirus [52, 53], CMV, and other herpesviruses, as well as community acquired respiratory RNA viruses including influenza [54], RSV [55, 56], HMPV [57, 58], and parainfluenza. Less data exists on the frequency of infection with rhinoviruses, coronaviruses, and respiratory enteroviruses as a cause of pneumonia in SOT recipients [55]. Additionally, viral respiratory tract infections can predispose to secondary bacterial pneumonia [59, 60].Lung transplant recipients are at high risk for lower respiratory tract

infection due to respiratory viruses [61, 62] with potential for significant post-infection increases in acute rejection rates and decline in lung function [63].

Parasitic infection is a rare cause of pneumonia in SOT recipients. *Toxoplasma* infection or reactivation is infrequently reported as a cause of pneumonitis either alone [64] or as part of a disseminated infection [65]. *Strongyloides* hyperinfection syndrome occurring as a result of antecedent recipient infection or donor-derived transmission can present with bilateral, multifocal, and/or interstitial pulmonary infiltrates with or without Gram-negative bacterial sepsis [66, 67].

Non-infectious etiologies

An array of non-infectious etiologies can mimic infectious pneumonia in the SOT recipient (Table 1). Post-transplant lymphoproliferative disease (PTLD) may present with lung/thoracic involvement including pulmonary nodules and mediastinal adenopathy, especially in lung/heart-lung transplant recipients [68, 69]. Pulmonary PTLD can also radiographically mimic infectious etiologies of pneumonia [70]. mTOR inhibitor-induced pneumonitis is an infrequent though potentially severe medication side-effect that generally resolves with discontinuation of mTOR inhibitor therapy and may co-exist with infectious etiologies including PJP or community acquired respiratory viruses [71]. Non-PTLD primary or metastatic lung cancer can also occur in SOT recipients [72]. Other complications such as pulmonary embolism, pulmonary hemorrhage, and pulmonary edema are also reported [73, 74].

Diagnostic Testing

No studies have prospectively compared diagnostic approaches to pneumonia in SOT recipients. While some specific diagnostic tests have been evaluated more systematically, individual test performance is often defined in healthy subjects or in groups of subjects with a variety of immunocompromising conditions. Therefore, the appropriate diagnostic evaluation for pneumonia in SOT recipients should be highly individualized based on local epidemiology, locally available tests and practice parameters, as well as patient-specific risk factors, exposures, and medical history. Guidelines for diagnosis of pneumonia by other groups can also be informative though do not always specifically apply to the SOT recipient [75-78]. A tiered approach to the diagnostic evaluation of pneumonia encompasses

an initial approach, followed by a more extensive evaluation if the diagnosis remains unclear or if the patient is deteriorating. If the clinical situation is critical or if a more specific diagnosis is initially suspected, respective tests are applied and the order of diagnostic tests modified. One potential diagnostic approach to pneumonia in the SOT recipient is outlined in Figure 1.

- The diagnostic evaluation of SOT recipients with suspected or confirmed pneumonia should be performed using a tiered approach with the pace and extent of evaluation informed by the severity and acuity of presentation, the degree of immunosuppression, and the patient's risk factor/exposure history (strong, low).
- We recommend against using current pneumonia severity scores in SOT recipients with pneumonia (strong, very low). Pneumonia severity scores have been evaluated in non-transplant patients with community acquired pneumonia and have variable ability to stratify for severity and clinical outcome [79]. No studies of pneumonia severity scoring systems have been performed in SOT recipients though the PSI and CURB-65 scores had poor performance characteristics in cancer patients presenting with pneumonia [80].
- Practitioners evaluating SOT recipients with symptoms or signs of pneumonia should assess the following at initial evaluation:
    - Key features of the patient's medical, transplant, immunization, and social histories (Strong, moderate).
    - Current and prior microbial colonization and current and prior antimicrobial prophylaxis regimens (Strong, moderate).
    - Social history for exposure(s) which would suggest risk of untreated latent infection such as latent TB infection, coccidioidomycosis, and strongyloidiasis (Strong, moderate).
    - The acuity of the patient's clinical presentation and use this information in guiding the differential diagnosis, diagnostic evaluation, and empiric antimicrobial therapy (Strong, low).
- The need for contact or respiratory isolation should be assessed and acted upon early in the patient evaluation to avoid exposure of other SOT recipients, patients, and/or staff to potentially contagious pathogens (strong, high) [81].
- Local epidemiology of respiratory viruses, and in particular influenza virus, should be reviewed and considered in the evaluation (strong, high) [54] .

The initial evaluation of a SOT recipient with pneumonia should include both blood and radiologic testing with consideration given to viral detection from the nasopharynx.

- Clinicians should obtain complete blood count with differential, electrolyte chemistries, and liver function testing as part of the initial laboratory evaluation both for aiding in diagnosis and determining risk of toxicity associated with empiric or directed antimicrobial treatment (strong, low).
- Blood cultures should be obtained at presentation of pneumonia and prior to initiation of antibiotic therapy, especially if the patient is febrile or requiring hospitalization (strong, low). While blood culture yields for etiologic organisms are low in both healthy and SOT recipients with pneumonia, a positive blood culture significantly impacts clinical care [2, 14].
- A chest x ray should be performed in all SOT patients with suspected pneumonia (strong, moderate).
- Performance of a chest CT scan in the initial evaluation for pneumonia is recommended in settings of high acuity or high net state of immunosuppression (weak, low).
- Risk for illness attributable to CMV should be assessed by considering CMV donor-receipient serostatus, status of CMV-active prophylaxis, duration of time post-transplant, and depth of immunosuppression in all SOT patients presenting with symptoms indicative of pneumonia (strong, low).
- Testing of urine for *Legionella* antigens is recommended (weak, very low low). Though sensitivity is low and urine testing does not detect non-*Legionella pneumophila* species, diagnosis of Legionella through this non-invasive test can accelerate diagnosis and institution of appropriate antimicrobial therapy [82].
- Testing of the nasopharynx for influenza virus by PCR in seasonally appropriate times is recommended to clarify need for antiviral treatment (strong, high) [54, 83].
- Multiplex molecular respiratory virus testing is recommended in the evaluation of pneumonia in SOT recipients in seasons of high respiratory virus incidence (weak, moderate). Identifying a respiratory viral etiology can impact clinical decisions regarding further evaluation as well as the need for antimicrobial therapy though the impact has not been specifically evaluated in SOT recipients [84, 85].
- In older children or adults in whom sputum production is present, sputum culture is recommended for gram stain and bacterial culture (weak, very low).

The contribution of inflammatory markers (leukocyte count, C-reactive protein, procalcitonin) has been extensively studied as a tool for the general practitioner to decide

whether empiric antibiotic treatment may be necessary with mixed results [89]. Several studies have evaluated the utility of procalcitonin measurement for detecting and differentiating bacterial infection from other solid organ transplant complications [90-97]; reviewed in [98]. Importantly, procalcitonin levels are impacted by surgery as well as by ATG administration which may decrease the utility of this assay in first week post-transplant [98]. In general, though few studies have evaluated procalcitonin use in the setting of SOT recipients with pneumonia, an elevated procalcitonin level may indicate the presence of an infection. . Elevated procalcitonin levels beyond the first week post-transplantation may indicate the presence of a bacterial infection. However, data are limited in SOT recipients and the specific clinical in scenarios in which to apply procalcitonin testing are not clear.

With pneumonia established by imaging and selected laboratory evaluation underway, empiric therapy as discussed below should be started (see Empiric Initiation Treatment section). Clinicians should progress to the second tier of evaluation (Figure 1) if, despite empiric therapy, the clinical situation does not improve in the first 24 to 48 hours or deteriorates and no diagnosis was made following the first tier of diagnostic evaluation (Figure 1). Second tier testing should be performed with focus on each of four areas—repeating of selected tests from the first tier as appropriate; imaging studies to further define the location and nature of pulmonary involvement; expanded diagnostic evaluation as guided by exposures, radiographic results, and clinical course; and, invasive testing with the goal of securing a microbiologic diagnosis for targeted treatment (Figure 1).

- Laboratory tests not obtained as part of the initial evaluation should be performed (weak, low).
-
- If not done yet, a CT scan of the chest should be performed to better delineate the radiologic pattern and location of infiltrate and to identity potential opportunity for invasive diagnostic procedures (strong, high).
- Additional blood testing guided by radiographic pattern, exposures, and degree of immunosuppression should include antigen and/or serologic evaluation for endemic mycoses (strong, high) [47] (see Endemic Fungi section of 4th edition of AST ID Guidelines).
- Fungal biomarkers measured in the blood/serum, such as galactomannan and 1,3β-d- glucan have poor performance characteristics in SOT recipients as compared with

HSCT recipients [18, 99, 100]. No studies have evaluated whether performance characteristics vary depending on post-transplant timing of infection. Given the paucity of data evaluating utility of 1,3β-d- glucan, we do not recommend use of this test currently in SOT recipients (strong, very low) [101-103] (see Aspergillus, Candida, and Pneumocystis sections of 4th edition of AST ID Guidelines.

In some cases more invasive testing is needed to obtain a diagnosis. Invasive, procedural diagnostic testing in the SOT recipient with pneumonia includes bronchoscopy with broncho-alveolar lavage (BAL), transbronchial biopsy, CT-guided biopsy, video-assisted thoracotomy (VATS) with lung biopsy, and open lung biopsy. These procedures are particularly important for the diagnosis of fungal disease (see the Aspergillus, Cryptococcus, Endemic Fungi, and Emerging Fungi sections of 4th edition of AST ID Guidelines), and to evaluate for non-infectious causes such as malignancy. Though potential exists for achieving a diagnosis with one of these methods, the decision to pursue further procedural evaluation in an SOT recipient with pneumonia must balance both procedural risks and potential benefits.

- Physicians caring for an SOT recipient with pneumonia should have a low threshold for procedural evaluation especially in settings in which patients are not improving, are highly immunocompromised, or the diagnosis remains uncertain (strong, moderate).

BAL offers the opportunity to obtain microbiologic diagnosis either with or without transbronchial biopsy. The utility of BAL in SOT recipients with pneumonia, lung infiltrates, or lung nodules has been evaluated in several small series [5, 22, 68, 104, 105]. Microbiologic yield for BAL in these studies ranges from 39% to 77%, with the highest yields in patients with nosocomial pneumonia [5], and those with onset of symptoms between 1 and 6 months post-transplant [105]. Importantly, microbiologic yield is clearly influenced by the pre-test probability of infection and the relative incidence of infections in distinct populations [105, 106]. BAL studies listed in Figure 1 are proposed as a complete list of diagnostic options. While extensive, performance of the complete list of these studies may not be needed in all SOT recipients with pneumonia.

- We recommend performance of BAL in the setting of diffuse or focal pulmonary infiltrate in patients with failure to improve on empiric antibacterial therapy in whom diagnosis has not been reached by non-invasive testing (strong, moderate). The decision to proceed with BAL versus lung biopsy for initial invasive testing must be highly individualized for each patient and is dependent on the clinician's risk/benefit analysis.
- We recommend the following studies as a complete BAL fluid evaluation with modifications as needed depending on an individual patient's clinical presentation, radiographic findings, and clinical course (Figure 1):
    - Traditional bacterial, fungal, viral, and mycobacterial culture (see Aspergillus, Cryptococcus, Endemic Fungi, Emerging Fungi, CMV, HSV, VZV, Respiratory Viruses, Nontuberculosis Mycobacterial, Tuberculosis, and Nocardia sections of 4th edition of AST ID Guidelines) (strong, moderate).
    - Diagnostic testing including PJP directed stains or nucleic-acid based testing for PJP from BAL fluid (strong, high), in particular in patients either no longer receiving prophylaxis or on non-TMP-SMX prophylaxis (see Pneumocystis section of 4th edition of AST ID Guidelines).
    - Fungal directed stains in patients with radiographic findings suggestive of invasive fungal infection (Strong, low)
    - Galactomannan in patients with radiographic findings suggestive of invasive fungal infection (weak, low) [100, 107]
    - Antigen-based testing for endemic fungal infections such as *Histoplasma*, *Blastomyces*, *Coccidioides*, and *Paracoccidioides* for patients with a compatible clinical history and geographic exposure risk (Strong, low)
    - Nucleic acid-based testing (PCR, QNAT, Film array) testing for the following pathogens depending on test availability and on the patient's clinical history, exposure risk, and radiographic findings (strong, low):
        - Respiratory viruses
        - CMV
        - *Mycoplasma spp*, *Ureaplasma spp*., and/or *Legionella spp.*
        - *Nocardia spp.*
        - Invasive mold species
        - *Mycobacterium tuberculosis*

Biopsy-based evaluation offers the ability to directly identify infectious agents in tissue and also determine the histologic pattern of inflammation present. Open lung biopsy (OLB) was studied in a single center kidney transplant population with bilateral lung

infiltrates [108]. The overall OLB diagnostic yield was 85.1% with findings from 53% of OLBs resulting in a therapeutic management change. Complications were frequent (28.7% of OLBs) and associated with higher mortality rate [108]. A similar study comparing SOT and non-SOT patients with diffuse lung disease demonstrated a therapeutic management change frequency of 33% [109]. Percutaneous CT-guided lung biopsy has been evaluated in one series of SOT recipients with parenchymal lung nodule(s) [110]. Diagnostic yield in this series of 45 biopsies was 53% with the most frequent diagnoses being fungal disease and malignancy. Yield was highest with use of both fine needle aspiration and core biopsy combined in the procedure. Complications occurred in 13% of patients [110]. The decision to proceed with lung biopsy must be highly individualized for each patient and is dependent on the clinician's risk/benefit analysis.

- We recommend lung biopsy (Open, VATS, or CT-guided) in the setting of diffuse or focal pulmonary infiltrate in patients with failure to improve on empiric antibacterial therapy and in whom diagnosis has not been reached by non-invasive testing or BAL (strong, moderate).
- We recommend lung biopsy (transbronchial, Open, VATS, or CT-guided) for patients with focal pulmonary nodule(s) where diagnosis has not already been established by other means due to the risk for malignancy (including PTLD) or invasive fungal infection (weak, low). Consideration can be given to close follow up with serial imaging prior to performance of invasive diagnostic procedures for cases in which the risk for malignancy and/or invasive fungal infection is felt to be low (weak, low).
- In patients who live in geographic areas that impart risk for endemic fungal infection and who have exposure history suggestive of a moderate to high risk for endemic fungal infection, we recommend deferral of lung biopsy until after antigen/serologic assessment for endemic fungal infection is complete (weak, low).

Non-hypothesis-driven tests such as broad-spectrum bacterial PCR based on 16sRNA, panfungal, or mycobacterial genus PCR are not universally available and not systemically studied in SOT recipients. However, these assays may be helpful in patients where all other tests do not identify an etiology. Unbiased next-generation sequencing may assist in defining a specific etiology if available, though more clinical studies are needed to define the utility of a sequencing-based diagnostic approach to pneumonia.

Empiric initial treatment

Given the complex and varied nature of specific treatment for individual pathogens that cause pneumonia in the SOT recipient, this section will address recommendations for empiric antimicrobial therapy in this setting. Various factors significantly impact empiric antimicrobial regimens for pneumonia in the SOT recipient. The degree of immunosuppression and pace of illness onset (acute, subacute, chronic) are significant determinants in the breadth of empiric antimicrobial therapy provided to an individual patient. Except during influenza season, where empiric therapy may include an agent directed against influenza, antibacterial therapy is the cornerstone of the initial empiric therapy for pneumonia in the SOT recipient [111]. Empiric antifungal chemotherapy is rarely initiated early, except in instances where the clinical and radiological presentation strongly suggests a fungal origin. The choice of the initial therapy will depend on the following considerations:

- Empiric treatment regimens for pneumonia in the SOT recipient should take into account each individual patient's known microbial colonization as well as prior antimicrobial resistance patterns of specific colonizing or pathogenic organisms with special emphasis on multi-drug resistant bacteria colonizing the airway in lung transplant recipients. (strong, low).
- During influenza season, empiric administration of an antiviral drug active against influenza is recommended in SOT recipients with influenza-like illness, including pneumonia, while awaiting results of influenza specific testing unless there is access to PCR-based detection methods with rapid turnaround time (strong, moderate) [54, 83] (See RNA Respiratory Viruses section of 4th edition of AST ID Guidelines).
- In a stable patient considered suitable for outpatient therapy who is at lower risk for opportunistic or hospital acquired infection and in whom no specific pathogen is suspected, empiric therapy should cover community acquired pneumonia and should follow national/international guidelines influenced by local resistance and prevalence patterns (strong, low). Beta lactams or fluoroquinolones (FQ) with coverage of respiratory pathogens may be considered for empiric therapy in this setting (strong, low). Practitioners should consider the role of drug interactions, adverse reactions, and increasing antimicrobial resistance when considering risks and benefits for the FQ use in SOT recipients.
- Consideration should be given to empiric coverage of intracellular pathogens(such as *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, and *Legionella spp.)* in SOT recipients with community-acquired pneumonia (weak, low) with greater

consideration given to empiric intracellular pathogen treatment of pediatric SOT recipients with community-acquired pneumonia (strong, moderate) [13, 14]. One important consideration is the selection and use of empiric therapy in this setting in which drug-drug interactions are present between macrolides and immunosuppressive agents. Respiratory fluoroquinolones may be considered in settings with a high incidence of macrolide resistance for *Mycoplasma spp* with consideration given to the above noted issues in considering risk and benefit of FQ use. (weak, low).

- With outpatient regimens discussed above, the inclusion of antibiotic therapy against methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas* spp. is dependent on local resistance patterns, prevalence, the individual patient's infection and bacterial colonization history, as well as the features of the presenting illness (e.g. radiographic evidence of lung abscess). (strong, low) (see MRSA and MDR GNR sections of 4th edition of AST ID Guidelines).
- In SOT recipients who require hospitalization for pneumonia, combination therapy with a beta-lactam agent (+/- MRSA and +/- antipseudomonal activity) and an agent active against intracellular organisms (*Mycoplasma* spp. in children and *Legionella* spp. in adults) is recommended (strong, low). The breadth of coverage of the penicillin-based agent used depends on local resistance patterns (especially for *S. pneumoniae*) and whether a nosocomial approach is warranted to cover hospital-acquired gram-negative pathogens (e.g. recent hospitalization, underlying chronic or bronchiectatic lung disease, or the presence prosthetic material). Fluoroquinolones are an alternative in this setting (strong, low). For hospitalized patients with nosocomial or ventilator-associated pneumonia, international/national guidelines apply with attention to local guidelines, prevalence, and epidemiology (strong, moderate).

Any empiric therapy must be adapted to new clinical and microbiological findings. As appropriateness of initial empiric therapy is measured in large part by the patient's clinical response, close monitoring including repeated clinical evaluation is a prerequisite for any outpatient approach. If this is not feasible or if any doubts prevail, inpatient management should be favored. Furthermore, with any empiric therapy for pneumonia, key gaps in antimicrobial coverage must be kept in mind. Most empiric regimens will not optimally treat *Nocardia* spp. or *Pneumocystis jirovecii*. Mycobacterial infections may be partially mitigated by the activity of drugs used for empiric pneumonia therapy (e.g. imipenem, quinolones,

oxazolidinones). In addition, empiric antibacterial regimens will clearly not provide coverage against invasive, opportunistic, and/or endemic fungal infections. Clinicians caring for SOT recipients with subacute or chronic illness presentations which include pneumonia should consider pathogens such as *Nocardia*, Tuberculosis, Nontuberculous mycobacteria, endemic fungi, and invasive molds. These pathogens require bronchoalveolar fluid or tissue testing for diagnosis and their treatment entails prolonged courses of antimicrobial regimens. Empiric therapy is usually not instituted prior to diagnostic testing or procedure. However, in unique situations of high acuity or inability to perform diagnostic procedures, empiric therapy for these pathogens may be needed.

Conclusions

The diagnosis and treatment of pneumonia in the SOT recipient is challenging due to varied clinical presentations, numerous potential etiologies, and breadth of both empiric and targeted treatment options. Diagnostic strategies must consider numerous factors including post-transplant timing, degree of immunosuppression, environmental/ community/hospital exposures, and seasonal epidemiology. Empiric treatment is in large part determined by local epidemiology and resistance patterns. Novel diagnostic techniques and future prospective studies will continue to impact the diagnosis and treatment of pneumonia in SOT recipients.

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Table 1: Differential Diagnosis of Pneumonia in the Solid Organ Transplant Recipient

Viral	Respiratory viruses: Influenza, Parainfluenza, Respiratory Syncytial virus, Human metapneumonvirus, Adenovirus, Rhinovirus, Coronavirus,
	Herpesviruses: Herpes simplex virus, Varicella zoster virus, Cytomegalovirus
Bacterial	Community-acquired: *Streptoccocus pneumonia, Haemphilus influenzae, Moraxella cattarhalis, Staphylococcus aureus*
	Healthcare associated: *Klebsiella spp., Enterobacter spp., Escherichia coli,* and other Enterobacteriaceae; *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila, Acinetobacter spp.*, others
	Atypical: *Mycoplasma pneumoniae, Ureaplasma urealyticum, Chlamydia trachomatis, Legionella spp.*
	Mycobacterial: *Mycobcaterium. tuberculosis* and Nontuberculous Mycobacteria
	Zoonoses: *Chlamydia psittaci*, *Francisella tularensis*, *Coxiella burnetti*, *Rhodococcus equi*, *Pasteurella multocida*
	Other: *Nocardia spp.* and *Actinomyces spp.*
Fungal	Endemic/Dimorphic Fungi: *Histoplasma capsulatum* (*var capsulatum* and *var duboisii*); *Blastomyces dermatiditis*; *Coccidioides immitis*; *Penicillium. marneffei*
	Yeasts and Yeast-like Fungi: *Cryptococcus spp.; Pneumocystis jirovecii*
	Molds: *Aspergillus* spp.; Mucormysosis; Fusariosis; *Scedopsporium* spp.
Parasitic	Protozoan: *Toxoplasma gondii*
	Helminth: *Strongyloides stercoralis*
	Flatworm: *Echinococcus spp.*
Non-infectious	mTORi-induced pneumonitis; Pulmonary embolism; Pulmonary hemorrhage; Lung tumor (primary or metastasis); PTLD; Pulmonary edema; Hepatopulmonary syndrome