The number of lung transplants has continued to increase each year, with >2,700 transplants performed worldwide in 2007. Lung transplant outcomes also appear to be improving incrementally, with the median survival increasing from 4.7 years in the late 1990s to 5.7 years for the 2000 to 2007 era. In 2005, a new lung allocation scoring system was introduced in the United States with the goal of prioritizing organ allocation based on the need for transplant and the likelihood of success. This system was designed to improve the overall transplant benefit and has resulted in shortened wait times and reduced mortality on the wait list. Thus far, the new system does not appear to have compromised survival, except for the sickest patients with the highest lung allocation scores whose posttransplant survival appears to be significantly reduced.

Primary graft dysfunction (PGD), infection, and late graft failure account for the majority of deaths in the first year after lung transplant. Chronic allograft rejection or bronchiolitis obliterans syndrome (BOS) develops in the majority of patients by 5 years and is the key factor limiting the long-term survival of these patients. This review focuses on the major pulmonary complications encountered by the pulmonologist in providing care to this complicated and growing group of patients.

**Primary Graft Dysfunction**

PGD is a leading cause of early posttransplant morbidity and mortality. It affects 10% to 25% of lung transplant recipients and is associated with a 30-day mortality that may be as high as 50%. It is characterized by the early development of diffuse parenchymal infiltrates associated with a reduced \( \frac{P_AO_2}{FIO_2} \) ratio (<300) in the absence of cardiogenic pulmonary edema, hyperacute rejection, pulmonary venous anastomotic obstruction, or infection (Fig 1). PGD resembles ARDS and manifests histologically by a similar pattern of diffuse alveolar damage. It is thought to occur because of ischemia/reperfusion injury with damage to the pulmonary endothelium and epithelium.

The risk factors for PGD may be both donor and recipient related. Increasing age, smoking history, prolonged mechanical ventilation, aspiration pneumonia, trauma, and hemodynamic instability of the donor are all associated with a higher risk of PGD.
Recipient-related risk factors include elevated pretransplant pulmonary artery pressures, diffuse interstitial lung disease, and the transfusion of blood products.\textsuperscript{5,8} The International Society for Heart and Lung Transplantation (ISHLT) classification scheme categorizes the severity of PGD based on the Pao\textsubscript{2}/FiO\textsubscript{2} ratio immediately postoperatively, and at 24, 48, and 72 h. It has been shown that the longer and the more severe the PGD, the greater the impact on patient outcomes.\textsuperscript{11}

Preventive strategies have focused on improving lung preservation techniques, preventing barotrauma of donor lungs, modifying organ preservation solutions, and minimizing ischemic times.\textsuperscript{9,12,13} Inhaled nitric oxide has been studied but has not been shown to be an effective prophylactic agent.\textsuperscript{14,15}

The treatment of PGD remains largely supportive. Management is similar to that of patients with ARDS, with low tidal volume ventilation and maintenance of patients’ volume status on the “dry” side with diuresis. Inhaled nitric oxide can be implemented for refractory hypoxemia, whereas extracorporeal membrane oxygenation can be a potentially lifesaving treatment, with a reported 42% survival rate in one study.\textsuperscript{16,17} Exogenous administration of surfactant has also been shown to attenuate reperfusion injury in animal models, and improvements in lung infiltrates and resolution of PGD have been reported in a small uncontrolled study.\textsuperscript{18}

Exploring the link between PGD and chronic allograft rejection or BOS is an area of emerging interest. Recently, it was shown that PGD induces proinflammatory cytokines and upregulates human leukocyte antigen-II expression, which can then increase donor-specific alloimmunity, thereby mechanistically linking PGD and BOS.\textsuperscript{19}

Infections

Infectious complications remain one of the most important causes of morbidity and mortality in lung transplant recipients.\textsuperscript{1,20} There are numerous reasons why lung recipients have a heightened predisposition to pulmonary infections. The lungs are more immunogenic than most other solid organs and therefore recipients generally require higher levels of immunosuppression. In addition, the donors are predisposed to aspiration and/or ventilator-associated pneumonias.\textsuperscript{21} Moreover, the allograft has direct exposure to microbes in the inspired air, the cough reflex is impaired because of graft denervation, there is abnormal mucociliary clearance, and lymphatic drainage is compromised during the procedure. Other potential complications, such as anastomotic strictures and infections of the native lung in single-lung recipients, may further increase the risk.

Bacterial Infections

Bacterial pneumonias are frequent complications after lung transplant.\textsuperscript{20,21} Late-onset bacterial pneumonia can be associated with BOS and is frequently the precipitating event leading to mortality.\textsuperscript{22} The underlying primary disease may play a role, especially in cystic fibrosis recipients who have a higher propensity for upper airway colonization and infection with Pseudomonas aeruginosa. Atypical bacterial infection such as Chlamydia pneumonia can also be seen in lung transplant recipients. Resistant and nosocomial pathogens, especially Staphylococcus and Pseudomonas, are prevalent because of frequent antibiotic use and hospitalizations. These organisms should therefore be considered in the differential diagnosis for any infectious episode.

Mycobacterial Infections

Infection with Mycobacterium tuberculosis may occur because of reactivation of a focus in the native lung or by transmission via the allograft. Colonization with nontuberculous mycobacteria occurs fairly frequently, with infections being reported occasionally.\textsuperscript{23,24}

Viral Infections

Cytomegalovirus (CMV) is one of the most important pathogens after lung transplant. All seropositive recipients are at risk, whereas seronegative recipients transplanted with a seropositive donor lung are at the highest risk of developing CMV infection and disease after lung transplant. The spectrum of involvement is defined as CMV infection (isolation of the virus in BAL or blood by culture, antigenemia, or polymerase chain reaction), CMV syndrome (viremia in conjunction with fever, leucopenia, or thrombocytopenia), or CMV disease (histologic evidence of viral cytopathic changes).

CMV may also provoke alterations of the immune system. This, in turn, may be associated with an increased risk of other opportunistic infections and a heightened predisposition for both acute and chronic rejection, possibly through increased antigen presentation.\textsuperscript{25}

Other human herpes viruses, including herpes simplex virus and varicella zoster virus, can rarely be seen. Epstein-Barr virus (EBV) is strongly associated with posttransplant lymphoproliferative disease (PTLD), which has an incidence of 1% to 20%. PTLD is a heterogeneous group of lymphoproliferative disorders, ranging from reactive polyclonal hyperplasias to aggressive non-Hodgkin’s lymphomas. PTLD may result from a decreased EBV-specific T-cell immune response induced by immunosuppression and is seen
ing these forms of aspergillosis. Along with other rare fungi such as Zygomycetes, Scedosporium, and Fusarium species, these organisms can be challenging to diagnose and treat. Early recognition and treatment is essential as the mortality rate for invasive fungal infections can be >80%.

Prophylactic and Preemptive Strategies for Reducing Infectious Complications

Primary immunization in the pretransplant period should be undertaken for influenza, 2009 influenza A(H1N1), Streptococcus pneumonia, tetanus, and hepatitis B. Live vaccines should be avoided after transplant. Routine postsurgical broad-spectrum antibiotic prophylaxis targeting the cultures from the donor lungs or known positive recipient cultures is commonly undertaken.

CMV prophylaxis in the form of IV ganciclovir and oral valganciclovir is administered routinely to at-risk patients for anywhere from 6 weeks to 12 months after transplant. In the past few years, oral valganciclovir-based regimens have shown greater efficacy against CMV infection and disease in solid organ transplant recipients.30-34 Recent data have shown that a 12-month prophylactic regimen is superior to shorter-duration regimens.30,31,34,35 Routine surveillance with serial CMV antigenemia testing and CMV DNA polymerase chain reaction is employed by most lung transplant programs.

Prophylaxis with sulfamethoxazole and trimethoprim is effective for the prevention of Pneumocystis pneumonia, with additional antimicrobial effects against Toxoplasma gondii, Nocardia, and Listeria species. Antifungal prophylaxis in the form of aerosolized Amphotericin B in the immediate postoperative period and itraconazole or voriconazole for 1 to 12 months are commonly employed.

Acute Cellular Rejection

Acute cellular rejection (ACR) can be seen at any time after the first week and is commonly seen in the first year posttransplant. Patients may present with cough, dyspnea, hypoxia, fever, rales on auscultation, decline in spirometry, or radiographic infiltrates.36 Findings of ground-glass opacities, septal thickening, and pleural effusions on CT scans suggest acute rejection; however, they have sensitivity as low as 35% and limited discriminatory value in excluding other processes.37 Because the clinical symptoms and signs are nonspecific, bronchoscopy with transbronchial biopsy and BAL are commonly employed. ACR tends to be a patchy process, and therefore a minimum of five alveolated biopsy specimens is recommended to

Fungal Infections

Fungal infections occur in 15% to 35% of lung transplant recipients, with Aspergillus and Candida species responsible for >80% of these cases.28 Aspergillus can result in a spectrum of manifestations, including colonization, infections of the bronchial anastomosis and tracheobronchial tree, invasive pneumonias, and disseminated disease.29 Chest CT scan, bronchoscopy, and the Aspergillus galactomannan assay may be helpful in diagnosing and differentiat-

**Figure 1.** Primary graft dysfunction (PGD) after lung transplant. A, Preoperative chest radiograph of a 55-year-old woman with idiopathic pulmonary fibrosis. B, Grade 3 PGD 6 h after right lung transplant. C, Improvement after 5 days on extracorporeal membrane oxygenation. D, Complete resolution of PGD 2 weeks after transplant.
provide adequate sensitivity.\textsuperscript{38} The diagnosis of ACR relies on the histologic identification of perivascular lymphocytic infiltrates (Fig 2). The ISHLT grading system for lung allograft rejection was revised in 2007 and is summarized in Table 1.

Surveillance biopsies in the first 6 months to 1 year after transplant are commonly employed to diagnose asymptomatic ACR, which may be found in a relatively high percentage (6.1%-39\%) of patients.\textsuperscript{39-42} Various cytokine surrogate markers for ACR from BAL analysis have been studied; however, neither these nor BAL cellular composition have displayed adequate accuracy in discriminating rejection from infection.

The diagnosis and empiric treatment of ACR based solely on clinical signs or symptoms is suboptimal, and histopathologic analysis to diagnose and grade ACR is always encouraged. However, under certain circumstances, biopsies may be contraindicated or limited by procedure-related bleeding. In such scenarios, in the context of a high clinical index of suspicion and a BAL that does not show evidence of infection, an alternate approach might be to treat empirically with a bolus dose of solumedrol. If there is an associated clinical response, then a presumptive clinical diagnosis of ACR is reasonable and therapy can be continued. The treatment of acute allograft rejection usually consists of pulsed IV steroids, typically 500 mg to 1,000 mg of methylprednisolone, administered daily for three doses followed by an oral prednisone taper.\textsuperscript{43}

Treatment of recalcitrant or recurrent rejection is more challenging. Repeating the pulsed steroids, altering the baseline immunosuppressive regimen, such as switching calcineurin inhibitors, or substituting azathioprine with mycophenolate mofetil represent some of the options. More aggressive therapy includes the use of cytolytic agents, such as polyclonal antithymocyte globulin or an anti-IL-2 receptor antagonist.

**Chronic Lung Allograft Rejection**

Chronic rejection is the leading cause of morbidity and late mortality after lung or heart-lung transplant.\textsuperscript{1} It is manifested pathologically as obliterative bronchiolitis (OB) (Fig 3) or clinically as BOS.\textsuperscript{44} OB is an inflammatory/fibrotic process that affects small airways or bronchioles.\textsuperscript{39} Because of the patchy nature of OB, the diagnosis is often missed by transbronchial lung biopsies. Documenting the histologic presence of OB is difficult, so the physiologic correlate of BOS has been established.\textsuperscript{45} The diagnosis of BOS is defined by an irreversible decline in the FEV\textsubscript{1} after excluding alternative causes of allograft dysfunction, such as anastomotic complications, infection, ACR, heart failure, and progression or recurrence of the native disease.\textsuperscript{45} The BOS classification system is shown in Table 2.

### Table 1—Pathologic Grading of Lung Rejection

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade</th>
<th>Meaning</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Acute rejection</td>
<td>0</td>
<td>None</td>
<td>Normal lung parenchyma</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Minimal</td>
<td>Inconspicuous mononuclear perivascular infiltrates</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Mild</td>
<td>More frequent perivascular infiltrates</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Moderate</td>
<td>Dense perivascular infiltrates, extension into interstitial space, can include endothelialitis</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Severe</td>
<td>Diffuse perivascular, interstitial, and air-space infiltrates with lung injury</td>
</tr>
<tr>
<td>B: Airway inflammation</td>
<td>0</td>
<td>None</td>
<td>No evidence of bronchiolar inflammation</td>
</tr>
<tr>
<td></td>
<td>1R</td>
<td>Low grade</td>
<td>Infrequent or single-layer mononuclear cells in bronchiolar submucosa</td>
</tr>
<tr>
<td></td>
<td>2R</td>
<td>High grade</td>
<td>Larger infiltrates of lymphocytes in bronchiolar submucosa</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>Ungradable</td>
<td>No bronchiolar tissue available</td>
</tr>
<tr>
<td>C: Chronic airway rejection</td>
<td>0</td>
<td>Absent</td>
<td>No obliterative bronchiolitis</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Present</td>
<td>If present, describes intraluminal airway obliteration with fibrous connective tissue</td>
</tr>
</tbody>
</table>

ISHLT = International Society for Heart and Lung Transplantation. Modified from the revised ISHLT guidelines for the nomenclature in the diagnosis of acute rejection.\textsuperscript{38}
BOS since even minimal ACR seems to be a predisposing risk factor. BAL neutrophilia is characteristic of BOS, and a combined neutrophilia and lymphocytosis without evidence of infection suggests BOS. However, BAL cell counts, cytokine levels, and other protein alterations lack sufficient sensitivity or specificity to be helpful in the diagnosis. CT scans can show evidence of air trapping with hyperlucency, a mosaic pattern of attenuation, thickened septal lines, and bronchiectasis.

The prevention and treatment of BOS have been largely unsuccessful. Augmentation of immunosuppression within the therapeutic classes is commonly undertaken. The diverse nature of the strategies employed for BOS attests to the lack of proven effective therapies and underscores this as a large unmet need in the field of lung transplantation. The various therapies reported in nonrandomized studies can be broadly categorized into trials of (1) cytolytic therapy, (2) switch therapy (azathioprine to mycophenolate mofetil; cyclosporine to tacrolimus), (3) add-on therapy (sirolimus, methotrexate, cyclophosphamide, inhaled corticosteroids, inhaled cyclosporine), and (4) ancillary immunomodulation, including macrolide therapy, total lymphoid irradiation, and extracorporeal photopheresis.

Macrolides, specifically azithromycin and more recently clarithromycin, have been used for the treatment of BOS, with numerous reports attesting to the potential recovery of lung function in some patients. It appears that those patients with increased neutrophils (>15%) on BAL are more likely to respond to azithromycin and it has been proposed recently that such patients be categorized as a distinct entity, termed “neutrophilic reversible allograft dysfunction.” It does appear likely that there are other forms of chronic lung allograft dysfunction that are not fully captured by the current BOS definition, and extricating patients with neutrophilic reversible allograft dysfunction might be the first step in providing a broader categorization.

Aerosolized cyclosporine has shown potential efficacy in the prevention of BOS in a single-center, randomized, placebo-controlled trial and is currently being subjected to further study through a multicenter, placebo-controlled trial.

### Table 2—BOS Classification System

<table>
<thead>
<tr>
<th>BOS</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>FEF&lt;sub&gt;25%-75%&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;90% of baseline</td>
<td>&gt;75% of baseline</td>
</tr>
<tr>
<td>0 p</td>
<td>81%-90% of baseline</td>
<td>≤75% of baseline</td>
</tr>
<tr>
<td>1</td>
<td>66%-80% of baseline</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>51%-65% of baseline</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>≤50% of baseline</td>
<td></td>
</tr>
</tbody>
</table>

BOS = bronchiolitis obliterans syndrome; BOS 0 p = potential BOS; FEF<sub>25%-75%</sub> = forced expiratory flow, midexpiratory phase. See Table 1 for expansion of the other abbreviation. Modified from the ISHLT guidelines.

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Data from the ISHLT registry attest to 28% and 74% of patients developing BOS by 2.5 years and 10 years, respectively. The course and loss of lung function may be insidious, over months to years, or abrupt, with a significant decline in lung function in a few weeks. BOS accounts for <5% of deaths within the first year after lung transplant but is responsible for about one-quarter of deaths after the first year. A further ~20% of patients die of graft failure, and, therefore, almost one-half of the patients who succumb beyond the first year will do so from some form of chronic allograft dysfunction. Respiratory infections may play a role in the onset and progression of BOS, with many patients subsequently colonized or infected with various organisms, including *Pseudomonas aeruginosa* and *Aspergillus*. A further ~20% of patients succumb from non-CMV infections; how many of these are in the context of BOS remains unknown.

The pathogenesis of BOS is complex and involves both alloimmune and nonalloimmune factors, alone and in combination. Alloimmune factors, such as ACR and lymphocytic bronchiolitis, are known to be associated with BOS. Alloimmune-independent factors such as PGD, allograft infections (especially CMV), airway ischemia, and gastroesophageal reflux might all foster an inflammatory milieu that initiates an alloimmune response. Studies have shown that ACR and lymphocytic bronchiolitis are the most important risk factors for BOS. Additional risk factors include CMV and non-CMV respiratory infections, injury to the allograft, human leukocyte antigen mismatching, and organizing pneumonia.

Strategies to detect early ACR with surveillance transbronchial biopsies may play a role in preventing
LARGE-AIRWAY COMPLICATIONS

A number of factors predispose to large-airway complications posttransplant. These include airway ischemia due to sacrifice of the bronchial circulation, airway colonization and infection, and possibly airway-targeted alloimmunity.

Bronchial Stenosis

Bronchial stenosis is the most common airway complication and is usually seen within 2 to 9 months after transplant, with an incidence of between 1.6% and 32%. It is mostly seen at the surgical anastomosis but on rare occasions can occur distally. The latter type can be progressive and severe, resulting in "vanishing airway syndrome." Bronchial stenosis may be asymptomatic or may present with declining expiratory flows, dyspnea, cough, or postobstructive pneumonia. Flexible bronchoscopy remains the gold standard for diagnosis. Several endoscopic techniques, including balloon bronchoplasty, cryotherapy, laser, and stent placement, can be used, with varying success. Immediate improvement in symptoms and flows in 90% of cases and long-term success in 50% of patients have been described.

Bronchial Necrosis and Dehiscence

Bronchial necrosis and dehiscence is a rare complication with an incidence of between 1% and 10%. Partial dehiscence can be managed with temporary placement of self-expanding metallic stents, which then promote granulation tissue and serves as a scaffold for healing. Complete dehiscence is fortunately rare (1%) as it is associated with a high mortality, which is related to sepsis.

Exophytic Granulation Tissue

Exophytic granulation tissue can cause significant airway obstruction in up to 20% of patients. Concurrent infection with Aspergillus makes it refractory to therapy and increases its morbidity. Debridement by cryotherapy, laser vaporization, or Argon plasma coagulation can be effective.

Tracheobronchomalacia

Tracheobronchomalacia is usually seen within 4 months after transplant. Patients typically present with dyspnea, cough, obstructive defect on spirometry, and recurrent infections. Bronchoscopy remains the gold standard for diagnosis and shows dynamic airway collapse (Fig 4). Treatment remains challenging and, in cases of severe symptoms, airway stenting may be required.

Thromboembolism

Thromboembolic complications tend to occur at a high rate (8.6%) in lung transplant recipients. Pulmonary embolism may occur at any stage after transplant from preexisting or transplant-related risk factors. Patients may be predisposed to thromboembolic events related to their underlying primary condition, such as the various connective tissue disorders. It is also possible that the transplant process may result in a hypercoagulable state through a systemic
Recent Advances in Chest Medicine

Recurrence of Primary Disease

Certain diseases, such as sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis, may recur in the allograft. Noncaseating granulomas have been reported in up to two-thirds of sarcoidosis recipients on routine transbronchial biopsies. These are usually a histologic curiosity and rarely manifest clinically, although clinically significant recurrence and pulmonary nodules due to sarcoidosis have been reported posttransplant.

Native Lung Complications

In the case of single-lung recipients, the native lung can be the source of significant pulmonary complications and should not be overlooked in the serial evaluation of these patients. Complications can include neoplasms, infections, pneumothoraces, and native lung herniation across the midline from progressive hyperinflation in the case of COPD single-lung recipients.26

Evaluation of Lung Transplant Recipients With Pulmonary Symptoms

The diagnostic algorithm for pulmonary symptoms in lung transplant recipients includes the consideration of additional nuances. Specifically, the acuity of onset of symptoms and time of occurrence posttransplant are important in honing in on the diagnostic

Pleural Effusions

Pleural effusions occur commonly in the immediate posttransplant period. As a consequence of the transplant procedure, the pulmonary lymphatics are severed, which reduces the ability to clear any fluid from the pleural space. Ongoing effusion might prolong the need for chest tube drainage postoperatively, but usually not beyond the first week or two. If the thoracic duct is severed, as can occur in patients with extensive mediastinal adhesions, then there is a risk of chylothorax, which should be considered for any persistent effusion. After the immediate posttransplant period, the occurrence of pleural effusions is usually in the context of other causes such as empyema, or as a manifestation of a parapneumonic process, heart failure, pulmonary embolism, acute rejection, or trapped lung.

Inflammatory response or for mechanical reasons related to central lines. A high index of suspicion should exist in patients who present with shortness of breath associated with hypoxemia or exercise desaturation, especially if there is no change in their spirometry and no evidence of parenchymal infiltrates. The diagnosis is usually obtained via CT scan angiography. In cases where this is contraindicated by impaired renal function, a ventilation-perfusion scan may be helpful. The treatment is generally the same as for any patient with thromboembolism, although there may be a heightened risk of hemothorax in the early posttransplant period.

Figure 6. Algorithm and diagnostic considerations for the evaluation of pulmonary complications after lung transplant. AFB = acid fast bacilli; CHF = congestive heart failure; CMV Ag = cytomegalovirus antigenemia; CXR = chest radiograph; echo = echocardiography; GERD = gastroesophageal reflux disease; ID = infectious disease; PCP = Pneumocystis carinii pneumonia; PCR = polymerase chain reaction; PH = pulmonary hypertension; RHC = right-sided heart catheterization; TBBx = transbronchial biopsies. See Figure 5 legend for expansion of other abbreviations.
possibilities. A schematic representation of the time course of major pulmonary complications is shown in Figure 5, with the time posttransplant represented on the x axis, the various complications on the y axis, and the relative incidence of the complication depicted by the vertical height. Testing to be considered in any patient presenting with pulmonary symptoms is shown in Figure 6. Not all tests need be performed in every patient and the need for each of these should be dictated by their clinical presentation.

CONCLUSIONS

Although the long-term survival of lung transplant recipients has improved, pulmonary complications continue to plague their posttransplant course and remain a major cause of morbidity and mortality. As more of these patients are comanaged or discharged to the care of their community pulmonologists, a better understanding of the spectrum and impact of these complications, a heightened awareness, and preemptive management may favorably impact the outcomes of this complicated group of patients.

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