Chronic Rejection This complication is the main impediment to long-term survival and is the source of substantial morbidity because of its impact on lung function and quality of life. Clinically, chronic rejection is characterized physiologically by airflow limitation and pathologically by bronchiolitis obliterans; the process is designated *bronchiolitis obliterans syndrome* (BOS). Transbronchial biopsies are relatively insensitive for detecting bronchiolitis obliterans, and pathologic confirmation is not required for diagnosis. Thus, after other causes of graft dysfunction have been excluded, the diagnosis of BOS is based primarily on a sustained decrement (≥20%) in forced expiratory volume in 1 s (FEV_1), although smaller declines in FEV_1 (≥10%) or in midexpiratory flow rate ($FEF_{25–75\%}$) may presage BOS. Spirometric criteria for diagnosis and staging of BOS have been standardized.

The prevalence of BOS approaches 50% by 5 years after transplantation. Antecedent ACR is the main risk factor, but PGD, CMV pneumonitis, other community-acquired respiratory viral infections, and gastroesophageal reflux have been implicated as well. BOS can present acutely and imitate infectious bronchitis, or it can manifest as an insidious decline in lung function. The chest radiograph is typically unchanged; CT may reveal mosaic perfusion, air trapping, ground-glass opacities, or bronchiolectasis. Bronchoscopy is indicated to rule out other processes, but transbronchial biopsies identify bronchiolitis obliterans in a minority of cases.

BOS usually is treated with augmented immunosuppression, but there is no consensus about therapy. Strategies include changes in the maintenance drug regimen, including the addition of azithromycin, antilymphocyte globulin, photopheresis, and total lymphoid irradiation. Although therapy may stabilize lung function, the overall results of treatment have been disappointing; the median survival period after onset has been ~3–4 years. Retransplantation is a consideration if clinical circumstances and other comorbidities are not prohibitive, but survival rates have been inferior to those with primary transplantation.

Humoral Rejection Consensus on the role of antibody-mediated rejection is still evolving. Hyperacute rejection is caused by preformed HLA antibodies in the recipient, but it is minimized by pretransplantation antibody screening coupled with virtual or direct cross-matching with any potential donor. Donor-specific HLA antibodies develop after transplantation in up to 50% of recipients, and their presence has been associated with an increased risk of both ACR and BOS and with poorer overall survival. However, the mechanisms by which these antibodies could contribute to ACR or BOS or could otherwise be detrimental have not been unraveled. Formal criteria for antibody-mediated rejection have been defined for renal transplantation, but few cases in lung transplantation fulfill these criteria. Nonetheless, episodes of acute lung allograft dysfunction occasionally have been attributed directly to antibody-mediated injury. If treatment is indicated, potential therapies include plasmapheresis and administration of IV immune globulin, rituximab, bortezomib, or eculizumab.

Infection The lung allograft is especially susceptible to infection, which has been one of the leading causes of death in recipients. In addition to a blunted immune response from immunosuppressive drugs, other normal defenses are compromised: the cough reflex is diminished, and mucociliary clearance is impaired in the transplanted lung. The spectrum of infections includes both opportunistic and non-opportunistic pathogens.

Bacterial bronchitis or pneumonia can occur at any time but is very common in the perioperative period. Later, bronchitis occurs frequently in recipients with BOS, and *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* is often the culprit.

CMV is the most common cause of viral infection. Although gastroenteritis, colitis, and hepatitis can occur, CMV viremia and CMV pneumonia are the main illnesses. Most episodes occur in the first 6 months, and treatment with ganciclovir is effective unless resistance develops. Other community-acquired viruses, such as influenza, parainfluenza, and respiratory syncytial viruses, also contribute to respiratory complications. The most problematic fungal infections are caused by *Aspergillus* species. The spectrum encompasses simple pulmonary colonization, tracheobronchitis, invasive pulmonary aspergillosis, and disseminated aspergillosis, and the clinical scenario dictates treatment.

Other Complications Other potential complications are listed in Table 320e-3. Many of them are related to side effects or toxicities of immunosuppressive drugs. Management of these general medical problems is guided by standard practices, but the complex milieu of transplantation requires close collaboration and good communication among health care providers.