Critical Care Perspective on Immunotherapy in Lung Transplantation

Jennifer L. Taylor, MD
Scott M. Palmer, MD, MHS

Lung transplantation is now a viable therapeutic option in the care of patients with advanced pulmonary parenchymal or pulmonary vascular disease. Lung transplantation, however, with chronic posttransplant immunosuppression, creates a uniquely vulnerable population of patients likely to experience significant life-threatening complications requiring intensive care. The introduction of several novel immunosuppressive agents, such as sirolimus and mycophenolate mofetil, in conjunction with more established agents such as cyclosporine and tacrolimus, has greatly increased treatment options for lung transplant recipients and likely contributed to improved short-term transplant outcomes. Modern transplant immunosuppression, however, is associated with a host of complications such as opportunistic infections, renal failure, and thrombotic thrombocytopenic purpura. The main focus of this review is to provide a comprehensive summary of modern immunotherapy in lung transplantation and to increase awareness of the serious and potentially life-threatening complications of these medications.

Key words: *lung transplant, immunosuppressive agents, complications, intensive care*

Lung transplantation is an acceptable therapeutic option for patients with a variety of advanced pulmonary or pulmonary vascular diseases. According to recent data from the International Society for Heart and Lung Transplantation (ISHLT) registry, more than 19 000 lung transplant operations have been performed since the introduction of this procedure, and roughly 1700 new transplant operations are performed each year [1].

Posttransplant obliterative bronchiolitis, likely a manifestation of chronic allograft rejection, is the major factor limiting long-term survival after lung transplantation. Currently 5-year survival is less than 50% in lung transplant recipients. However, short-term survival after lung organ transplantation has improved significantly from the 1980s to the present era, with 1-year survival currently at 76% for lung transplant recipients according to International Registry data and approaching 90% at several selected large experienced centers (Fig 1) [1-4]. Improvements in early postoperative critical care, aggressive use of antimicrobial prophylaxis, and an increasing armamentarium of immunosuppressive therapies have made this possible.

Although posttransplant immunosuppression is critical to the survival of the graft and the patient, these medications also contribute to significant morbidity and mortality in the lung transplant population. Serious complications that occur as a result of chronic immune suppression include opportunistic infections, renal failure, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS), and posttransplant lymphoproliferative disorder (PTLD), all of which may lead to the requirement for intensive care. In this review, we focus on lung transplant immunotherapy and highlight serious potentially life-treating complications of these medications.

Historical Perspective on Lung Transplantation

In 1963, Hardy and colleagues performed the first human pulmonary allotransplantation. The patient suffered from squamous cell lung cancer occluding the left mainstem bronchus and underwent left single lung transplantation. He survived 18 days, highlighting the technical feasibility of pulmonary transplantation in humans as well as the high price one pays for immunosuppression, as he succumbed to pancytopenia, pneumonia, and renal failure as a result of total body irradiation and high-dose azathioprine [5]. From 1963 to 1986, more than

From Duke University Medical Center, Durham, North Carolina.

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Address correspondence to Scott M. Palmer, MD, MHS, DUMC 3876, Room 128 Bell Bldg, Duke University Medical Center, Durham, NC 27710, or e-mail: Palme002@mc.duke.edu.

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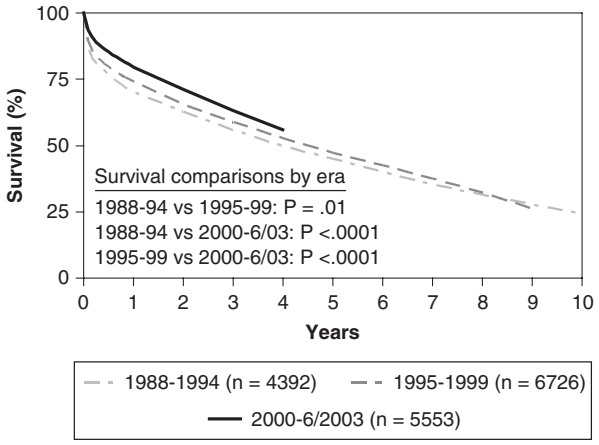

Fig 1. Survival after lung transplant by era. Significant improvements in early posttransplant survival are evident in recent years compared with earlier eras. Courtesy of Elsevier.

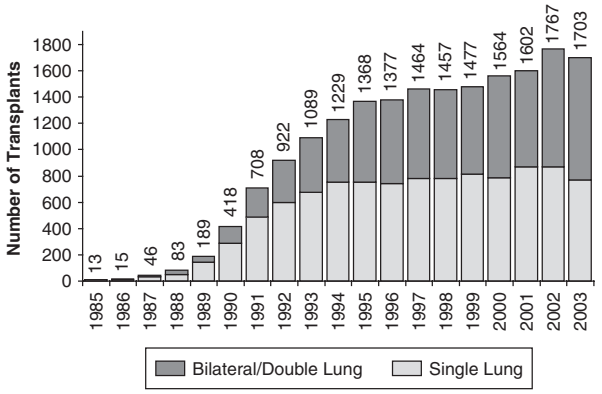

Fig 2. Worldwide growth of lung transplantation over the past 20 years. Courtesy of Elsevier.

40 attempts at human lung transplantation were used without long-term clinical success [5-7].

In the early 1980s, cyclosporine became available for use in solid organ transplantation and was quickly recognized as superior to existing agents. Cyclosporine, the first calcineurin inhibitor, is a lipophilic peptide derived from the fungus *Trichoderma polysporin*. Cyclosporine binds to the cellular protein cyclophilin and inactivates calcineurin [8]. Calcineurin inhibition prevents interleukin (IL)-2 gene transcription, thus inhibiting IL-2 production, and subsequent T-cell activation and T-cell-mediated immune responses. In heart transplantation, cyclosporine, in combination with prednisone, was shown to decrease the incidence of rejection and the amount of infection when compared with high-dose azathioprine and prednisone [9, 10]

Thus, the introduction of cyclosporine overcame many of the problems with early, rejection-related graft loss allowing the widespread growth of solid organ transplantation in the 1980s, including the rapid and exponential growth of lung transplant from the mid-1980s to the mid-1990s with current transplant volumes plateaued because of the limits of donor organs (Fig 2).

Current Lung Transplant Immunosuppression

In 1986, the Toronto group first described successful long-term outcomes in 2 unilateral lung transplant recipients with idiopathic pulmonary fibrosis using a regimen of cyclosporine and azathioprine [7]. The use of the cyclosporine/azathioprine combination as well as improvements in surgical technique likely contributed to the successful application of transplantation in these patients. Subsequent reports indicated that successful lung or heart–lung transplantation generally used a triple-drug regimen of cyclosporine, azathioprine, and prednisone. Although prospective studies comparing 2- with 3-drug combinations were not replicated in lung transplant recipients, the successful application of organ transplant to lung allografts using a cyclosporine-based triple-drug regimen led to the widespread acceptance of this combination as standard therapy [11]. Within the past few years, however, a variety of new agents have been introduced for use in transplantation, including a second calcineurin inhibitor, tacrolimus; a synergistic IL-2 inhibitor, sirolimus; and a potent alternative agent to azathioprine that inhibits B- and T-cell lymphocyte proliferation, mycophenolate mofetil. Current immunotherapy options with lung transplant are summarized in Table 1. Of note, however, none of these drugs are approved for use in lung transplantation because trials of novel immunotherapeutic agents have been focused almost exclusively on the kidney transplant population.

According to the Registry of the ISHLT, in 2002, more than 95% of patients receive a calcineurin inhibitor, 80% receive a cell-cycle inhibitor, and more than 95% receive steroids [12]. Registry data suggest that tacrolimus plus mycophenolate mofetil (MMF) is the most common combination of immunosuppression used in conjunction with prednisone in lung transplant recipients at both 1 year and 5 years posttransplant; the 4 most common regimens reported to the ISHLT used at 1 year posttransplant in lung transplantation are shown in Figure 3 [1].

Table 1. Commonly Used Immunosuppressive Agents and Their Mechanism of Action and Acute Side Effects

Generic Name (Trade)	Mechanism of Action	Serious/Acute Toxicities
Cyclosporin (Neoral) (alternatives: Gengraf, SanCya, Sandimmune)	T-lymphocyte inhibitor via suppressed IL-2 production	Nephrotoxicity, hypertension, tremors, confusion, seizures, hyperkalemia, hemolytic uremic syndrome
Tacrolimus (Prograf)	T-lymphocyte inhibitor via suppressed IL-2 production	Nephrotoxicity, hypertension, tremors, confusion, seizures, hyperkalemia, hemolytic uremic syndrome
Azathioprine (Imuran)	Inhibits lymphocyte proliferation via inhibition of nucleotide synthesis	Bone marrow suppression, hepatotoxicity
Sirolimus (Rapamune)	Blocks IL-2-mediated T-cell activation	Hyperlipidemia, bone marrow suppression, hypertension, bronchiolitis obliterans organizing pneumonia
Mycophenolate (Cellcept)	Inhibits B- and T-lymphocyte proliferation	Nephrotoxicity, hypotension or hypertension, leucopenia, thrombocytopenia, fever, hepatotoxicity, hypokalemia or hyperkalemia, tremor
Prednisone (Deltasone)	Removes lymphocytes from intravascular space, inhibits lymphokine-mediated amplification of macrophages and lymphocytes	Hyperglycemia, hypokalemia, fluid retention, impaired wound healing, psychosis, promoting gastric ulceration
Methylprednisolone (Solu-medrol)	Removes lymphocytes from intravascular space, inhibits lymphokine-mediated amplification of macrophages and lymphocytes	Hyperglycemia, hypokalemia, fluid retention, impaired wound healing, psychosis, promoting gastric ulceration
Basiliximab (Simulect)	IL-2 receptor antagonist (chimeric monoclonal antibody)	Anaphylaxis, vomiting, fever, hyperglycemia, edema, bronchospasm, tachycardia, hypotension or hypertension, renal dysfunction
Daclizumab (Zenapax)	IL-2 receptor antagonist (human monoclonal antibody)	Anaphylaxis, vomiting, fever, hyperglycemia, edema, bronchospasm, tachycardia, hypotension or hypertension, renal dysfunction
Lymphocyte immune globulin-antithymocyte globulin (ATGAM, RATG)	Reduces number and alters function of circulating T-lymphocytes (equine or rabbit polyclonal antibody)	Hypersensitivity, thrombocytopenia, renal dysfunction, hemolysis, serum sickness, pulmonary edema, toxic epidermal necrolysis, seizures
Muromonab-CD3 (OKT3)	Inhibits T-cell proliferation and differentiation (murine monoclonal antibody)	Hypersensitivity, "cytokine release syndrome," renal dysfunction, encephalopathy, seizures, meningitis

IL = interleukin.

Although large, well-designed, randomized prospective studies are lacking to guide the selection of initial immunosuppression after lung transplantation, several studies suggest that tacrolimus might offer some clinical advantages over cyclosporine as the primary calcineurin inhibitor [13-15]. Keenan et al [13] studied the use of tacrolimus versus cyclosporine in a prospective, randomized, nonblinded study of 133 lung transplant patients. A nonsignificant reduction in acute rejection was observed in the tacrolimus-treated patients, and there appeared to be a lower rate of obliterative bronchiolitis in patients treated with tacrolimus. The overall incidence of infection was similar between the 2 groups, although slightly increased fungal infections were observed with tacrolimus. This study, however, was conducted without the use of any early posttransplant antifungal prophylaxis [13]. A cyclosporine- versus tacrolimus-based regimen after lung transplant regimen was also examined by Zuckermann et al [15]. As in the study from Pittsburgh, there was no significant difference in incidence of acute rejection or infection between the 2 groups of patients, although a trend toward less rejection was observed with tacrolimus. Significantly more patients in the cyclosporine group also developed hypertension in this study [15].

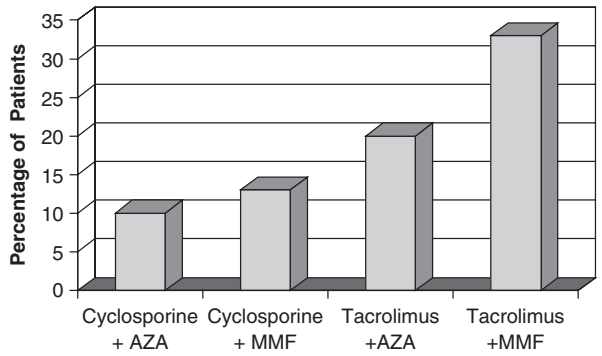

Fig 3. Immunosuppressive combinations at 1 year after lung transplant, as reported to the International Society for Heart and Lung Transplantation Registry [1]. AZA, azathioprine; MMF, mycophenolate mofetil.

Finally, in a retrospective multivariate analysis, researchers at the University of Pittsburgh examined risk factors for death among 239 lung transplant recipients. Cyclosporine versus a tacrolimus-based immunosuppression regimen was a risk factor for late death and late infection [14]. Thus, limited evidence suggests that tacrolimus offers some clinical advantages to cyclosporine. Until larger multicenter studies are completed, both calcineurin inhibitors should be considered relatively equivalent.

The use of MMF versus azathioprine is also controversial, but both appear equivalent in lung transplantation. Two small nonrandomized studies suggested a decreased rate of rejection with MMF [16, 17]. However, a multicenter prospective randomized trial of lung transplant patients treated with cyclosporine, prednisone, and either azathioprine or MMF showed no difference in rates of rejection at 6 months in either group. Furthermore, more patients required dose reduction or discontinuation of therapy in the MMF group, often as a result of gastrointestinal complaints [18]. These results were also recently confirmed in a larger European randomized trial, which found no difference in the rates of acute rejection or incidence of bronchiolitis obliterans syndrome (BOS) at 1 or 3 years with MMF versus azathioprine regimen [19].

Finally, there is considerable interest in using sirolimus in conjunction with either tacrolimus or cyclosporine after lung transplant given its complementary mechanisms of action to the calcineurin inhibitors (sirolimus acts to inhibit signaling downstream of the IL-2 receptor). However, early experience with this drug and its potent antifibrotic effects demonstrated that sirolimus should be avoided in the early posttransplant period. Researchers at the University of Minnesota undertook a prospective trial in lung transplant patients receiving tacrolimus, prednisone, and sirolimus. The trial was terminated after 4 of 15 patients developed airway anastomotic dehiscence with an associated mortality rate of 75%. Retrospective analysis of patients from the same center who had received cyclosporine or tacrolimus plus MMF and prednisone confirmed an increased rate of airway dehiscence and decreased survival in patients receiving sirolimus [20]. Its role after initial healing of the bronchial anastomosis is less clear, but until further research is performed, sirolimus should only be used after failure of other agents in lung transplant patients [21].

Monoclonal or polyclonal antibody agents are frequently used at the time of transplant (a practice known as induction) to provide additional augmented immunosuppression. Basiliximab and daclizumab are humanized monoclonal antibodies specific for the IL-2 receptor, whereas the polyclonal antithymocyte globulins such as antithymocyte globulin (ATG) or rabbit antithymocyte globulin (RATG) target a host of cell surface molecules. Wain et al [22] showed a reduction in the incidence of acute rejection following muromonab-CD3 (OKT3) induction in lung transplant patients. In a study at our institution, RATG induction resulted in a statistically significant decrease in the incidence of acute rejection and a trend toward decreased incidence of BOS [23]. A retrospective report of a trial of basiliximab versus ATG induction demonstrated a reduction of 26% in the actuarial incidence of acute rejection in the basiliximab group, which also experienced fewer adverse events [24]. However, a trial that compared OKT3, ATG, and daclizumab induction for lung transplantation found no difference in rates of rejection between the 3 treatment groups [25]. More recently, researchers at the University of Pittsburgh used high-dose ATG or Campath induction to create a state of pre–lung transplant lymphoid depletion followed by minimal posttransplant immunosuppression. Patient outcomes were compared with those of lung transplant recipients who had received daclizumab induction followed by posttransplant triple-drug immunosuppression. At 6 months, survival of patients and grafts was 90% or greater in the lymphocyte-depleted patients (nonsignificant increase in survival compared with daclizumab) without a significant increase in infection rate [26]. In 2003, only 46% of patients received some form of induction therapy at the time of lung transplant, with IL-2 receptor antagonists accounting for the majority of prescriptions. Furthermore, retrospective analysis of registry data demonstrates similar survival in patients treated with or without induction regardless of which induction agent was used [1]. Although recent data for induction therapy

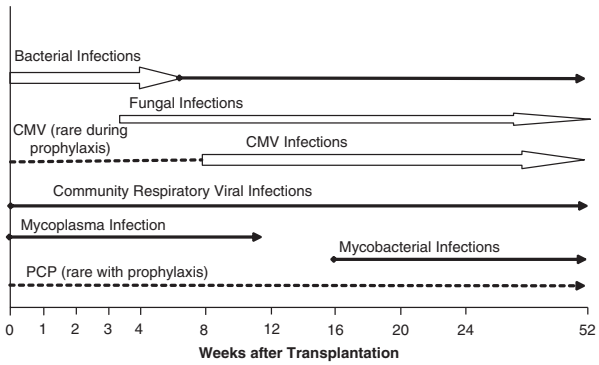

Fig 4. Timeline of infectious complications after lung transplantation with consideration of posttransplant infectious prophylaxis. Increased incidence of infection indicated by increasing thickness of lines. CMV = cytomegalovirus; PCP = *Pneumocystis carinii pneumonia*.

are promising, the optimal drug regimen and timing remain unknown.

Currently, all immunotherapy regimens appear roughly equivalent in terms of the prevention of rejection, and decisions regarding selection should be based mainly on side effect profile and efficacy in an individual patient. Ongoing large multicenter randomized trials are needed to evaluate the efficacy of the many immunosuppressive regimens and support a more evidence-based practice of lung transplantation. Given the high rates of lung rejection and many chronic complications of chronic immunosuppression, the use of a targeted approach at the time of transplant (eg, induction) should be considered worthwhile and a high priority for future clinical trials. In addition, many exciting agents are being developed that specifically target T-cell activation signals [27]. Such novel approaches might permit the development of tolerance and thus eliminate the need for many current immunotherapies and their many undesirable toxic effects.

Complications of Immunosuppression

Posttransplant Infection: Bacterial Pathogens and Sepsis

Following surgical replacement of the lungs, lung transplant recipients are immediately at high risk for infectious complications as a result of impaired pulmonary defense including diminished cough and mucociliary clearance and impaired lymphatic drainage. Carriage of organisms in the nares and sinuses of the recipient as well as organisms transmitted from the donor airways results in risk for development of infectious disease. These patient-related factors are compounded by iatrogenic suppression of patient defenses with immunotherapy, particularly if induction immunosuppression is used at the time of transplant. Thus, infection is a leading cause of morbidity and mortality immediately posttransplant and throughout the posttransplant period. Infection has a significant contribution to the 50% rate of readmission during the first year posttransplant [28]. For data gathered by ISHLT from 1992 to 2004, 33% of deaths within the first postoperative year were caused by infection [1].

The type of infection and pathogen varies by posttransplant time, net host immunosuppression, and antimicrobial prophylaxis. Bacterial infections tend to predominate in the early posttransplant period, either as nosocomial pathogens or donor-transmitted infections. *Mycoplasma* also rarely have been reported as a cause of early posttransplant wound infection [29]. Over time as a result of chronic immune suppression, the risk for opportunistic pathogens increases significantly. Fungal infections tend to occur later posttransplant, although early anastomotic infections with fungal pathogens can occur. Mycobacterial infections, particularly infection with nontuberculous mycobacteria, have been reported after lung transplant although their significance is unclear [30]. With most centers using some form of cytomegalovirus (CMV) prophylaxis, CMV infection is usually delayed until several weeks to months after transplant but remains a lifelong concern in at-risk patients. Community viral pathogens are also recognized at all time points posttransplant and should be considered in the differential of any patient presenting with symptoms suggestive of infection. Figure 4 shows a timeline of infectious complications after lung transplantation with consideration of posttransplant infection prophylaxis.

In the early posttransplant period, bacterial infections tend to predominate and cause significant mortality [31]. Most commonly, Gram-negative pathogens such as *Klebsiella*, *Haemophilus*, *Enterobacter*, and *Pseudomonas* species and Gram-positive organisms such as *Staphylococcus* cause infection. Mixed aerobic–anaerobic infections also occur [32]. In their review of 20 years of lung transplantation in Toronto, de Perrot et al [2] found that sepsis was the leading cause of death in the first 6 months posttransplant at a rate of 50% and remained a significant cause of death throughout the observation period with 35% of all transplant deaths attributable to sepsis. Trzeciak et al [33] examined emergency room visits for 352 solid organ transplant recipients over an 18-month period. Infections were the most common cause of admission (35%), with

the urinary tract and lungs being the most frequent site of infection. Of the 77 patients with documented infection, 11.7% had severe sepsis requiring intensive care unit admission. The mortality rate for severe sepsis was 11.1% [33].

The incidence and epidemiology of bloodstream infections (BSI) in the posttransplant population were determined in an analysis of our center's experience with 176 consecutive lung transplants at Duke University. Twenty-five percent of all lung transplant patients acquired a BSI, with 67% of the infections occurring during the transplant hospitalization. *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Candida* species were the most commonly isolated organisms. Survival was significantly worse in the patients with BSI than those without BSI (P = .0001); 3-year survival was 44% in patients with BSI compared with 71% in patients without BSI. Survival was worst among those patients with multiple bloodstream organisms and fungal isolates [34]. In review of BSIs following pediatric lung transplantation, Danziger-Isakov et al [35] found that the highest rate of infection occurred in the first 30 days following transplantation. As in adult transplants, the organisms isolated most commonly were *S aureus*, *P aeruginosa*, and *Candida* species. Patients who experienced early BSI had an increased risk of death in the first year of transplantation with relative risk (RR) 3.9 (95% confidence interval [CI] 1.6-9.4; P = .002) [35].

Host- and pathogen-specific risk factors for sepsis have been evaluated in cystic fibrosis (CF) patients following transplant. De Soyza and colleagues [36] examined the preoperative and postoperative courses of 85 patients with cystic fibrosis who underwent lung transplantation. Mortality rate from sepsis was 10%. Factors that did not predict outcome were gender, pretransplant C-reactive protein (CRP), forced expiratory volume in 1 second, weight, diabetic status, or infection with multiresistant *Pseudomonas* organisms. Pretransplant pyrexia and leukocytosis as well as colonization with *Burkholderia cepacia* predicted subsequent risk of postoperative death [36]. The observation of increased mortality attributable to posttransplant sepsis with *B cepacia* has been confirmed in other reports and led many centers to avoid transplantation in CF patients colonized with *B cepacia* [37, 38]. *Burkholderia cenocepacia* (genomovar 3) appears associated with the greatest risk for posttransplant complications and death [38].

The routine use of posttransplant prophylactic antibiotics appears to have contributed to improvements in early postoperative survival after lung transplantation. Most centers now use broad-spectrum antibiotics in the immediate posttransplant period [2, 31, 39]. For example, at Duke we use a regimen of ceftazidime and vancomycin to cover nosocomial and donor-acquired staphylococcal and Gram-negative organisms. If cultures are persistently negative and a patient does clinically well, these intravenous antibiotics will be changed to oral fluoroquinolone to complete 7 to 14 days of prophylaxis after surgery. Vancomycin is typically discontinued when the chest tubes are removed. In CF patients, a more complex antibiotic regimen is used to cover known pretransplant pathogens. In general, antibiotic therapy should be tailored to cover perioperative cultures from the recipient, cultures from the donor lungs, and organisms common at the transplant institution [31].

Posttransplant Infection: Opportunistic Pathogens

Cell-mediated immune suppression after lung transplant also places patients at significant risk for viral infection. CMV is the most common opportunistic infection observed after lung transplant and occurs in approximately 50% of at-risk patients (either donor or recipient serologically positive for CMV) [40]. Although direct mortality is diminished with CMV in the modern era, CMV appears to increase the risk for posttransplant chronic rejection and other concurrent infections (eg, fungus), making its prevention, early diagnosis, and treatment critical to successful long-term transplant outcomes [41]. The patients with the highest risk for CMV disease are those who are seronegative at the time of transplant and receive CMV-positive donor lungs [42, 43]. Prophylaxis of at-risk patients with intravenous ganciclovir has significantly reduced the incidence and morbidity observed in lung transplant [39, 43, 44]. Even in low risk (D–/R–) patients, CMV-negative or leukocyte-reduced blood products are used to prevent infection. As an alternative to prophylaxis, some centers use highly sensitive polymerase chain reaction (PCR)–based monitoring for CMV in the peripenial blood and initiate preemptive therapy if viremia is detected [45, 46]. Such PCR-based assays also appear useful in monitoring patients after prophylaxis is complete or in assessing the response to treatment in lung transplant recipients with CMV disease.

Disease that develops and does not respond to intravenous ganciclovir is treated with foscarnet or cidofovir, and documented resistance to ganciclovir appears to be an emerging problem in lung transplantation [43]. Herpes simplex virus (HSV) occasionally causes non-CMV viral infections [47] but is uncommon because of the suppressive effects of

Table 2. Route of Administration, Mechanism of Action, and Drug Interactions of Commonly Used Immunosuppression Therapies

Generic Name (Trade)	Route of Administration	Mechanism of Action	Important Drug Interactions
Cyclosporin (Neoral) (alternatives: Gengraf, SanCya, Sandimmune)	PO, IV	Hepatic (CYP450-3A4)	Contraindicated: Bosentan, Cisapride Increased Cya levels: azole antifungals, macrolides, calcium-channel blockers Decreased Cya levels: St. John's wort, rifampin, rifabutin, barbiturates, phenytoin Avoid other nephrotoxic agents
Tacrolimus (Prograf)	PO, IV, SL	Hepatic (CYP450-3A4)	Contraindicated: Bosentan, Cisapride Increased tacrolimus levels: azole antifungals, macrolides, calcium-channel blockers Decreased levels: St. John's wort, rifampin, rifabutin, barbiturates, phenytoin Avoid other nephrotoxic agents
Azathioprine (Imuran)	PO, IV	Hepatic (CYP450) and red blood cells	Avoid allopurinol, ACE inhibitors, mycophenolate mofetil, other agents that suppress bone marrow
Sirolimus (Rapamune)	PO	Hepatic (CYP450-3A4)	Contraindicated-Voriconazole Interactions with Azole antifungals, Bosentan, cimetidine, macrolides, calcium-channel blockers, griseofulvin, NSAIDs, rifampin, rifabutin
Mycophenolate (Cellcept)	PO, IV	Hepatic, glucuronyl transferase	Avoid antacids, bile acid binding resins, oral iron salts, which decrease levels; avoid azathioprine and other agents that suppress bone marrow
Prednisone (Deltasone) Methylprednisolone (Solu-Medrol)	PO, IM, IV	Hepatic (CYP450-3A4)	Potential for interactions with Mifepristone, growth hormone, thiazide diuretics, macrolides, quinolones, rifabutin, rifampin, sulfonylureas, warfarin
Monoclonal and polyclonal antibodies (basiliximab, daclizumab, ATGAM, RATG, OKT3)	IV	Hepatic (CYP450-3A4)	Avoid agents that suppress bone marrow while concurrently administering antibody therapy

PO = orally; IV = intravenously; CYP450 = cytochrome P450; SL = sublingual; ACE = angiotensin-converting enzyme = NSAIDs, nonsteroidal anti-inflammatory drugs; IM = intramuscularly.

ganciclovir (used for CMV prophylaxis) on HSV. In HSV-seropositive patients who are CMV negative, most centers use acyclovir prophylaxis [48].

Unfortunately, a wide range of fungal pathogens have also been described in lung transplant recipients as a result of cell-mediated defects [31, 49, 50]. Although *Candida* is the most common cause of fungal blood infection, *Aspergillus* is the most common cause of fungal pulmonary disease. Both *Aspergillus* and *Candida* can manifest as invasive anastomotic infection (shown in Fig 5). Typically, only *Aspergillus* causes pulmonary nodules and disseminated pulmonary disease. Invasive or disseminated disease attributable to *Aspergillus* causes mortality rates of up to 60% [51]. There is not universal agreement on standard fungal prophylaxis after lung transplantation, but many centers use oral azole therapy or inhaled amphotericin preparations (or some combination of both) [52]. We have had a favorable experience with aerosolized amphotericin B and have demonstrated the safety and efficacy of this approach [53, 54]. Although azoles also represent a reasonable option for prevention of fungal infection, the limited spectrum of activity of some agents (eg, fluconazole) and systemic drug interactions (eg, voriconazole) limit their widespread use [39, 55]. Table 2 lists some of the serious and contraindicated drug interaction with drugs commonly used in lung transplant immunosuppression.

Lung transplant patients also are at risk for a variety of other infections, including community-acquired viruses, tuberculous and atypical mycobacterial infections, *Pneumocystis carinii* pneumonia (PCP), and *Nocardia* species [32, 56]. Because of the link between respiratory viral infection and BOS, increasing attention is given to these community-acquired viruses. There are few effective therapies for treatment; thus, prevention of infection through patient education is the best option [57-61]. Although limited to case reports and case series,

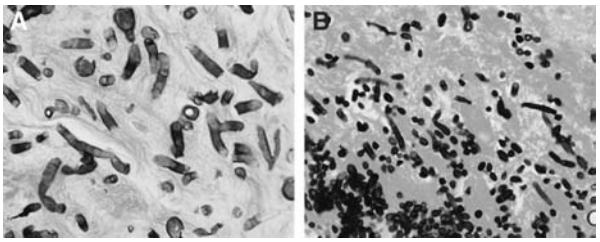

Fig 5. Endobronchial fungal infection after lung transplant. (A) True hyphae with occasional branching and septa suggestive of *Aspergillus* species are seen in necrotic bronchial wall tissue of lung transplant recipient. (B) Yeasts and occasional pseudohyphae suggestive of *Candida* species are present in devitalized bronchial wall tissue obtained from an endobronchial biopsy just distal to the transplant anastomosis.

tuberculous and nontuberculous mycobacterial infections have also been described in transplant patients. Conventional antimycobacterial therapy is generally adequate, but skin testing before lung transplant and treatment for latent disease are recommended [30, 62-67]. Fortunately, as a result of the routine use of prophylaxis against *Pneumocystis* in immunocompromised hosts with Septra or pentamidine, PCP infection in lung transplant recipients is uncommon [68]. In their retrospective review of *Nocardia* infections in 473 lung transplant recipients, however, Husain et al [56] found that trimethoprim-sulfa prophylaxis for PCP did not always prevent development of *Nocardia* infection, which can present with skin lesions, nodular lung lesions, or central nervous system disease [56, 69]. Although isolates remained sensitive to trimethoprim-sulfa, of the 10 patients who developed nocardial infection, 4 patients died. Although this organism is a rare cause of disease in lung transplant patients, because of high mortality rates, careful examination for this organism should be considered despite concurrent prophylactic trimethoprim-sulfa therapy.

Posttransplant Infection: General Approach to Workup

Lung transplant patients with infection present with fever, cough, and infiltrates on chest radiography. Thus, in general, the presentation of infection often overlaps with the signs and symptoms of rejection. Because the management of infection is quite different from that of rejection, urgent bronchoscopy with bronchoalveolar lavage and transbronchial biopsy is required to discern the specific etiology of infiltrates. As shown in Figure 6, it is often difficult to distinguish infection from rejection in a lung transplant recipient based on radiographic studies alone. In a review of the use of flexible bronchoscopy in lung transplant recipients, Chan et al [70] diagnosed infection and rejection in 58.9% and 67.4% of samples, respectively. Bronchoscopy samples must be sent to evaluate for the numerous possible etiologies of posttransplant infection. Our approach to the bronchoscopic evaluation of the transplant patient with new infiltrates is shown in Table 3. Furthermore, the approach to cover both infection and rejection is often used until additional histopathological and culture data are obtained, because lung transplant patients can deteriorate very quickly in the absence of appropriate therapy.

In summary, the cell-mediated defects caused by immunosuppression put the transplant patient at risk for development of a wide spectrum of bacterial, viral, and fungal infections. Vigilance in surveillance and prophylaxis against common infections are paramount to improving outcomes. In the transplant patient with possible infection, urgent bronchoscopy must be performed to rule out rejection and determine the etiology of infection so that appropriate therapy can be instituted as quickly as possible.

Renal Dysfunction

Renal insufficiency is a well-recognized complication of solid organ transplantation. To characterize the incidence of renal insufficiency and its related morbidity and mortality following solid organ transplant, Ojo and colleagues [71] examined database records on more than 69 000 nonrenal transplant patients. Chronic renal failure developed in 16.5% of patients and was associated with an increased risk of death (RR 4.55; $P < .001$). In addition to age, gender, hypertension, and diabetes, risk varied with the organ transplanted. The relative risk of renal failure was intermediate among lung transplant patients, highest among patients with intestinal transplant at 1.36 (CI 1.00-1.86), and lowest among patients following heart–lung transplant at 0.48 (CI 0.36-0.65) [71].

Several factors during the postoperative period put lung transplant recipients at risk for renal insufficiency including hemodynamic stability following a significant surgical procedure and use of lasix for postoperative edema [72]. These patients are also being treated with calcineurin inhibitors, which are known to cause renal vasoconstriction [73-75]. The risks are compounded by administration of medications used in the treatment of pulmonary infections including antifungals, antibiotics, and antivirals that

Table 3. Bronchoscopy in Evaluation of Posttransplant Infection

Indication	Evaluation
Bacterial infection	Gram stain, bacterial culture, AFB smear, AFB culture
Fungal infection	India ink, silver stain, KOH, fungal culture
Viral infection	Respiratory viral battery, viral culture, CMV and adenoviral culture, electron microscopy[a]
Posttransplant lymphoproliferative disease	Cytology, flow cytometry

AFB = acid fast bacilli; CMV = cytomegalovirus.
a. If highly suspicious of viral etiology.

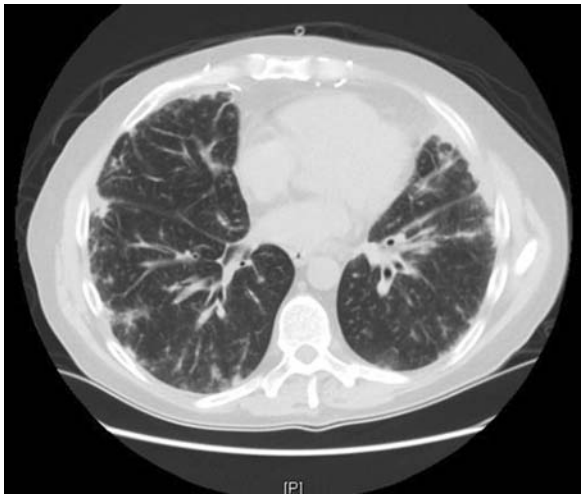

Fig 6. Infection versus rejection in the differential diagnosis of pulmonary infiltrates in a lung transplant recipient. A bilateral lung transplant recipient presented with increasing shortness of breath and a decrease in lung function. Chest computed tomography revealed scattered peripheral ground glass and nodular opacities suspicious for an atypical infection. Open lung biopsy at that time, however, demonstrated only extensive ongoing acute and chronic allograft rejection.

require renal clearance, particularly in patients with preexisting renal dysfunction. Thus, some degree of renal insufficiency is likely to occur during the immediate postoperative period.

Ishani et al [76] retrospectively studied the postoperative renal function of 219 lung transplant patients at their institutions. During the 30-day postoperative period, 16.9% of their patient population had a doubling of serum creatinine; 4.6% of patients required hemodialysis, and of those 20% later developed end-stage renal disease. Cumulative incidence of doubling of serum creatinine was 34% at 1 year, 43% at 2 years, and 53% by 5 years. The 2 risk factors found to be associated with time to doubling of serum creatinine in multivariate analysis were number of cumulative periods with diastolic hypertension and serum creatinine value at 1 month posttransplant [76].

We examined the risk of renal insufficiency and renal failure in our lung transplant population through a retrospective review of clinical records of 296 patients consecutively undergoing lung transplant at Duke University between April 1992 and December 2000. The incidence of acute renal failure (ARF), defined as doubling of baseline creatinine within 2 weeks after surgery, was 56% in our patient population, which was slightly older and had more systemic hypertension than the Ishani cohort. Of the patients who suffered ARF, 8% required hemodialysis (HD). Those patients who suffered ARF had longer duration of ventilation and hospitalization and increased mortality rate. The independent risk factors for acute renal failure requiring HD were abnormal baseline renal function (glomerular filtration rate), pulmonary diagnosis other than chronic obstructive pulmonary disease, ventilator requirement >1 day, and aminoglycoside or amphotericin use. Importantly, 1-year survival for patients who had ARF requiring HD was 21.7% versus 81.8% in those patients with ARF not requiring HD and 92.3% in those patients who did not experience ARF. Even when we controlled for covariates, ARF requiring HD was associated with a higher risk of death (hazard ratio 6.77, CI 4.00-11.44, $P < .0001$). Therefore, in the immediate postoperative period, it is important to identify those patients who are at risk of ARF, to minimize conditions and medications that will increase this risk, and to potentially exclude from transplant those patients whose creatinine clearance is less than 50 mL/min [72].

Data from the ISHLT registry show that at 1-year follow-up, 12.6% of lung transplant patients had some degree of renal dysfunction. By 5-year follow-up, this number rose to 17.6%, with 3.2% of these patients requiring chronic dialysis, demonstrating that renal dysfunction is an important cause of morbidity in lung transplant survivors at all centers around the world [28]. These data highlight a major limitation of calcineurin-based immunotherapy,

namely that almost all patients develop some degree of renal dysfunction and a small minority progress to chronic renal failure. Use of induction therapy, and the resultant opportunity to delay initiation of calcineurin inhibitors in the immediate postoperative period when renal function is at increased risk, may decrease the contribution of renal dysfunction to the morbidity and mortality of lung transplant recipients [12].

TTP-HUS

TTP-HUS is a rare syndrome characterized by microangiopathic hemolysis, thrombocytopenia, renal failure, neurologic abnormalities, and fever. Clinical distinction between the 2 syndromes may not be apparent in an individual patient. Patients with neurologic symptoms and systemic platelet aggregation are diagnosed with TTP, whereas patients who have predominant renal involvement are diagnosed with HUS. Because of the development of curative therapy, an adult patient who presents with the minimal constellation of symptoms of thrombocytopenia and microangiopathic hemolysis should be treated [77].

In the general population, the incidence of suspected TTP-HUS (patients who presented with a constellation of symptoms and for whom treatment was initiated) was estimated at 11 cases/million population per year from data in the Oklahoma TTP-HUS registry. Incidence rates for women and African Americans were higher and were believed to be related to their increased incidence of autoimmune disease. The majority of cases were idiopathic (37%); autoimmune disease and drug-associated cases each accounted for 13% of cases [78].

Among idiopathic cases, 1 risk factor for development of TTP is acquired deficiency of the enzyme that cleaves von Willebrand factor to its normal circulating size: ADAMTS13. This deficiency may lead to platelet aggregation and thus contribute to development of thrombosis [79]. Because the sensitivity and specificity of ADAMTS13 assays are variable, their use for diagnosis of TTP is still controversial, but this approach might hold great promise for the diagnosis of transplant-related TTP as well [80].

The most frequently reported drug-related cases of HUS in transplant patients are the immunosuppressive agents cyclosporine and tacrolimus [81-87]. The anti-T-cell monoclonal antibody OKT3 has been associated with an HUS-like picture exclusively in renal transplant patients [88, 89], and high-dose valganciclovir has been reported in association with an HUS-like syndrome in end-stage HIV patients [90, 91]. Knowledge of the mechanism by which these agents cause TTP-HUS is incomplete. In the case of cyclosporine and tacrolimus, it is speculated to be related to direct endothelial damage/enhancement of platelet aggregation [83, 92]. The majority of transplant drug–related cases of TTP appear early within the first year after transplantation. Transplant-related TTP, like other forms, carries a high risk of mortality [82].

In the case of transplant drug-induced TTP-HUS, many cases are successfully treated by substitution of 1 calcineurin inhibitor for another [93-95]. In some cases, reinitiation of the medication has been successful following resolution of symptoms [96]. Both a switch from cyclosporine to tacrolimus and a switch from tacrolimus to cyclosporine were reported to have been successful in treatment of TTP [87, 97-99], although some patients develop the syndrome on both medications [85]. As with non-transplant TTP, other therapeutic options include high-dose prednisone and plasma exchange [94, 100-103]. Approximately 10% to 20% of patients have incomplete response or do not respond to plasmapheresis. Adjunctive therapies that have been used to treat relapsing or nonresponding transplant patients include antiplatelet/anticoagulant therapy [81, 94, 104, 105], intravenous gamma globulin [106-108], and rituximab [109].

Antibody-Induced Hypersensitivity, Acute Cytokine Release Syndrome, and Serum Sickness

As with all immunosuppressive therapy, there is risk of infection; however, the most serious complication associated with monoclonal antibodies is severe immunoglobulin E (IgE)–mediated hypersensitivity reactions ranging from facial flushing and rash to life-threatening bronchospasm and anaphylaxis [110]. The first uses of monoclonal or polyclonal antibodies included rodent, horse, and rabbit proteins and were associated with much higher incidence of acute reactions. Chimeric antibodies (such as basiliximab) contain approximately 30% foreign protein, whereas humanized antibodies (ie, daclizumab) contain about 10%, thus reducing the potential immunogenicity [111]. Despite the reduced immunogenicity of chimeric antibodies compared with rodent antibodies, there are still reports of hypersensitivity reactions [111-117].

IgE-mediated anaphylaxis after reexposure to OKT3 has been reported [118, 119]. Although rare, there are also reports of anaphylactic reactions to

basiliximab in both pediatric and adult renal transplant patients [111-113]. In all cases, the reaction was on second exposure, and it was proven to be IgE mediated in 2 of the cases [111, 112]. Interestingly, Leonard et al [111] reported successful administration of daclizumab to a patient following hypersensitivity reaction to basiliximab. The authors hypothesized that lack of reaction to daclizumab may have been related to the smaller quantity of murine protein in the humanized antibody or that altered configuration of the murine protein made it unrecognizable [111]. Thus, this medication and others in its class should be used with caution and only when appropriate supportive care measures are readily available. It may be possible to administer the humanized form of the antibody subsequent to hypersensitivity reaction to the chimeric antibody.

The cytokine release syndrome (associated with polyclonal antibodies such as ATG) is thought to be mediated by T-cell release of cytokines such as tumor necrosis factor (TNF), IL-2, and interferon-γ. Patients typically present with fever, chills, and gastrointestinal upset. Chest pain, dyspnea, and wheezing as well as pulmonary edema, multiorgan failure, and death may also occur [120]. Complement activation and neutrophil sequestration in the lungs may play a role in pulmonary symptoms [121]. Cytokine release syndrome has been most frequently reported with use of the murine monoclonal antibody OKT3 [120-123]. In lung, heart, and renal transplant recipients, in both pediatric and adult patients, numerous trials have been performed without reported incidence of cytokine release syndrome with use of daclizumab or basiliximab [25, 122, 124, 125].

Serum sickness is an immune complex–mediated disease that results from circulating antibodies against foreign animal epitopes present in the antithymocyte globulin preparations. Patients present with fever, arthritis, rash, and lymphadenopathy. Renal failure may also occur when immune complexes are deposited in the kidneys resulting in nephritis [126]. Serum sickness has been reported following treatment with the polyclonal antibodies (antithymocyte globulins) in solid organ transplant recipients [126, 127]. The incidence following treatment with polyclonal antibodies ranges from 7% to 27%. Prin Mathieu et al [126] reported an incidence of serum sickness of 18% in 89 renal transplant recipients who underwent induction therapy with horse or rabbit antilymphocyte globulins. Although the disease is generally self-limited, its resolution might be augmented by use of steroid therapy; plasma exchange has been successfully used in severe cases [127].

PTLD

Posttransplant lymphoproliferative disorders are among the most common malignancies seen in the organ transplant population, with a trend toward increasing frequency in recent reports [128-130]. The overall incidence is reported from 1% to 20% and varies with the type of organ transplanted, the Epstein-Barr virus (EBV)–seronegative status of the recipient, and the amount/type of immunosuppression used [128-130]. In most patients, the pathogenesis is thought to be attributable to posttransplant immunotherapy leading to suppression of T cells that normally function in cancer surveillance, allowing for proliferation of EBV-positive B cells [129]. There is a wide range of disease, from a benign form that presents with an infectious mononucleosis-like picture with enlarged tonsils and cervical lymph nodes to a rapidly progressive form with multiple organ involvement that often results in death. PTLD occurs with greatest frequency in the transplanted organ although extrapulmonary involvement of other sites such as the gastrointestinal tract or tonsils occasionally occurs in the lung transplant population [130]. A typical radiographic presentation of PTLD in lung transplantation is shown in Figure 7.

In a series of pediatric patients who underwent heart, heart–lung, or lung transplant, 14 of 120 patients (11.7%) developed PTLD a mean of 5.1 months after transplantation. Four of the 14 patients with PTLD presented with concurrent opportunistic infection and multiple organ dissemination, including 2 with central nervous system involvement. PTLD-related mortality rate was 37.5% including all 4 patients who presented with multiple organ disease. Two of the remaining 3 deaths were a result of rejection within 1 to 2 years of the reduced immunosuppression used to treat the patients' PTLD [131]. Other reports in adults and pediatric patients suggest a bimodal distribution of disease with some early and some late presentations [130, 132-134].

The drugs most frequently associated with the development of the disease are the calcineurin inhibitors and polyclonal/monoclonal induction agents such as ATG or OKT3 [133-141]. There is some debate regarding whether tacrolimus or cyclosporine is more likely to cause disease. Although the FK506 Kidney Transplant Study Group showed that an equal number of patients treated with cyclosporine or tacrolimus developed disease in their study [139], data from the Collaborative Transplant Study database showed that tacrolimus increased the risk 2-fold compared with cyclosporine in renal transplant recipients [140]. In pediatric patients, tacrolimus appears more likely to cause disease [134, 142, 143].

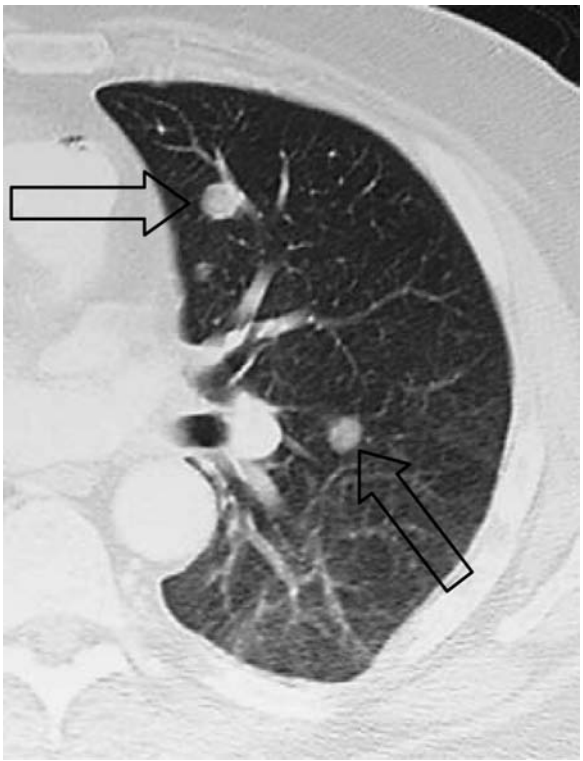

Fig 7. Posttransplant lymphoproliferative disease (PTLD) in a single lung transplant recipient. A single lung transplant recipient presented with asymptomatic nodules in the transplanted left lung (arrows) that were determined to represent B-cell PTLD by open lung biopsy.

The diagnosis of PTLD can be made by fine needle aspiration depending on the location of the lesion and organ system involved; however, the gold standard is excisional biopsy. For patients who are at high risk of development of disease, serologic monitoring can be performed. Stevens et al [144] evaluated the use of weekly EBV DNA load monitoring in lung transplant recipients with and without PTLD. Seventy-eight percent of whole blood samples from lung transplant recipients with PTLD had greater than 2000 EBV DNA copies/mL. Furthermore, in non-PTLD patients who developed disease, rapid increase in peripheral blood EBV DNA was predictive and diagnostic of disease [144]. Similarly, Wagner et al [145] demonstrated that EBV viral load measured in peripheral blood mononuclear cells or plasma could be used to distinguish healthy individuals from those with PTLD. Thus, in patients who are at high risk to develop PTLD (recipient EBV negative before transplant), screening with EBV DNA titers may aid in detecting subclinical disease.

The first line of treatment for PTLD is reduction in immunosuppression. For patients with less aggressive disease, reduction or discontinuation of the immunosuppression in combination with antiviral therapy may be all that is required to cure the disease [131, 132, 146, 147]. For patients who do not respond to conservative therapy, a variety of measures have been used including multidrug chemotherapy, radiation, surgical resection, and interferon-α [131, 132, 146-150].

Because of risk of rejection with reduction or discontinuation in immunosuppression and concerns about sepsis and death with use of chemotherapeutic agents, clinicians have been testing the efficacy of the humanized anti-CD20 monoclonal antibody rituximab as first-line or rescue therapy for lung transplant patients with PTLD [150-152]. In a retrospective review of all lung transplant patients at Duke University, Reams et al [147] reported the use of rituximab in combination with reduction in immunosuppression in 4 of the 10 patients who developed PTLD during the 10-year review period. All of these patients had remission or regressing disease. In 1 patient with resolution of disease radiographically and by small bowel biopsy, death occurred 371 days following diagnosis of PTLD. None of the other 3 patients had complications associated with use of rituximab [147]. Milpied et al [151] performed a retrospective review of 32 patients who developed PTLD following bone marrow or solid organ transplantation. The majority of patients received rituximab after failure of reduction of immunosuppression. Two patients had failed chemotherapy before rituximab therapy, and 3 patients received rituximab as first-line therapy. There were 20 complete responses and 2 partial responses, for an overall response rate of 69%. The remission rate in solid organ transplant was 58% compared with 83% in bone marrow transplant. The authors did not report any significant toxicity associated with therapy [151]. Thus, although PTLD remains 1 of the most serious and potentially life-threatening complications of immunotherapy after lung transplantation, several recent reports highlight the use of rituximab as an effective treatment for this condition.

Drug-Induced Interstitial Lung Disease

Sirolimus was introduced in renal transplant patients in 1999. Early studies showed the major side effects to be thrombocytopenia and hyperlipidemia [153]. However, by 2000, there were reports of development of interstitial lung disease in kidney, liver, and heart transplant patients treated with sirolimus [154-156]. Lung diseases reported included interstitial pneumonitis, bronchiolitis obliterans with organizing pneumonia (BOOP), interstitial pneumonia,

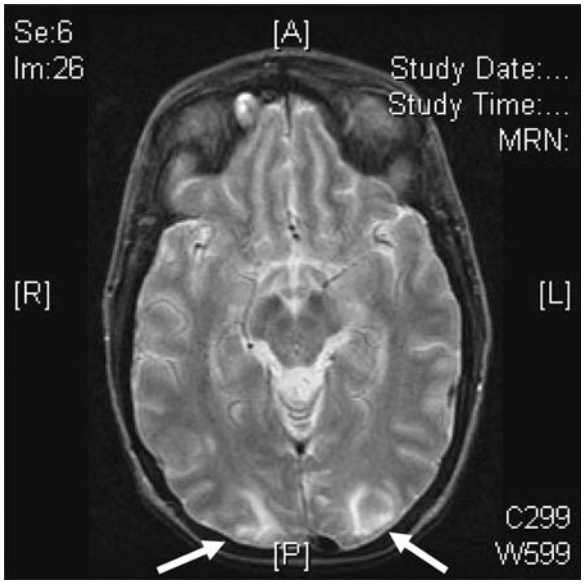

Fig 8. Posterior reversible encephalopathy syndrome in a bilateral lung transplant patient. A bilateral lung transplant recipient receiving tacrolimus therapy presented with headache, photophobia, and extremity weakness, which later progressed to seizures. Magnetic resonance imaging showed bilateral occipital lobe T2 hyperintensity (arrows.)

alveolar hemorrhage, and pulmonary alveolar proteinosis. Since that time, sirolimus-associated lung disease has also been reported in a heart–lung transplant recipient [157].

In 2004, Pham et al [158] reviewed the incidence and epidemiology of sirolimus-associated pulmonary toxicity. At that time a total of 43 cases had been reported in 37 kidney transplants, 1 orthotopic liver transplant, 1 orthotopic heart transplant, and 1 heart–lung recipient. Patient ages ranged from 22 to 69 years. Onset of illness occurred 2.5 to 12 months after initiation of sirolimus therapy. Dyspnea on exertion, cough, fatigue, and fevers were the most common presenting symptoms. Chest radiography demonstrated bilateral patchy air space disease or ground glass infiltrates. In those patients on whom complete data were available, discontinuation or dose reduction of sirolimus resulted in improvement in all patients within 3 weeks, although some patients failed to achieve complete resolution [158]. More recently, development of BOOP was reported at a rate of 24% in review of 29 consecutive cardiac transplant patients switched from calcineurin inhibitors to sirolimus. As in previous reports, symptoms in most patients resolved within 3 to 4 weeks of discontinuation of therapy, although 1 patient died of respiratory failure [159]. A total of 6 deaths have been reported in solid organ transplant recipients treated with sirolimus [155, 159, 160].

The mechanism by which sirolimus causes pulmonary toxicity is unknown. Although it was initially thought to be a dose-related effect [154, 155], more recent reports are in patients with normal trough levels/low-dose therapy [158, 159]. Therefore, clinicians should be vigilant in monitoring for signs of symptoms of pulmonary toxicity in all patients treated with sirolimus. In lung transplant patients, this toxicity will be particularly challenging and must be distinguished from infection and rejection.

Posterior Reversible Encephalopathy Syndrome (PRES)

A wide range of neurotoxic effects have been associated with use of the calcineurin inhibitors, from minor symptoms such as headache, sleep disturbance, and tremors to paresthesias, seizures, and encephalopathy [161]. Singh et al [162] reviewed 50 cases of cyclosporine and tacrolimus-associated neurotoxicity in solid organ transplant recipients. Six of the 50 cases occurred in lung or heart–lung transplant patients. The range of onset of symptoms was from 3 days to more than 4 years, with a median of 28 days. Many patients were noted to have altered mental status with confusion, lethargy, or disorientation before the abrupt onset of seizures, visual abnormalities, or speech or movement impairment. The most commonly reported symptoms were seizures (78%), altered mental status (50%), and visual disturbances (28%). Although fever was uncommon (5%), temperature was often markedly elevated, prompting evaluation for infectious disease [162].

Clinical examination is often remarkable for altered level of alertness, visual abnormalities, hyperreflexia, and weakness or discoordination [161, 162]. Diagnosis of drug-related neurotoxicity is made by radiographic imaging, either computed tomography (CT) or magnetic resonance imaging (MRI). The most common finding is bilateral posterior white matter edema, seen as low-density, unenhanced lesions on CT scan or high-intensity densities on T2-weighted MRI [161, 163]. Figure 8 shows the MRI from a patient treated with tacrolimus who developed PRES. Lesions are found at a particularly high rate in the parieto-occipital lobes, although disease in other areas of the brain including the brain stem, cerebellum, and frontal lobes has been reported [161].

Numerous mechanisms have been considered in the pathophysiology of calcineurin-induced neurotoxicity. One theory is that there is a direct neurotoxic effect through damage of endothelial cells at the blood–brain barrier. This damage increases blood–brain permeability, allowing direct contact of

the drug with brain parenchyma [164]. Because cyclosporine neurotoxicity has been reported to occur at higher rates in patients with hypocholesterolemia, it has been proposed that patients with low cholesterol may not be able to bind the lipophilic drug as effectively, and thus the brain may be exposed to higher levels of unbound drug [163, 165]. Alternatively, because patients with hypertension develop leukoencephalopathy in the absence of calcineurin-inhibitor therapy, intracerebral hypertension with subsequent transudation of fluid leading to brain edema has been postulated to contribute [162]. Elevation of blood pressure has been frequently reported in the setting of PRES in patients receiving cyclosporine [161, 166, 167] but has been much less common in patients who develop PRES while taking tacrolimus [161, 162]. In the Singh et al [162] review, elevated serum levels of cyclosporine or tacrolimus were reported in 61% of patients. However, in 39% of patients, disease occurred in patients with therapeutic drug levels, and occurrence of neurotoxicity in the presence of therapeutic drug levels has been confirmed in other reports [162, 167, 168].

Fortunately, dose reduction or discontinuation (including interchanging calcineurin inhibitors) in combination with blood pressure reduction when indicated usually results in complete resolution of disease [161, 162, 166-168]. In a series of 15 patients studied by Hinchey et al [161], symptoms resolved within 1 week in 10 of 15 patients and within 2 weeks in all patients. Resolution of radiographic abnormalities occurred between 8 days and 17 months [161]. Singh and colleagues' [162] review of 50 cases demonstrated a median of 4 days to resolution of symptoms and a median of 20 days to resolution of radiographic findings. Very rarely, symptoms have persisted despite discontinuation of the offending drug [169, 170].

Pharmacologic Considerations

Other important challenges in managing posttransplant immunosuppression regimens in patients requiring intensive care include consideration of the numerous possible drug interactions, adjustment of dose based on organs affected by their illness, and necessary changes in route of administration based on the patient's ability to take oral medications [68]. For example, many of the antibiotics that might be used to treat infection, such as the azoles or macrolides, or medications that might be used to treat hypertension such as calcium-channel blockers cause increased cyclosporine, tacrolimus, and sirolimus levels [68]. Table 2 shows serious drug interactions, metabolism, and route of administration for commonly used immunosuppressant agents. Thus, a patient who required therapy with these combinations of medications would need dosage adjustment and close monitoring of drug levels. Furthermore, if the patient is intubated, a medication that is usually administered orally may have to be changed to an intravenous preparation. Because trough levels may not be equivalent for both routes of administration, careful monitoring of drug levels is necessary.

Conclusion

Since the first lung transplant in 1963 [5], great strides have been made in the immunotherapy regimens used to treat transplant patients, resulting in improved patient survival. However, all of the currently used immunosuppressive medications in lung transplantation have toxic side effects; some of them severe enough to cause significant morbidity and mortality. In some cases, substitution of 1 calcineurin inhibitor for another can effectively treat certain posttransplant complications (eg, TTP or PRES), but in other cases complete discontinuation of a drug is required (eg, sirolimus-induced lung disease). Clinicians must be aware of wide range of common and potentially serious complications that occur related to immunosuppression after lung transplantation. Successful outcomes of lung transplantation require a concerted multidisciplinary effort from the intensive care team to select appropriate posttransplant immunotherapy and diagnosis and manage immunotherapy-related complications. Continued improvement in immunotherapy after lung transplant should contribute to even greater improvement in posttransplant survival.

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