The use of nonsteroidal immunosuppressive drugs to treat systemic and pulmonary inflammatory disorders has increased considerably. These drugs are used to prevent and suppress posttransplant lung allograft rejection and to treat various forms of inflammatory lung disease, such as sarcoidosis, pulmonary vasculitis, and idiopathic interstitial pneumonias. Because these medications have become more widely used for a variety of indications, it has become increasingly common for these drugs to be administered and monitored by primary pulmonologists in community settings.

The objective of this guideline is to provide recommendations for monitoring the use of immunosuppressive drugs so that clinically significant side effects can be either avoided or recognized in a timely fashion. This guideline does not provide recommendations concerning indications for use of these drugs. Rather, it should be used exclusively to achieve maximal patient safety when these nonsteroidal immunosuppressive medications are prescribed. Sufficient information related solely to treating pulmonary diseases was available for some of the drugs covered by this guideline; however, recommendations were partially or entirely abstracted from nonpulmonary studies for a number of these agents because of a lack of information in the published literature about their use for pulmonary disorders or for lung transplant recipients. Because of its focus on common and unique side effects associated with specific drugs, this guideline can provide important information to both physicians and patients. Treating physicians are also encouraged to use other resources (eg, package inserts and regulatory agency guidelines, such as the US Food and Drug Administration MedWatch program, Micromedex,
These guidelines were developed by a carefully selected committee of pulmonologists and pharmacists with expertise in the use of these drugs for lung transplantation and inflammatory lung disease. Committee members not only were experts in the field but also used these drugs in their clinical practices. The ultimate goal of the guideline is to provide an easily accessible, single source that is based on the best-available evidence in best practices for monitoring these drugs and preventing adverse events related to therapy.

Specific guidelines for each drug are provided. One section of the document reviews the evidence for potential toxic side effects of each drug as well as protocols for monitoring therapy that are based on clinical reports for pulmonary conditions. Studies for nonpulmonary conditions are included if important cautions and monitoring information did not exist in the pulmonary literature. Therefore, this guideline provides two levels of recommendations. The first level comprises evidence-based recommendations (formal recommendations made on the basis of evidence obtained from a comprehensive literature review) that were reviewed by the committee for quality and graded. The second level comprises a section for each drug that outlines what clinicians should consider when using these drugs to treat patients; these recommendations focus on issues where there was no evidence in the pulmonary literature to support specific recommendations. These are based on expert consensus and recommendations from a variety of sources and summarize what is commonly done to monitor patients when treated with a specific medication. For example, cyclophosphamide can cause neutropenia; hence, patients should have their WBC counts monitored during treatment. However, no study could be found that specifically compared monitoring blood counts monthly vs weekly.

This guideline also contains a general section regarding the use of immunosuppressive drugs, including a review of drug/drug interactions and a summary of recommendations regarding the various antibiotic prophylaxis regimens that should be considered for use when intense immunosuppression is given (eg, as must be done for lung transplant recipients). These prophylactic regimens have markedly reduced certain infections, such as *Pneumocystis jiroveci* pneumonia and cytomegalovirus infection. The use of a specific antibiotic agent for prophylaxis depends on the clinical situation; once the decision has been made to give prophylaxis, this section helps to define what regimen should be considered.

The guideline is a Web-based document. Although we have used currently available information, we realize that specific comments may need to be updated on the basis of new information as it appears in the literature, and new sections will be added as new immunosuppressive agents are approved for clinical use. As chairs and panelists of the Guidelines Committee, we appreciate comments and corrections from the pulmonology community. We thank the American College of Chest Physicians for its help in developing these guidelines, specifically Joe Ornelas, Sandra Lewis, the Health and Science Policy Committee, and the American College of Chest Physicians Board of Regents.

### Summary of Recommendations

#### 3.0 Monitoring of Nonsteroidal Immunosuppressive Drugs in Patients With Lung Disease and Lung Transplant Recipients

#### 3.1 Anti-Tumor Necrosis Factor-α (TNF-α) Agents

**3.1a.** For patients who will undergo anti-TNF-α therapy, a chest radiograph is recommended prior to treatment *(Grade 1C)*.

**3.1b.** For patients who will undergo anti-TNF-α therapy, a tuberculin skin test is recommended to screen for latent TB prior to treatment *(Grade 1C)*.

**3.1c.** For patients who will undergo anti-TNF-α therapy and present with a chest radiograph consistent with prior TB or a positive tuberculin skin test and/or are high-risk individuals, active TB infection should be excluded prior to treatment with adalimumab *(Grade 1C)*, etanercept *(Grade 1B)*, or infliximab *(Grade 1B)*.

**3.1d.** For patients with latent *Mycobacterium tuberculosis*, active prophylactic treatment following published guidelines before initiation of anti-TNF-α therapy is recommended *(Grade 1B)*.

**3.1e.** For patients with latent *M tuberculosis* who will undergo anti-TNF-α therapy, close monitoring for TB is recommended for up to 6 months after discontinuing therapy *(Grade 1C)*.

**3.1f.** For patients who develop symptoms indicative of TB, prompt evaluation for active disease is recommended *(Grade 1C)*.

**3.1g.** For patients with known grade III or IV New York Heart Association class heart failure, administration of adalimumab *(Grade 1C)*, etanercept *(Grade 1C)*, and infliximab *(Grade 1B)* is not recommended.
3.1h. For patients with a history of congestive heart failure who undergo anti-TNF-α therapy, close observation for congestive heart failure exacerbation is recommended (Grade 1C).

3.1i. For patients with a history of demyelinating disease, administration of etanercept is not recommended (Grade 1C), and administration of adalimumab and infliximab is not suggested (Grade 2C).

3.1j. For patients with no history of demyelinating disease who undergo anti-TNF-α therapy and experience symptoms or display signs of a demyelinating process, discontinuation of therapy is suggested (Grade 2C).

3.1k. For patients who undergo anti-TNF-α therapy and develop symptoms of a lupus-like disorder, discontinuation of therapy is suggested (Grade 2C).

3.1l. For patients who will undergo anti-TNF-α therapy and who are at risk for viral hepatitis, serologic screening for hepatitis B is recommended prior to treatment (Grade 1C).

3.1m. For patients who have hepatitis B virus infection, anti-TNF-α therapy should not be administered (Grade 1C).

3.1n. For patients who undergo anti-TNF-α therapy and develop unresolved infections, discontinuation of treatment until the infection is resolved is recommended (Grade 1B).

3.1o. For patients who are pregnant, administration of anti-TNF-α therapy is used only if alternatives are not able to be used (Grade 2C).

3.2 Calcineurin Inhibitors

3.2a. For patients who will undergo calcineurin inhibitor (CNI) therapy, the monitoring of drug concentrations, BP, glucose, potassium, magnesium, lipids, CBC count, and renal function is recommended (Grade 1B).

3.2b. For patients who undergo CNI therapy, monitoring of drug levels when CYP3A4 inducers or inhibitors are added or stopped and adjusting doses are recommended when using cyclosporin A (Grade 1A) or tacrolimus (Grade 1B) therapy.

3.2c. For lung transplant recipients receiving CNI therapy who develop renal dysfunction, a reduction in the target dose concentration is suggested (Grade 2C).

3.3 Antilymphocyte Antibodies

3.3a. For patients who undergo antilymphocyte antibody therapy, monitoring for infusion reactions is recommended (Grade 1B).

3.3b. For patients who undergo antithymocyte globulin or muromonab therapy, monitoring of CBC counts and liver function tests is recommended during therapy (Grade 1B).

3.3c. For patients with lung disease and lung transplant recipients who will undergo antithymocyte globulin or muromonab therapy, laboratory evaluation for host antibodies (where available) before reinstitution of therapy is suggested (Grade 2C).

3.3d. For patients who undergo muromonab therapy, monitoring for pulmonary edema and systemic inflammatory response syndrome during therapy is recommended (Grade 1B).

3.4 IL-2 Receptor Antagonists

3.4a. For patients who undergo IL-2 receptor antagonist therapy, monitoring for infusion reactions is recommended (Grade 1C).

3.4b. For patients who undergo IL-2 receptor antagonist therapy, monitoring of renal function, CBC counts, and infection is recommended (Grade 1C).

3.4c. For patients who undergo IL-2 receptor antagonist therapy, the simultaneous use of either basiliximab (Grade 1C) or daclizumab (Grade 1B) with antilymphocyte antibodies is not recommended.

3.5 Cytotoxic Agents

3.5a. For patients who will undergo concurrent therapy with azathioprine and allopurinol, a reduction in dose of azathioprine is recommended (Grade 1A).

3.5b. For patients who undergo azathioprine therapy, obtaining CBC counts and renal/hepatic profiles every 1 to 3 months is recommended (Grade 1B).

3.5c. For patients who will undergo cyclophosphamide therapy, monitoring of CBC count, renal profile, and urinalysis at least monthly for dose adjustment is recommended (Grade 1B).

3.5d. For patients who will undergo cyclophosphamide therapy, increased fluid intake (eg, 2 L in addition to normal intake in adults; additional
volume given to children needs to be calculated on the basis of body weight) on the days of therapy is recommended (Grade 1C).

3.5e. For patients who undergo or have undergone cyclophosphamide therapy and develop hematuria, further evaluation is recommended (Grade 1B).

3.5f. For patients who will undergo leflunomide or methotrexate therapy, screening for the use of alcohol and chronic viral hepatitis prior to treatment is recommended (Grade 1B).

3.5g. For patients who undergo methotrexate or leflunomide therapy, performance of liver function tests and CBC counts is recommended (Grade 1C).

3.5h. For patients who undergo methotrexate therapy, folic acid supplementation is recommended (Grade 1A).

3.5i. For patients who undergo leflunomide therapy and develop neuropathic symptoms, prompt consideration of discontinuing therapy and washing out with cholestyramine is recommended (Grade 1C).

3.5j. For patients who undergo methotrexate (Grade 1B) or leflunomide (Grade 1C) therapy and develop new or worsening signs or symptoms of lung disease, further evaluation is recommended.

3.5k. For patients who undergo methotrexate therapy and develop persistently elevated liver transaminases above their own baseline, cessation of treatment or evaluation by liver biopsy is recommended (Grade 1B).

3.5l. For patients with renal insufficiency, ascites, or pleural effusions who undergo methotrexate therapy, decreased methotrexate clearance may be present, and dose reduction may be required (Grade 2C).

3.5m. For patients who undergo mycophenolic acid therapy and develop adverse GI affects, including diarrhea, interruption of therapy or reduction in dose is recommended (Grade 1B).

3.5n. For patients who undergo mycophenolic acid therapy and develop signs or symptoms of progressive multifocal leukoencephalopathy, cessation of treatment is suggested (Grade 2C).

3.6 Mammalian Target of Rapamycin (mTOR) Inhibitors

3.6a. For patients who will undergo mTOR inhibitor therapy, obtaining cholesterol and triglyceride levels prior to treatment is recommended (Grade 1B).

3.6b. For patients who present with an abnormal elevation of fasting triglycerides, avoidance of mTOR therapy or careful monitoring of triglycerides is recommended (Grade 1B).

3.6c. For patients who undergo mTOR therapy, monitoring for hyperlipidemia is recommended (Grade 1A).

3.6d. For patients who undergo mTOR therapy, monitoring of CBC counts, creatinine, and BP is recommended (Grade 1B).

3.6e. For patients who undergo sirolimus therapy, monitoring of drug concentration is recommended (Grade 1B).

3.6f. For lung transplant recipients scheduled to undergo sirolimus therapy, administration of sirolimus during the early perioperative period is contraindicated due to the risk of airway dehiscence (Grade 1A).

3.6g. For patients who undergo sirolimus therapy and are at risk for poor wound healing, consideration of dose adjustments or an alternative therapy to lower this risk is suggested (Grade 2C).

3.6h. For patients who undergo sirolimus therapy and develop new or worsening respiratory symptoms or signs, an evaluation for sirolimus-induced pulmonary toxicity is recommended (Grade 1B).

3.7 Other Immunosuppressive Drugs

3.7a. For patients receiving hydroxychloroquine and chloroquine, an eye examination at least once per year is suggested (Grade 2B).

3.7b. For patients who undergo imatinib mesylate therapy, monitoring of CBC and hepatic function is suggested (Grade 2C).

Acknowledgments

Author contributions: Dr Baughman is the guarantor of the manuscript. All authors contributed equally to the guidelines and the executive summary.

Dr Baughman: contributed to the design, execution, and review of the guidelines.

Dr Meyer: contributed to the design, execution, and review of the guidelines.
Dr Nathanson: contributed to the design, execution, and review of the guidelines.

Dr Angel: contributed to the design, execution, and review of the guidelines.

Dr Bhorade: contributed to the design, execution, and review of the guidelines.

Dr Chan: contributed to the design, execution, and review of the guidelines.

Dr Culver: contributed to the design, execution, and review of the guidelines.

Mr Harrod: contributed to the design, execution, and review of the guidelines.

Dr Hayney: contributed to the design, execution, and review of the guidelines.

Dr Highland: contributed to the design, execution, and review of the guidelines.

Dr Limper: contributed to the design, execution, and review of the guidelines.

Dr Patrick: contributed to the design, execution, and review of the guidelines.

Dr Strange: contributed to the design, execution, and review of the guidelines.

Dr Whelan: contributed to the design, execution, and review of the guidelines.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Baughman’s institution (University of Cincinnati) has received grants for research in sarcoidosis and idiopathic pulmonary fibrosis from Actelion Pharmaceuticals Ltd; Celgene Corporation; Cephalon, Inc; Centocor Ortho Biotech, Inc; Gilead Sciences, Inc; and InterMune. Dr Hayney has received grant support from the University of Wisconsin and the National Institutes of Health. She serves on the speakers’ bureau for Merck Vaccines. Dr Patrick received a travel stipend from Omneotech, Inc; owns stock in pharmaceutical/medical device companies, including Human Economics, Rite Aid Corp, Numec, and Hospira, Inc; and is a member of the speakers’ bureau for Gilead Sciences, Inc. Dr Strange has received grant monies and salary support from the National Institutes of Health to study cyclophosphamide and mycophenolate mofetil in scleroderma. He has received grant monies and salary support from Centocor Ortho Biotech, Inc, for the study of ustekinumab and golimumab in sarcoidosis. He has been a consultant for AstraZeneca; Uptake Medical; PneumRx, Inc; Pulmone; Aeris Therapeutics; Talecris Biotherapeutics, Inc; CSL Behring; Baxter; Gilead Sciences, Inc; MedImmune, LLC; and Actelion Pharmaceuticals Ltd in the past 3 years. For the past 3 years, he has received grant monies and salary support from Centocor Ortho Biotech, Inc, for the study of ustekinumab and golimumab in sarcoidosis. He has been a consultant for AstraZeneca; Uptake Medical; PneumRx, Inc; Pulmone; Aeris Therapeutics; Talecris Biotherapeutics, Inc; CSL Behring; Baxter; Gilead Sciences, Inc; MedImmune, LLC; and Actelion Pharmaceuticals Ltd in the past 3 years. For the past 3 years, he has received grants from the France Foundation for InterMune on topics not related to the subject of this article. Dr Whelan has received research support from Actelion Pharmaceuticals Ltd; Celgene Corporation; Centocor Ortho Biotech, Inc; and InterMune. He has also received consultant fees from InterMune. His contributions to this article were free from potential conflicts of interest related to these activities. Drs Meyer, Nathanson, Angel, Bhorade, Chan, Culver, Highland, and Limper and Mr Harrod have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

References