B cells are an essential component of the adaptive immune system. Since the late 1990s biologic drugs targeting B cells have been used to treat not only lymphoproliferative diseases of B-cell lineage cells but also autoimmune diseases, in particular, those associated with autoantibody production. Although some of these agents are relatively safe, they have been associated with serious infections including opportunistic infections. To what extent the infectious complications reported are directly related to the use of the B-cell targeting agent or to previous and/or concomitant immunosuppressive therapies and/or the specific disease being treated is often difficult to ascertain. A comprehensive knowledge of infectious risks associated with B-cell targeting agents in general and with each individual drug and of the measures available to decrease these risks are important for patient education and for early diagnosis and adequate treatment of infectious complications. Adaptation of general prevention guidelines in response to endemic conditions and local guidelines should be considered when appropriate.

Co-stimulatory T-cell inhibitors are used in the treatment of rheumatoid arthritis and to prevent rejection of renal transplants. Inhibitors of the interleukin (IL)-17 cytokine are indicated for psoriasis, psoriatic arthritis and ankylosing spondylitis and anti-IL-23 drugs for psoriasis. Serious infections occur in 4.2% to 25.0% of co-stimulatory inhibitors and 1.0% to 2.0% with IL-17 or IL-23 inhibitors. Underlying disease, steroid dose greater than 7.5 to 10.0 mg, and comorbidities influence risk in individual patients. Opportunistic infections or reactivation of tuberculosis are rare.
and members of α4- and β2-integrin families acting as cell-adhesion molecules. An outline of the mechanisms of action, approved indications and off-label uses, expected impact on the host immune response, and available clinical evidence is provided for each of these agents.

Infectious Implications of Interleukin-1, Interleukin-6, and T Helper Type 2 Inhibition

Anne Y. Liu

Targeting interleukins that drive innate inflammation has expanded treatments of autoinflammatory and autoimmune disorders. Interleukin (IL)-1 inhibition has proven useful for monogenic autoinflammatory syndromes, and IL-6 inhibition for autoimmune arthritides. Biological therapies impeding these pathways impair detection and containment of pathogens, particularly invasive bacteria, reflecting the importance of IL-1 and IL-6 in communicating danger throughout the immune system. Biologics targeting T helper type 2 inflammation are used to treat specific allergic, atopic, and eosinophilic diseases. They may impair protections against local herpesvirus reactivations while augmenting antiviral responses to respiratory viruses. Their risks with helminth exposures have yet to be defined.

Infectious Complications of Immune Checkpoint Inhibitors

Michael S. Abers and Michail S. Lionakis

The clearance of both tumors and microbes depends on highly coordinated immune responses that are sufficiently potent to kill malignant or microbial cells while avoiding immunopathology from an overly exuberant inflammatory response. A molecular understanding of the immune pathways that regulate these responses paved the way for the development of checkpoint inhibitors (CPIs) as a therapeutic strategy to boost endogenous antitumor immunity. CPIs have demonstrated survival benefits across a wide spectrum of cancers. While infectious complications of CPIs are uncommon, immune-related adverse events occur frequently and often require immunosuppressive therapies that increase the risk of infection.

Infectious Complications of Tyrosine Kinase Inhibitors in Hematological Malignancies

Andrew Kin and Charles A. Schiffer

Tyrosine kinase inhibitors represent the standard of care for several diseases and drug targets in hematologic malignancies. Infectious complications vary by disease status and prior therapy, but overall incidence of infections generally is low. In chronic diseases, such as chronic myeloid leukemia and chronic lymphocytic leukemia, patients can remain on tyrosine kinase inhibitor therapy for many years, with few infectious complications from therapy. Bruton tyrosine kinase inhibitors overall are well tolerated in lymphoproliferative disorders, with long-term follow-up of many years in patients with chronic lymphocytic leukemia. Although opportunistic infections have been reported, they are uncommon and routine prophylaxis is not recommended.
Epidermal Growth Factor Receptor Inhibitors and Other Tyrosine Kinase Inhibitors for Solid Tumors 257
Isabel Ruiz-Camps and Juan Aguilar-Company

This article analyzes the risk of infection associated with small molecule kinase inhibitors used to treat solid organ malignancies and establishes specific recommendations. Most of these drugs are orally administered and have the ability to inhibit distinct kinases, which play a major role in cancer initiation and progression. Although the true extent of adverse events is not yet known, risk of infection does not seem to be a major problem with these drugs. Because of the limited clinical experience and the constant evolution of targeted therapies, recommendations may evolve in the near future.

Infectious Risks Associated with Biologics Targeting Janus Kinase-Signal Transducer and Activator of Transcription Signaling and Complement Pathway for Inflammatory Diseases 271
Esther Benamu

The recognition of the role of complement and Janus kinase (JAK)-dependent cytokines in the pathogenesis of inflammatory and immune-mediated disorders has revolutionized the treatment of a myriad of rheumatological and inflammatory diseases. C5 inhibitors and Janus kinase inhibitors have emerged as attractive therapeutic options. Because of the blockage of immune pathways, these targeted therapies carry an increased risk of infection. This article reviews the mechanism of action and the approved and off-label indications of the agents with most clinical experience within this drug classes. It discusses the associated risks of infection, proposing screening, prevention, and risk mitigation strategies.

Herpesvirus Infections Potentiated by Biologics 311
Dora Y. Ho, Kyle Enriquez, and Ashrit Multani

Herpesviruses such as herpes simplex virus (HSV) type 1 and 2, varicella-zoster virus (VZV), and cytomegalovirus (CMV) maintain lifelong latency in the host after primary infection and can reactivate periodically either as asymptomatic viral shedding or as clinical disease. Immunosuppression, including biologic therapy, may increase frequency and severity of herpesvirus reactivation and infection. Licensed biologics are reviewed regarding their risks of potentiating HSV, VZV, and CMV reactivation and infection. Approaches to prophylaxis against HSV, VZV, and CMV infection or reactivation are discussed.

Hepatitis B Virus Reactivation Potentiated by Biologics 341
Eiichi Ogawa, Mike T. Wei, and Mindie H. Nguyen

Hepatitis B virus (HBV) reactivation can be a serious complication for patients with chronic or resolved HBV infection when treated with biologics. For HBsAg-positive patients receiving biologics, the risk of HBV reactivation is moderate to high. HBsAg-negative/anti-HBc positive patients are at lower risk of HBV reactivation than HBsAg-positive patients. However, patients taking anti-CD20 agents, such as rituximab,
have high risk of HBV reactivation (>10%), so antiviral prophylactic therapies are required. This review provides the different classes of biologics associated with HBV reactivation, stratifies the various reactivation risk levels by HBV status and biologic agent, and discusses management strategies.

**JC Polyomavirus Infection Potentiated by Biologics**  
Ashrit Multani and Dora Y. Ho

The risk of JC polyomavirus encephalopathy varies among biologic classes and among agents within the same class. Of currently used biologics, the highest risk is seen with natalizumab followed by rituximab. Multiple other agents have also been implicated. Drug-specific causality is difficult to establish because many patients receive multiple immunomodulatory medications concomitantly or sequentially, and have other immunocompromising factors related to their underlying disease. As use of biologic therapies continues to expand, further research is needed into pathogenesis, treatment, and prevention of JC polyomavirus encephalopathy such that risk for its development is better understood and mitigated, if not eliminated altogether.

**Fungal Infections Potentiated by Biologics**  
Matthew R. Davis, George R. Thompson III, and Thomas F. Patterson

Biologic therapies including monoclonal antibodies, tyrosine kinase inhibitors, and other agents represent a notable expansion in the pharmacotherapy armamentarium in treatment of a variety of diseases. Many of these therapies possess direct or indirect immunosuppressive and immunomodulatory effects, which have been associated with bacterial, viral, and fungal opportunistic infections. Careful screening of baseline risk factors before initiation, targeted preventive measures, and vigilant monitoring while on active biologic therapy mitigate these risks as use of biologics becomes more commonplace. This review compiles reported evidence of fungal infections associated with these agents with a focus on the tumor necrosis factor-α inhibitor class.

**Mycobacterial Infections Potentiated by Biologics**  
Cassandra Calabrese and Kevin L. Winthrop

Biologic therapies have revolutionized the treatment of immune-mediated inflammatory diseases but are associated with an increased risk of serious and opportunistic infections, including tuberculosis and nontuberculous mycobacterial disease. Despite this increased risk, the overall risk-benefit ratio remains favorable with appropriate screening and risk assessment. Further population-based studies are needed to establish the risk of tuberculosis and nontuberculous mycobacterial disease with the new biologics. This article highlights the incidence and drug-specific risk of tuberculous and nontuberculous mycobacterial infection in the setting of biologics, screening and prevention, and treatment of latent tuberculosis in this setting.
The emergence of biologics has revolutionized the way physicians treat many autoimmune inflammatory conditions. Although biologics have become a vital component of the treatment approach to many inflammatory diseases, these agents may potentially disrupt the natural immune response against pathogens, thereby increasing the risk for infections. Some infections may be preventable or have a lessened risk through appropriate vaccinations; thus, vaccination history should be taken carefully in preparation for biologics and updated annually to maximize benefits while minimizing adverse effects. The objective of this review is to summarize recent articles, including guidelines, published that address vaccinations among patients on biologics.