Review

A Clinician's Guide to Opportunistic Infections in the Era of Biologic and Targeted Synthetic DMARDs

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A Clinician's Guide to Opportunistic Infections in the Era of Biologic and Targeted Synthetic DMARDs

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Abstract

Background: Immunomodulatory therapies, including biologics, JAK inhibitors, immune checkpoint inhibitors (ICIs), and bispecific antibodies (BsAbs), have reshaped the treatment of autoimmune diseases and malignancies. They alter host defenses, but the current landscape of associated infectious risk is not fully defined. **Objective:** I conducted a scoping review of recent literature to characterize infectious complications associated with modern immunomodulatory drugs, summarize current pathogen patterns, and highlight recommendations for prevention and early recognition in clinical practice. **Methods:** Following PRISMA-ScR guidelines, I systematically searched Scopus, Science Direct, and PubMed for studies published since 2023. Inclusion criteria focused on adult human subjects, exposure to immunomodulatory therapy, and reported infectious outcomes. After screening 1,046 unique records, 24 studies were included in the final review. **Findings:** High-dose glucocorticoids remain a primary driver of serious infections across autoimmune diseases. Newer agents present mechanism-specific risk profiles. JAK inhibitors are associated with herpes zoster, while TNF-α inhibitors are linked to opportunistic bacterial infections and reactivation of granulomatous infections. B-cell depletion with rituximab correlates with hypogammaglobulinemia and its associated infections, whereas belimumab may offer a lower infection risk in non-renal SLE. In oncology, bispecific antibodies have a high incidence of severe infections, driven by neutropenia and hypogammaglobulinemia. Immune checkpoint inhibitors were associated with a 26.9% serious infection rate, with complications difficult to distinguish from immune-related adverse events. **Conclusion:** The infectious risk associated with modern immunomodulators is not one profile, but a spectrum of specific vulnerabilities. This review shows the urgent need for individualized risk stratification, targeted prophylaxis (e.g., for *Pneumocystis* or zoster), and pre-therapy screening to balance therapeutic efficacy with patient safety.

Keywords: opportunistic; immunomodulation; immune deficiency; steroids; scoping review

Introduction:

Immunomodulatory therapies have reshaped the treatment of autoimmune diseases, immune-mediated inflammatory disorders, hematologic malignancies, and solid tumors. These agents include biologics, monoclonal antibodies, JAK inhibitors, B and T-cell directed therapies, and conventional immunosuppressants. [1] They exert therapeutic benefits by altering cytokine signaling, lymphocyte activation, or cellular proliferation. However, by modulating innate and adaptive immunity, they also influence host defense mechanisms and modify susceptibility to infection. [1]

The risk and severity of infection during immunomodulatory therapy are not consistent. They vary according to the selectivity and intensity of immune suppression, concomitant corticosteroid exposure, underlying disease activity, comorbid conditions, and latent infection status. [2] Reported infectious complications range from common bacterial infections to viral reactivation (e.g. varicella-zoster virus, cytomegalovirus, hepatitis B), invasive fungal disease, *Pneumocystis jirovecii* pneumonia, mycobacterial infections, and parasitic hyperinfection syndromes. Clinical presentations span from mild mucocutaneous disease to severe sepsis and opportunistic, disseminated, or fatal infections. [2]

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Recently, the infection landscape has begun to shift as clinical practice increasingly incorporates high-efficacy biologics, immune checkpoint inhibitors, targeted small-molecule immunosuppressants, and bispecific antibodies [3]. Emerging pharmacovigilance reports and real-world data suggest evolving patterns of infectious risk that are not yet fully defined. Understanding these trends is critical for optimizing screening strategies, vaccination planning, prophylaxis, and individualized risk counseling.

To address this gap, I conducted a scoping review of contemporary literature since 2023 to characterize infectious complications associated with modern immunomodulatory therapies.

Rationale: Modern immunomodulatory therapies have improved outcomes in autoimmune and malignant diseases, yet infections remain a major cause of morbidity and mortality. Because each agent alters immune function through distinct mechanisms, infectious risk varies across drug classes. Existing literature often precedes newer agents or lacks practical, mechanism-based clinical guidance.

Objective: To summarize current pathogen patterns, identify clinical and treatment-related risk factors, and highlight implications for prevention and early recognition in routine clinical practice.

Methods:

This scoping review followed the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines (Figure 1). [4]

To ensure clinical relevance to current therapeutic practice, I restricted inclusion to studies published from 2023 onward, capturing infection risk patterns reflective of modern immunomodulatory agents, updated dosing strategies, and contemporary patient populations. I searched Scopus, ScienceDirect, and PubMed using predefined Boolean strategies.

Records were imported into Rayyan for deduplication and screening. Inclusion criteria were: (1) adult human subjects; (2) exposure to immunomodulatory therapy; (3) reported infectious outcomes; and (4) publication year ≥ 2023. We excluded studies involving HIV-associated immunosuppression, pediatric populations, animal models, cadaveric or in-vitro data, or publications prior to 2023.

For this review, a search was conducted on, Scopus, Science Direct and Pubmed. The search criteria were as follows:

Scopus:

TITLE-ABS-KEY ("immunosuppressive agent" OR "immune checkpoint inhibitor") AND TITLE-ABS-KEY ("serious infection") AND NOT TITLE-ABS-KEY (HIV OR "human immunodeficiency virus") AND PUBYEAR > 2022 AND PUBYEAR < 2026 AND (LIMIT-TO (SUBJAREA , "MEDI"))

Science Direct:

("immunosuppressive agent" OR "immune checkpoint inhibitor") AND "serious infection" AND NOT HIV

Pubmed:

("Immunosuppressive Agents" [Mesh] OR "Immune Checkpoint Inhibitors" [Mesh] OR "Antibodies, Monoclonal" [Mesh] OR biologic [tiab] OR immunomodulat* [tiab]) AND (infection [Mesh] OR infection [tiab] OR infections [tiab] OR reactivation [tiab]) AND Humans [Mesh] AND NOT ("HIV Infections" [Mesh] OR HIV [tiab])

The 1064 articles were exported and then uploaded to Rayyan.ai [5] for detection of duplicates and applying selection criteria.

Data Charting: Extraction was conducted using a structured charting table. Extracted variables included study design, disease indication, immunomodulatory agent(s), steroid co-administration, infection type and severity, and any prophylaxis strategies reported. Charting highlighted identification of infection patterns and risk modifiers rather than pooled incidence estimates, consistent with scoping review methodology.

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Results:

The initial database search yielded 1,064 articles (483 from Scopus, 244 from Science Direct, and 337 from PubMed). After records were imported to Rayyan.ai [5], 18 duplicate records were removed, leaving 1,046 unique manuscripts for title and abstract screening.

After title and abstract screening, 974 records were excluded. The primary reasons for exclusion are detailed in Figure 1 and included studies not focused on infections (n=329), HIV-related studies (n=325), and basic science (n=135).

This left 72 reports sought for retrieval. Of these, one report could not be retrieved, leaving 71 reports assessed for eligibility. After full-text review, 47 reports were excluded, because they were centered on the immunomodulatory agents rather than infectious outcomes.

A final set of 24 studies were included in this review. The final dataset therefore represents the current infection risk profile within the modern immunomodulatory treatment landscape, rather than a historical overview of infection incidence across the entire field.

Table 1 shows the evaluation of sources of evidence retrieved.

Table 1. Evaluation of Sources of Evidence.

Source of Evidence (Citation)	**Characteristics of Evidence**	**Relevant Charted Data (Relating to Review Questions & Objectives)**
Tumor Necrosis Alpha (TNF-α) Antagonists Used in Chronic Inflammatory Rheumatic Diseases: Risks and their Minimization Measures, 2024	Comprehensive Review	Risk Factors: Use of TNF-α inhibitors. Pathogen Patterns: Serious infections (general), Tuberculosis (TB), malignancy, heart failure. Prevention/Management: Highlights the critical need for Risk Management Plans (RMPs), including routine measures (labeling, package leaflets) and additional measures (educational programs for providers and patients) to minimize known risks.
Brucellosis in a patient with Crohn's disease treated with infliximab: A case report, 2025	Case Report	Risk Factors: Treatment with infliximab (a TNF-α antagonist) and azathioprine for Crohn's disease. Pathogen Patterns: Brucellosis (*Brucella species*), an opportunistic infection, contracted from raw milk. Prevention/Management: Infliximab and azathioprine were held; patient was treated with antibiotics (rifampin, doxycycline, streptomycin) and biologics

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		were resumed after 4 weeks. Highlights the need for multidisciplinary (Gastroenterology, Infectious Disease) management.
A rare case of Pseudomonas aeruginosa enteritis induced by pembrolizumab, 2023	Case Report	Risk Factors: Treatment with pembrolizumab (an immune checkpoint inhibitor, ICI). Pathogen Patterns: Pseudomonal enteritis (*P. aeruginosa*), leading to septic shock. Prevention/Management: Recommends a high level of alertness for infectious complications with biologic-targeted drugs. Patient was successfully treated with corticosteroids and antibiotics.
Pos0912 A Novel Scoring System to Predict Serious Infections In Patients With Rheumatic Diseases Receiving Prolonged, High-Dose Glucocorticoid Treatment, 2024	Cohort Study (Development & Validation)	Risk Factors: Prolonged high-dose glucocorticoids (GCs). Developed a scoring system identifying 7 key predictors for serious infection: age ≥65, interstitial lung disease (ILD), lymphopenia, decreased renal function, low serum albumin, concomitant cyclophosphamide use, and concomitant rituximab use. Pathogen Patterns: Serious infections (general). Incidence rate was 10.5 per 100 person-years in the derivation cohort. High-risk group (score ≥4) had an IR of 40.1 per 100 person-years.
Pos0835 Long-Term Safety And Efficacy Of Upadacitinib In Patients With Psoriatic Arthritis: 5-Year Results From the Phase 3 Select-PSA 1 Study, 2025	Phase 3 Clinical Trial (Long-term Extension)	Risk Factors: Long-term (5-year) treatment with upadacitinib (a JAK inhibitor) vs. adalimumab (a TNF-α inhibitor). Pathogen Patterns: Rates of serious infection were low and similar between

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		groups. Rates of herpes zoster were higher with upadacitinib compared to adalimumab.
Risk factors for hypogammaglobulinemia and association with relapse and severe infections in ANCA-associated vasculitis: A cohort study, 2024	Cohort Study	Risk Factors: Rituximab treatment. Hypogammaglobulinemia (gammaglobulin <6 g/L and >25% decline) was a key biomarker, associated with a 2.3-fold increased risk (aHR 2.3) of severe infection. Methylprednisolone pulses at induction also independently increased infection risk (HR 5.6). Prevention/Management: Gammaglobulin decline was *not* associated with a lower risk of vasculitis relapse, suggesting infection risk can be managed separately from disease control.
Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial, 2023	Randomized Controlled Trial (RITAZAREM)	Risk Factors: Rituximab vs. azathioprine for AAV maintenance. Pathogen Patterns: Rituximab was superior for preventing relapse. Critically, the rituximab group experienced fewer serious adverse events (22%) compared to the azathioprine group (36%). No difference in rates of hypogammaglobulinemia or general infection was reported between groups.
Risk of infections associated with the use of bispecific antibodies in multiple myeloma: a pooled analysis, 2023	Pooled Analysis / Meta-Analysis	Risk Factors: Treatment with bispecific antibodies (BsAbs). BCMA-targeting BsAbs (30% Grade III/IV infection) carried a higher risk than non-BCMA-targeting BsAbs (11.9%). Pathogen Patterns: High infection rates: 50% of patients developed an infection

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		(24.5% Grade III/IV). Specific pathogens included Grade III/IV pneumonia (10%) and Grade III/IV COVID-19 (11.4%). Infections caused 25.5% of all deaths. Prevention/Management: Highlights need for precautions (e.g., IVIG use) to mitigate risk.
Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II), 2023	Phase 3 Clinical Trial	Risk Factors: Treatment with baricitinib (a JAK inhibitor). Pathogen Patterns: The trial failed to meet its primary efficacy endpoint. Serious adverse events (SAEs) occurred in 11-13% of patients (vs. 9% placebo). No new safety signals were identified.
Incidence and risk factors of serious infections occurred in patients with lung cancer following immune checkpoint blockade therapy, 2025	Retrospective Analysis	Risk Factors: Treatment with Immune Checkpoint Inhibitors (ICIs). Key risk factors were patient comorbidities: COPD, asthma, and low lymphocyte count. Pathogen Patterns: High serious infection rate of 26.90%. Pathogens were predominantly bacterial (85.07%), but also included Mycobacterium tuberculosis (6.47%), viral (4.98%), and fungal (3.48%). The lung was the main site.
Infectious complications of Belimumab with standard care in systemic lupus erythematosus: a systematic review and meta-analysis, 2025	Systematic Review & Meta-Analysis	Risk Factors: Belimumab + standard care. Pathogen Patterns: Belimumab was found to not significantly increase the risk of infections or serious infections compared to standard care alone. The overall incidence of serious infections was low.

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Infection Risk Associated with High-Efficacy Disease-Modifying Agents in Multiple Sclerosis: A Retrospective Cohort Study, 2025	Retrospective Cohort Study	Risk Factors: High-Efficacy Disease-Modifying Agents (heDMAs) vs. moderate-efficacy (meDMAs). Pathogen Patterns: heDMAs were associated with a 1.24-fold higher risk (aHR 1.24) of serious infection and a 1.21-fold higher risk (aHR 1.21) of urinary tract infections (UTIs). Prevention/Management: Highlights the need for careful monitoring and management of infection risk in this group.
Rate of severe and fatal infections in a cohort of patients with interstitial lung disease associated with rheumatoid arthritis: a multicenter prospective study, 2024	Multicenter Prospective Cohort Study	Risk Factors: Disease state of Rheumatoid Arthritis-associated Interstitial Lung Disease (RA-ILD). Pathogen Patterns: Extremely high incidence rate of serious infection: 52.6 per 100 person-years. 65% of all deaths in the cohort were directly related to infection. Common sites: respiratory tract, urinary tract, skin/soft tissue.
Risk of serious infection between belimumab and oral immunosuppressants for non-renal systemic lupus erythematosus: comment on the article by Materne et al, 2023	Letter/Commentary	Risk Factors: Belimumab vs. oral immunosuppressants. Prevention/Management: Supports the findings of the main paper, reinforcing the observation that belimumab may have a favorable safety profile regarding infection risk.
Comparative Risks of Infection With Belimumab Versus Oral Immunosuppressants in Patients With Nonrenal Systemic Lupus Erythematosus, 2023	Observational Cohort Study	Risk Factors: Belimumab vs. Azathioprine (AZA) vs. Mycophenolate (MMF). Pathogen Patterns: Belimumab was associated with a *lower* risk of serious

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		infection compared to AZA (aHR 0.82) and MMF (aHR 0.69). Prevention/Management: Suggests belimumab may be a safer treatment option regarding infection risk for SLE patients without lupus nephritis.
Multiple Sclerosis, Disease-Modifying Therapies, and Infections, 2023	Review / Registry Data Analysis	Risk Factors: Specific MS therapies. Pathogen Patterns: Fingolimod and Rituximab were associated with a higher risk of serious infection (especially pneumonia) compared to injectable therapies. Natalizumab was associated with a lower risk.
The factors predicting development of serious infections in ANCA-associated vasculitis, 2023	Retrospective Cohort Study	Risk Factors: Disease-specific factors in AAV. Identified independent predictors: renopulmonary involvement, age over 65, and elevated C-reactive protein (CRP) levels. Pathogen Patterns: Serious infections occurred in 50% of the 84 AAV patients.
Serious infections in patients with systemic lupus erythematosus: how can we prevent them?, 2023	Editorial / Commentary	Risk Factors: SLE disease state, glucocorticoids, immunosuppressants. Prevention/Management: Calls for better risk stratification to identify high-risk patients, use of steroid-sparing agents (like belimumab), and implementation of preventive measures (e.g., vaccinations, *Pneumocystis* prophylaxis).
Early infection risk in patients with systemic lupus erythematosus treated with rituximab or belimumab from the British Isles Lupus Assessment Group Biologics Register	Prospective Longitudinal Cohort Study	Risk Factors: Rituximab vs. Belimumab in SLE. Pathogen Patterns: Incidence of serious infection in the first 12 months was 13.9% for rituximab and 12.5% for belimumab.

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(BILAG-BR): a prospective longitudinal study, 2023		The risk was not significantly different between the two drugs. Risk Factors: Baseline hypogammaglobulinemia and higher glucocorticoid dose were predictors of serious infection.
Serious Infection Rates Among Patients with Select Autoimmune Conditions: A Claims-Based Retrospective Cohort Study from Taiwan and the USA, 2023	Retrospective Cohort Study	Risk Factors: Disease states of SLE, Rheumatoid Arthritis (RA), and primary membranous nephropathy. Pathogen Patterns: Rates of serious infection were significantly higher in all autoimmune cohorts compared to the general population. Patients with lupus nephritis had the highest burden (7- to 25-fold higher risk). Infections were driven by bacterial, respiratory, urinary tract, and opportunistic infections.
Incidence of serious infections in patients with ANCA-associated vasculitis receiving immunosuppressive therapy: A systematic review and meta-analysis, 2023	Systematic Review & Meta-Analysis	Risk Factors: Different immunosuppressants for AAV maintenance. Pathogen Patterns: Overall cumulative incidence of SI was 15.99%. Incidence for rituximab was 14.61%; for azathioprine, 5.93%; for CYC+AZA, 20.81%. Most fatal SIs were pneumonia and sepsis.
Ratio of lymphocyte to monocyte area under the curve as a novel predictive factor for severe infection in multiple sclerosis, 2023	Retrospective Review	Risk Factors: Disease-modifying drugs (DMDs) in MS. Prevention/Management: Identified a novel biomarker: a lower ratio of lymphocyte AUC to monocyte AUC (L_AUC/t to M_AUC/t) was associated with decreased risk of serious infection. Suggests monitoring these cell count

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		ratios may be more important than the specific drug used.
Immune Checkpoint Inhibitors and Infection: What Is the Interplay?, 2023	Narrative Review	Risk Factors: Treatment with ICIs. Pathogen Patterns: ICIs per se do not seem to generally increase infection risk. However, infectious complications are often related to the immunosuppressive therapy (e.g., corticosteroids) used to manage the immune-related adverse events (irAEs) caused by the ICIs.
Aging and infectious diseases in myasthenia gravis, 2025	Review	Risk Factors: Myasthenia Gravis (MG) disease state, aging, and immunosenescence. Pathogen Patterns: Increased susceptibility to infection; respiratory tract disease is a frequent precipitating factor for myasthenic crisis and a major contributor to mortality.

Findings:

The goal of immunomodulatory therapy is to suppress autoimmune inflammation. This compromises host defense, leading to an increased susceptibility to infection. However, this risk is not uniform; it is a complex interplay between the patient's disease, their degree of immune suppression, and the mechanism of action of the drug used. [6] In fact, infections are a leading cause of hospitalization and death in autoimmune diseases, including systemic lupus erythematosus (SLE), ANCA-associated vasculitis (AAV), and rheumatoid arthritis (RA). [7–9] Data confirms that patients with autoimmune conditions like SLE and RA have higher baseline rates of serious infections compared to the general population, and this risk is increased by immunosuppression. [10]

Glucocorticoids: The Primary Driver of Infectious Risk

In the world of immunomodulatory therapies, glucocorticoids (GCs) are considered a main cause of serious infectious risk. A "serious infection" (SI) is defined in the literature as an infection requiring hospitalization, intravenous (IV) antimicrobials, or resulting in death.

In patients with SLE, daily prednisone doses exceeding 15 mg/day are a main driver for hospitalization due to serious infection. [9] With higher doses, the risk increases. A paper aimed at creating a risk-prediction model for patients with autoimmune rheumatic diseases (AIRDs) defined "high-dose" as more than or equal to 30 mg/day of prednisolone equivalent for at least 4 consecutive weeks. [11]. This high-risk group showed an incidence rate of 40.1 serious infections per 100 person-years. [11]

The use of methylprednisolone pulse therapy for rapid remission in severe autoimmune flareups, was also separately identified as a predictor for SIs in SLE. [9] The mechanism for this risk is multifactorial, affecting almost all immune cells. Steroid suppress pro-inflammatory mediators, impair neutrophil, macrophage and dendritic cell function, causes lymphopenia and poor wound

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healing and masks infective symptoms. [9] In patients with ANCA-associated vasculitis (AAV), the use of methylprednisolone pulses during induction therapy was found to have an independent negative impact on gamma globulin levels. This increases risk of severe infections. [12]

B-Cell Targeting Therapies: Rituximab and Belimumab

Therapies targeting B-cells have unique infection risk profiles, primarily related to B-cell depletion and effects on immunoglobulin levels.

Rituximab (Anti-CD20)

Rituximab's powerful B-cell depletion is a known risk factor for hypogammaglobulinemia, which directly correlates with infection risk. In AAV patients, a significant decline in gammaglobulin levels following rituximab induction was associated with a 2.3-fold increased risk of severe infections. [12] A systematic review and meta-analysis quantified the cumulative incidence of serious infections during rituximab maintenance therapy for AAV at 14.61%. [13]

However, when compared directly to conventional immunosuppressants for maintenance, the risk may be comparable. The RITAZAREM trial, a randomized study in relapsing AAV, found that while rituximab was superior to azathioprine for relapse prevention, there were no differences in the rates of infection or hypogammaglobulinemia between the two groups. [14] The infections associated with rituximab were bronchitis, tuberculosis, pneumonia, *Pneumocystis jirovecii* pneumonia, bacterial endocarditis, atypical mycobacterial infection, prostatitis, herpes zoster infection, cholecystitis, septicemia, esophageal candidiasis, hepatitis B reactivation and infectious diarrhea. [14] In SLE, a prospective longitudinal study (BILAG-BR) directly compared the early infection risk of rituximab and belimumab, providing head-to-head real-world safety data with similar safety and infection risk. [15]

Belimumab (Anti-BLyS)

Belimumab, which inhibits B-lymphocyte stimulator (BLyS), is also associated with infection risk. A 2023 study found that it was associated with a lower risk of serious infection compared to oral immunosuppressants like azathioprine and mycophenolate in patients with non-renal SLE. [16] This finding was debated, specifically in clinical decision-making, where it is thought that belimumab may have a favorable safety profile regarding serious infections when compared to some oral immunosuppressants for non-renal SLE. [17] A separate 2025 systematic review and meta-analysis synthesized data on infectious complications, aiming to clarify the overall safety profile of belimumab in SLE, where doses ≤10mg/kg did not increase infection risk when coupled with standard of care. [18]

TNF-α Inhibitors

Inhibitors of Tumor Necrosis Factor-alpha (TNF-α) are established therapies, like Adalimumab, Etanercept, Infliximab, Golimumab, and Certolizumab, but their association with serious and opportunistic infections is a concern. A 2024 review showed that serious infections are among the most significant risks of this class, necessitating robust risk minimization plans. [19] Infections associated with these drugs include TB, Histoplasma, Listeria, Legionella, Salmonella, Candida, Aspergillus infections and hepatitis B virus (HBV) or varicella zoster virus (VZV) reactivations. [19]

A 2025 case report shows the risk of specific opportunistic pathogens, describing a 40-year-old Crohn's disease patient on infliximab and azathioprine who was diagnosed with brucellosis after consuming raw milk. This case highlights the need for patient education on avoiding specific exposures while on anti-TNF therapy. [20] Anti-TNF therapy (specifically adalimumab) served as a standard in a 5-year study on psoriatic arthritis, where rates of serious infection and herpes zoster were higher in the upadacitinib (JAK inhibitor) group than in the adalimumab group. [21]

JAK Inhibitors (JAKinibs)

This class of oral small molecules is very potent, but long-term data has clarified a specific infection risk profile, particularly for herpes zoster.

Upadacitinib

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The 5-year follow-up of the SELECT-PsA 1 trial provided long-term safety data for upadacitinib in psoriatic arthritis. Compared to adalimumab, upadacitinib was associated with higher rates of serious infection and, most distinctly, herpes zoster. [21]

Baricitinib: The SLE-BRAVE-II phase 3 trial evaluated baricitinib in active SLE. While the study failed to meet its primary efficacy endpoints, it provided safety data. Serious adverse events, including TB, herpes zoster, serious or opportunistic infections were reported in 11%–13% of patients in the baricitinib arms, compared to 9% in the placebo group. [22]

Immune Checkpoint Inhibitors (ICIs)

ICIs, such as PD-1 inhibitors, function by removing inhibitory signals for T-cell responses, leading to immune dysregulation and functional exhaustion, and treatment of immune-related adverse events with high-dose steroids can contribute to infection risk. A 2025 study of lung cancer patients treated with ICIs found a serious infection rate of 26.90%. [23]. The infections were predominantly bacterial (85.07%) and most often involved the lungs (75.61%). This study also identified Mycobacterium tuberculosis (6.47%), viral (4.98%), and fungal (3.48%) infections as complications. [23]

Beyond typical infections, ICIs can cause severe immune-related adverse events (irAEs) that manifest as infections. A 2023 case report detailed a patient on pembrolizumab who developed Pseudomonal (P. aeruginosa) enteritis, which was diagnosed as an irAE, highlighting the risk of severe gut-related bacterial complications. [24]

Bispecific Antibodies (BsAbs)

This novel class of therapeutics, used primarily in hematologic oncology, carries a high risk of infection driven by profound neutropenia and hypogammaglobulinemia. A 2023 pooled analysis of 1,185 patients with multiple myeloma treated with BsAbs showed that 50% of all patients developed infections of any grade, and 24.5% developed Grade III/IV infections. [25] Severe infections included pneumonia (10%) and COVID-19 (11.4%). These infections were strongly associated with Grade III/IV neutropenia (34.8%) and hypogammaglobulinemia (75.3%). [25]

Disease-Modifying Therapies (DMTs) in Multiple Sclerosis (MS)

Infection risk in MS is a significant factor in therapy selection. A 2025 retrospective cohort study directly compared high-efficacy DMTs (heDMAs, e.g Alemtuzumab, Cladribine, Natalizumab and Ocrelizumab) with moderate-efficacy DMTs (meDMAs, e.g interferon-beta, Teriflunomide, Siponimod, Ozanimod). The study found that heDMAs were associated with a significantly higher risk of serious infections (Adjusted Hazard Ratio aHR 1.24) and, specifically, urinary tract infections (UTIs) (aHR 1.21). [26] This aligns with other 2023 studies confirming that both the disease and its treatments predispose MS patients to infections and that predictive factors, such as the lymphocyte-to-monocyte ratio, are needed to stratify this risk. [27,28]

Table 2 shows the infectious risk associated with each immunomodulatory agent.

Table 2. Agent-specific Infectious Risks.

Drug Class	Specific Drug(s)	Associated Disease(s)	Infectious Risks
Glucocorticoids (GCs)	Prednisone Prednisolone Methylprednisolone	Autoimmune Rheumatic Diseases (AIRDs)	Serious Infections (general); Incidence Rate 10.5 per 100 person-years. Risk factors: age ≥65, ILD, lymphopenia, low albumin, low eGFR.

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	Dexamethasone	ANCA-Associated Vasculitis (AAV)	Severe Infections (general); associated with GC-induced hypogammaglobulinemia (aHR 2.3 for infection if low).
TNF-α Antagonists	Infliximab, Adalimumab, others	Chronic Inflammatory Rheumatism	Serious infections (general), Tuberculosis (TB) reactivation, malignancy, heart failure. Requires Risk Management Plans (RMPs).
	Infliximab (with Azathioprine)	Crohn's Disease	Brucellosis (opportunistic infection).
B-Cell Modulators	Rituximab	ANCA-Associated Vasculitis (AAV)	Fewer serious adverse events (22%) than azathioprine (36%). No difference in general infection rates. Cumulative incidence of serious infections: 14.61% (vs 5.93% for azathioprine). Fatal SIs: Pneumonia, Sepsis. Severe Infections (general); strongly associated with hypogammaglobulinemia (aHR 2.3 for infection if low).
		Systemic Lupus Erythematosus (SLE)	Serious infection incidence: 13.9% in the first 12 months.
	Belimumab	Systemic Lupus Erythematosus (SLE)	No significant increase in infection risk compared to standard care.
		Non-renal SLE	*Lower risk* of serious infection compared to Azathioprine (aHR 0.82) and Mycophenolate (aHR 0.69).
JAK Inhibitors	Upadacitinib	Psoriatic Arthritis (PsA)	Herpes zoster (higher rate than adalimumab). Rates of serious infection, malignancy, MACE, and VTE were low.

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	Baricitinib	Systemic Lupus Erythematosus (SLE)	Serious adverse events (SAEs) occurred in 11-13% of patients (vs. 9% placebo). No new safety signals.
Immune Checkpoint Inhibitors (ICIs)	Pembrolizumab	Hypopharyngeal Carcinoma	Pseudomonal enteritis (*P. aeruginosa*), septic shock.
	ICIs (general)	Lung Cancer	Serious infection rate: 26.90%. Pathogens: Bacterial (85.07%), Mycobacterium tuberculosis (6.47%), Viral (4.98%), Fungal (3.48%). Risk factors: COPD, asthma.
		Cancer (general)	Infectious complications are often related to the immunosuppressive therapy (e.g., corticosteroids) used to treat irAEs, not the ICI itself.
Bispecific Antibodies (BsAbs)	BCMA-targeting & non-BCMA-targeting	Multiple Myeloma	All-grade infections: 50%. Grade III/IV infections: 24.5%. Grade III/IV Pneumonia: 10%. Grade III/IV COVID-19: 11.4%. Infections caused 25.5% of deaths. BCMA-targeting BsAbs had higher risk (30%) than non-BCMA (11.9%).
MS Therapies	High-Efficacy DMAs (heDMAs)	Multiple Sclerosis (MS)	Higher risk of serious infection (aHR 1.24) and Urinary Tract Infections (UTIs) (aHR 1.21) compared to moderate-efficacy DMAs.
	Fingolimod, Rituximab, Natalizumab		Fingolimod and Rituximab: Higher risk of serious infection (especially pneumonia). Natalizumab: Lower risk.
Other Immunosuppressants	Azathioprine	ANCA-Associated Vasculitis (AAV)	Serious adverse events (36%). Cumulative incidence of serious infection: 5.93%.
	Mycophenolate	Non-renal SLE	*Higher risk* of serious infection compared to Belimumab (aHR 0.69 for Belimumab vs Mycophenolate).

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Disease-Specific (No Drug Specified)	N/A	Myasthenia Gravis (MG)	Increased susceptibility to infection; respiratory tract disease is a frequent cause of death.
		Rheumatoid Arthritis w/ ILD	Extremely high serious infection rate: 52.6 per 100 person-years. 65% of all deaths were infection-related.
		Systemic Lupus Erythematosus (SLE)	High baseline risk, especially lupus nephritis.
		Multiple Sclerosis (MS)	A novel biomarker (L_AUC/t to M_AUC/t ratio) was identified as a predictive factor for severe infections.

Discussion:

Upon reviewing the results, we find some patterns.

Glucocorticoids: Still Our Biggest Problem

We use glucocorticoids across almost every autoimmune condition. They're our go-to for induction therapy and flare management, but they are also the reason patients end up hospitalized with serious infections.

To mitigate this, we need to advocate for using steroid-sparing agents. Starting them early allows a faster steroid taper. Getting them to the lowest effective dose and keeping them on steroids for shortest time would decrease this infection risk. [29]

For Pneumocystis prophylaxis, the standard is that any patient on 20 mg or more of prednisone for longer than 4 weeks needs coverage, usually with trimethoprim-sulfamethoxazole. [30] Screening for latent TB, hepatitis B and C, and Strongyloides (if in endemic areas) is important. [31]

B-Cell Therapies: Two Different Stories

How we target B cells makes a difference in infection risk. Rituximab works by depleting CD20-positive B cells. We use it in ANCA-associated vasculitis, rheumatoid arthritis, and off-label in SLE. The problem is the profound B-cell depletion leads to hypogammaglobulinemia in many patients. [32]

With Rituximab, it is important to regularly check baseline IgG levels. Besides, vaccination before starting rituximab, especially against pneumococcus, influenza, hepatitis B and COVID-19 2 to 4 weeks before the infusion. [33] Also, live vaccines are to be avoided.

Belimumab targets B-lymphocyte stimulator (BLyS), which modulates B-cell activity more gently with less infection risk. For clinical practice, this makes belimumab an attractive steroid-sparing option for non-renal SLE patients who already have high baseline infection risk or keep getting recurrent mild-to-moderate infections. [34] Except with concurrent high dose steroid use, routine antimicrobial prophylaxis is not warranted. [35]

TNF Inhibitors: The Granuloma Problem

We use TNF-alpha inhibitors widely, in rheumatoid arthritis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. These drugs have a specific infection signature that comes from their role in maintaining granulomas and cell-mediated immunity. [36]

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The big worry is reactivation of latent tuberculosis. [37] We also see opportunistic infections with intracellular pathogens like Histoplasma, Listeria, Legionella, and Salmonella, plus viral reactivations including hepatitis B and varicella zoster. [38]

Before initiating TNF inhibitors, the patient should be screened for TB, and check for hepatitis B and C before starting therapy. [38] Patient education is important, as it is recommended to talk to patients about food safety and environmental exposures. For example, they need to avoid unpasteurized milk and soft cheeses because of Listeria and Brucella risk. [20] They should also stay away from activities that disturb soil in areas where Histoplasma is common, and avoid cleaning bird coops. [38] Basic food safety with poultry matters because of Salmonella risk. Make sure they get the recombinant zoster vaccine (Shingrix) since VZV reactivation is a real concern. [38]

JAK Inhibitors: The Zoster Problem

JAK inhibitors are used in rheumatoid and psoriatic arthritis. The SELECT-PsA 1 trial showed that the risk of zoster reactivation is high. [39] The rate is significantly higher than with anti-TNF therapy. There is also an increase in serious infections and TB risk. This happens because the JAK-STAT pathway is crucial for interferon signaling and T-cell antiviral responses. [39] The recombinant zoster vaccine is thus essential before starting therapy, in addition to screening for latent TB and viral hepatitis. [40]

High-Risk Cancer Therapies: Two Extremes

Immune checkpoint inhibitors used in lung cancer and melanoma have a 26.9% rate of serious infections. Any new symptom, like diarrhea, cough, fever requires a workup to rule out both infection and an immune-related adverse event. This matters guides treatment options that are very different; antibiotics versus high-dose steroids. [41]

Bispecific antibodies in multiple myeloma have the most concerning profile in the literature. We're seeing a 50% rate of infections at all grades, with 24.5% being Grade III or IV. This is driven by severe therapy-induced neutropenia (34.8% of patients) and hypogammaglobulinemia (75.3% of patients). [25] These patients thus need comprehensive prophylaxis: coverage for Pneumocystis, antifungals like fluconazole, and antivirals like acyclovir. [42] G-CSF is also to be used to help with the neutropenia. Given that three-quarters of patients develop low immunoglobulin levels, IgG monitoring and intravenous immunoglobulin (IVIG) replacement reduces infectious complications. [42]

MS Disease-Modifying Therapies: The Efficacy-Safety Trade-off

The data on multiple sclerosis treatments shows that high-efficacy DMTs carry a higher risk of serious infections compared to moderate-efficacy DMTs. Much of this risk relates to how much lymphopenia the drug causes. [26]

This information needs to be part of your shared decision-making conversation with patients, discussing higher relative risk of serious infection vs better control of their MS. [43]

Risk stratification is also helpful. There's evidence that things like the lymphocyte-to-monocyte ratio might help predict who's at higher risk. [44] At minimum, monitoring lymphocyte counts regularly to hold or adjust therapy if the absolute lymphocyte count drops below 200 to 500 cells per microliter, depending on which drug is being used. [44]

Table 3 shows the agent-specific recommendations to reduce infection risk.

Table 3. Agent-specific recommendations.

Drug Class	Screen Before Starting	Vaccines	Prophylaxis Needed?
Glucocorticoids ≥20 mg/day	TB, Hep B, Strongyloides (if endemic)	Influenza & pneumococcal	Yes: TMP-SMX for PCP ≥4 weeks

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Rituximab	IgG levels, Hep B (core Ab)	Give vaccines ≥2–4w pre-infusion	Consider PCP prophylaxis if also on steroids
TNF-α Inhibitors	TB (IGRA/TST), Hep B/C	Give Shingrix pre-therapy	No routine antimicrobial prophylaxis
JAK Inhibitors	TB, Hep B/C	Shingrix required	No routine prophylaxis unless on steroids
Bispecific Antibodies	CBC + IgG baseline	COVID, pneumococcal	Yes: PCP + antiviral (acyclovir) ± antifungal

Limitations:

This scoping review summarizes contemporary evidence but does not quantify comparative infection risks. Study heterogeneity, variation in definitions of serious infection, and differing background disease activity limit direct comparison across agents. Data for some newer therapies rely on real-world observational studies or case reports, which may under- or over-estimate infection risk. Restricting the search to 2023 onward improves relevance to current practice but may exclude earlier systematic data. Individual patient factors, including comorbidities and cumulative immunosuppression, could not be stratified. Therefore, the findings should guide clinical reasoning rather than be interpreted as absolute risk estimates.

Conclusion

The evidence from 2023 to 2025 shows that while newer immunomodulatory agents offer targeted efficacy, they are universally associated with significant infectious risk, presenting as a plethora of specific vulnerabilities. Glucocorticoids, especially at high and pulse doses, remain a primary driver of serious infections across all autoimmune diseases. [9,11,12]

Targeted biologics and small molecules present unique risk profiles: JAK inhibitors show a clear signal for herpes zoster, [21] TNF-α inhibitors for opportunistic pathogens like Brucella [20], ICIs for severe bacterial pneumonias and tuberculosis [23], and novel BsAbs for severe infections secondary to neutropenia and hypogammaglobulinemia. [25]

Across RA-ILD, AAV, SLE, and MS, infections remain a leading cause of death and hospitalization. [8,10,26,45] This underscores the urgent, ongoing need for risk stratification models [11] and individualized prophylactic strategies to balance therapeutic efficacy with patient safety, consisting of screening and vaccination in the right context. Therefore, infection risk mitigation must be individualized, based on cumulative immunosuppression, steroid exposure, comorbidities, and specific agent-associated pathogen profiles.

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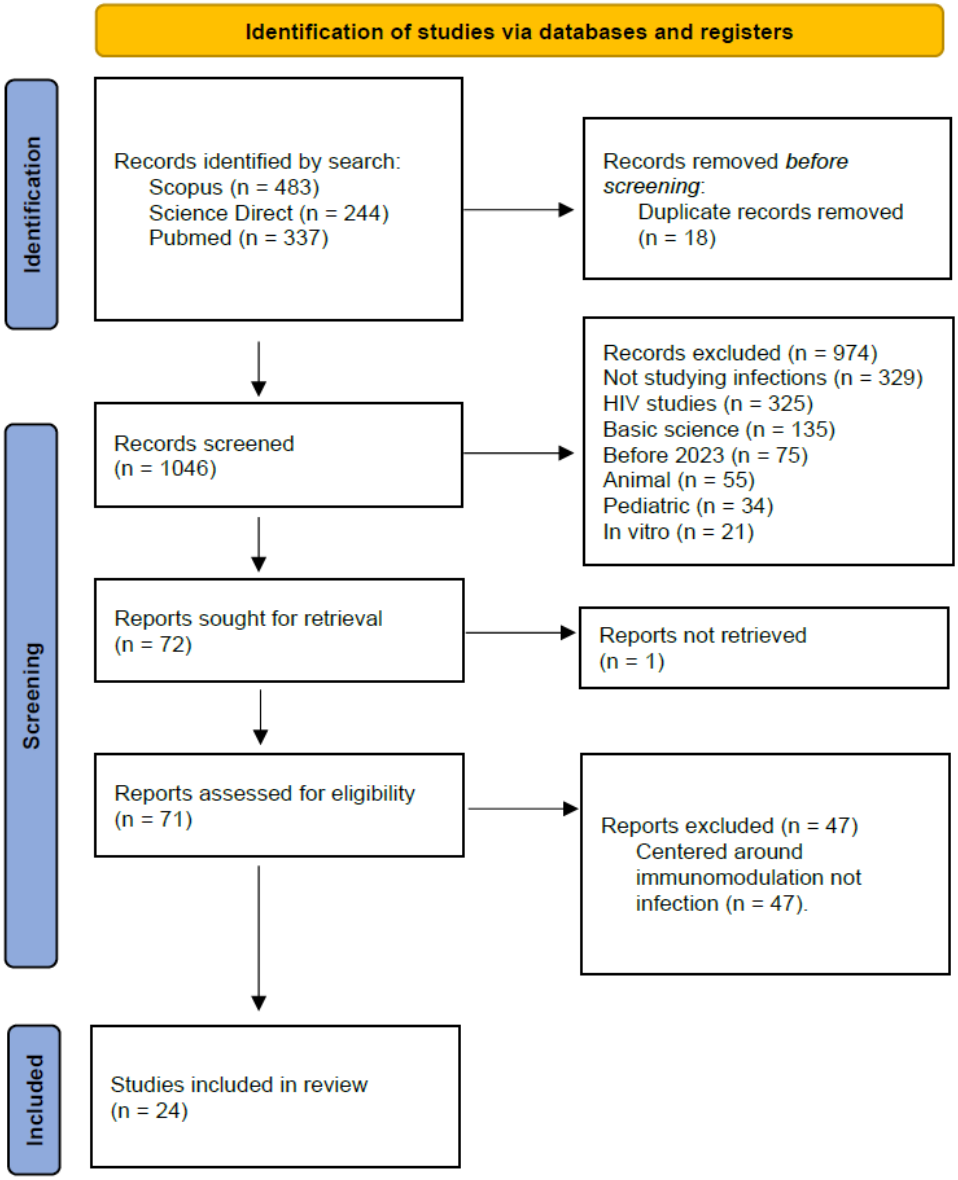

Figure 1. PRISMA 2020 flow diagram for this scoping review.

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