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Review

A Clinician's Update on Infection Risk in Patients Receiving Biologic and Targeted Synthetic DMARDs for Autoimmune Disease

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Abstract

Background: Immunomodulatory therapies, including biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) have reshaped the treatment of autoimmune diseases. They alter host defenses, but the current landscape of associated infectious risk is not fully defined. **Objective**: A scoping review of recent literature was conducted to characterize infectious complications associated with modern immunomodulatory biologic agents, summarize current pathogen patterns, and highlight recommendations for prevention and early recognition in clinical practice. **Methods**: Following PRISMA-ScR guidelines, a systematic search was performed on 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. Studies focusing exclusively on antineoplastic agents without established use in autoimmune diseases were excluded. After screening 1046 unique records, 16 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. Recent post hoc analyses (2023–2025) quantify the elevated risk of herpes zoster with JAK inhibitors compared to TNF inhibitors, particularly in older populations. **Conclusions**: The infectious risk associated with biologic and targeted DMARDs varies by mechanism. While glucocorticoids remain a primary driver of serious infections, newer data highlights specific vulnerabilities with JAK inhibitors (herpes zoster) and B-cell depletion (hypogammaglobulinemia) that require targeted risk stratification. 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: infection; immunomodulation; immune deficiency; steroids; scoping review; DMARDs; biologics; JAK inhibitors

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Academic Editors: Roberta Ramonda and Fausto Salaffi

Received: 11 November 2025
Revised: 19 December 2025
Accepted: 7 January 2026
Published: 22 January 2026

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1. Introduction

Immunomodulatory therapies have reshaped the treatment of autoimmune diseases and immune-mediated inflammatory disorders. 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].

Recently, the infection landscape has begun to shift as clinical practice increasingly incorporates high-efficacy biologics and targets small-molecule immunosuppressants [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, a scoping review of contemporary literature since 2023 was conducted 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. Although immunomodulatory agents are used across oncology and autoimmune disease, this review focuses exclusively on autoimmune and immune-mediated inflammatory diseases. While infectious risks of corticosteroids and TNF inhibitors are well-established, recent data (2023–2025) have provided clearer comparative safety profiles for newer agents (e.g., JAK inhibitors vs. TNF inhibitors) and quantified risks in real-world autoimmune cohorts. This review synthesizes this contemporary evidence.

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.

2. Methods

This scoping review followed the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines (Figure 1—PRISMA flow diagram) [4]. The PRISMA checklist is provided as Supplementary Material with this manuscript.

To ensure clinical relevance to current therapeutic practice, inclusion was restricted to studies published from 2023 onward, capturing infection risk patterns reflective of modern immunomodulatory agents, updated dosing strategies, and contemporary patient populations. The search was performed on Scopus, Science Direct, and PubMed using predefined Boolean strategies.

Records were imported into Rayyan for deduplication and screening. Inclusion criteria were as follows: (1) adult human subjects; (2) exposure to immunomodulatory therapy; (3) reported infectious outcomes; and (4) publication year $\geq$ 2023. Studies involving HIV-associated immunosuppression, pediatric populations, animal models, cadaveric or in vitro data, or publications prior to 2023 were excluded. To ensure relevance to the rheumatology readership, studies focusing exclusively on antineoplastic agents without established or

investigational use in autoimmune or immune-mediated inflammatory diseases were excluded at full-text screening. Immune checkpoint inhibitors were included in the search to ensure comprehensive capture of immunomodulatory literature, to be assessed for relevance later.

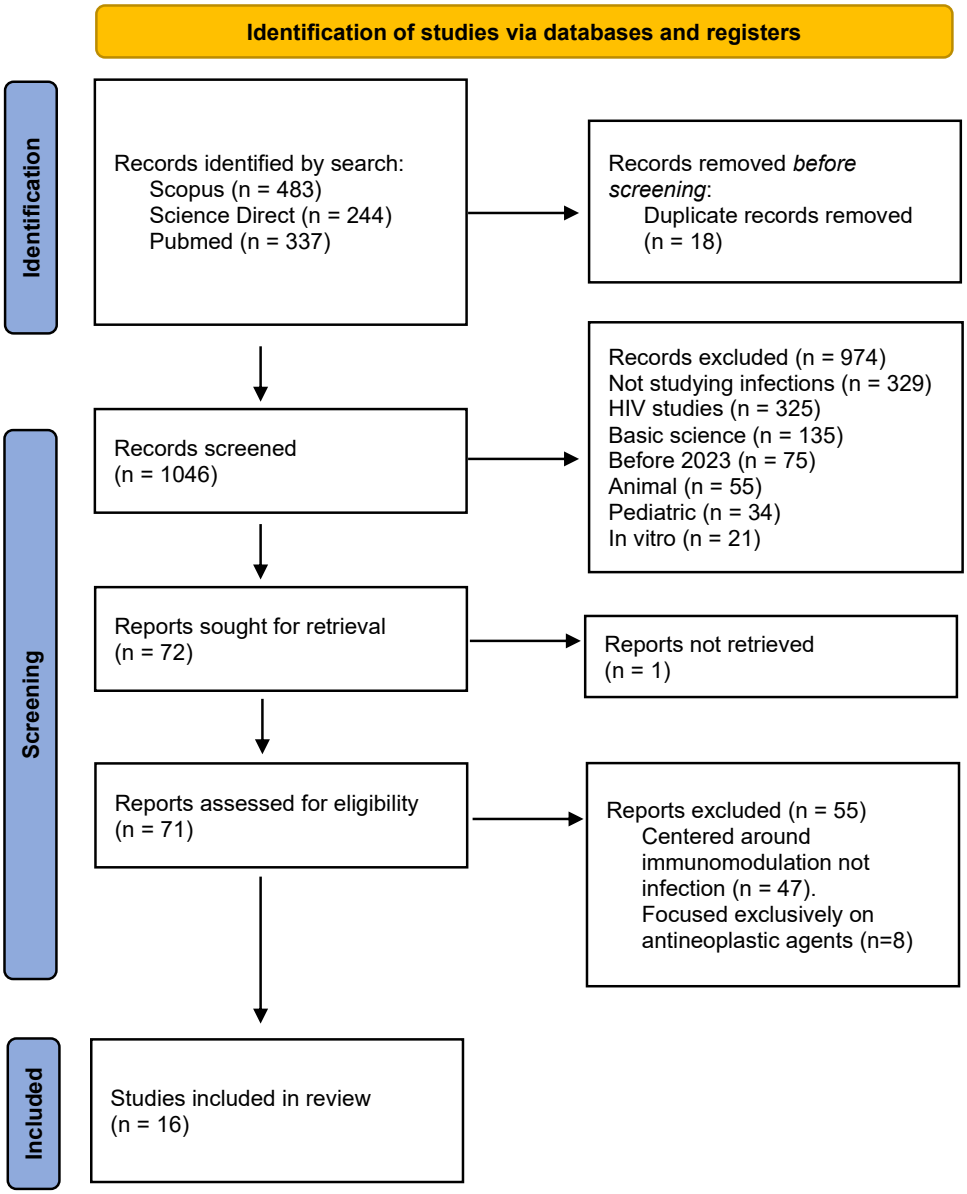


Figure 1. PRISMA 2020 flow diagram for this scoping review.

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.

Registration: This review protocol is registered in Open Science Framework under the title "A Clinician's Guide to Opportunistic Infections in the Era of Biologic and Targeted Synthetic DMARDs" with registration DOI: 10.17605/OSF.IO/2WGJ9.

3. Results

The initial database search yielded 1064 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 1046 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. An additional eight reports were excluded as they focused exclusively on antineoplastic agents.

A final set of 16 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.

Supplementary Table S1 shows a detailed evaluation of included studies (Supplementary Materials).

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]. To note, most reported outcomes are serious infections rather than opportunistic ones.

- 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. Steroids suppress pro-inflammatory mediators, impair neutrophil, macrophage and dendritic cell function, causes lymphopenia and poor wound 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 the 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 $\leq$ 10 mg/kg did not increase infection risk when coupled with standard of care [18].

This risk profile is consistent with data from other autoimmune conditions, specifically in multiple sclerosis where infection risk is a significant factor in therapy selection. DMAs 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) [19]. 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 [20,21].

- 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 [22]. 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 [22].

Opportunistic infections with intracellular pathogens are of concern, as demonstrated by a case report of brucellosis in patients consuming unpasteurized dairy [23]. 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 [24].

- 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

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 [24].

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, and serious or opportunistic infections, were reported in 11–13% of patients in the baricitinib arms, compared to 9% in the placebo group [25].

Table 1 shows the infectious risk associated with each immunomodulatory agent.

Table 1. Agent-specific Infectious Risks.

Drug Class	Specific Drug(s)	Associated Disease(s)	Infectious Risks	Reported Risk Estimates (HR, IRR, 95% CI)
Glucocorticoids (GCs)	Prednisone Prednisolone Methylprednisolone Dexamethasone	Autoimmune Rheumatic Diseases (AIRDs)	Serious Infections (general).	Serious infections: IR 40.1 per 100 PY in high-risk group (≥30 mg/day ≥4 weeks); [11] Overall IR: 10.5 per 100 PY (derivation cohort) [11].
		ANCA-Associated Vasculitis (AAV)	Severe Infections (general); associated with GC-induced hypogammaglobulinemia (aHR 2.3 for infection if low).	Pulse methylprednisolone: HR 5.6 for severe infection in AAV [12].
TNF-α Antagonists	Infliximab, Adalimumab, others	Chronic Inflammatory Rheumatism	Serious infections (general), Tuberculosis (TB) reactivation, malignancy, heart failure. Requires Risk Management Plans (RMPs).	Quantitative comparative estimates not reported in included studies; risks described qualitatively [22].

Table 1. *Cont.*

Drug Class	Specific Drug(s)	Associated Disease(s)	Infectious Risks	Reported Risk Estimates (HR, IRR, 95% CI)
B-Cell Modulators	Rituximab	ANCA-Associated Vasculitis (AAV)	Serious infection, most commonly respiratory, genitourinary and skin and soft tissue.	Cumulative incidence of serious infection: 14.61% during maintenance therapy (meta-analysis) [13]. Infection risk 15.99% when induction phase is included, and 7.62% during maintenance phase [13]. If azathioprine or cyclophosphamide is added to induction, cumulative incidence of infection rises to 20.81% during maintenance [13]. Respiratory infections contribute to 53% of all serious infections and 50% of infection-related deaths [13].
		Systemic Lupus Erythematosus (SLE)	Serious infection Hypogammaglobulinemia-associated infections. Herpes zoster, cytomegalovirus (CMV), tuberculosis (TB), cellulitis, cholecystitis.	First-year serious infection (SLE): 13.9% [15]. Hypogammaglobulinemia → severe infection: adjusted HR 2.3 (95% CI not reported) [12].
	Belimumab	Systemic Lupus Erythematosus (SLE)	Lower risk of serious infection compared to Azathioprine and Mycophenolate.	Serious infection vs. azathioprine: adjusted HR 0.82; vs. mycophenolate: adjusted HR 0.69 [16]. No increased serious infection risk vs. standard care (meta-analysis) [18].
JAK Inhibitors	Upadacitinib	Psoriatic Arthritis (PsA)	Herpes Serious Infection.	Herpes zoster: 3 per 100 PY for 15 mg dose and 5.6 for 30 mg dose [24]. Serious infections: 3.5 per 100 PY for 15 mg dose and 6.4 for 30 mg dose [24].
	Baricitinib	Systemic Lupus Erythematosus (SLE)	Serious infections. Herpes zoster Opportunistic infections: CMV, BK virus, esophageal candidiasis, pneumocystis pneumonia, histoplasmosis, cryptococcosis TB.	Overall serious/opportunistic infection rate: 11–13% vs. 9% for placebo [25]. Zoster: 4% of patients taking 4 mg, 3% of patients taking 2 mg [25]. Serious infection: 6% of patients taking 4 mg, 4% of patients taking 2 mg [25]. Opportunistic infection: 7% of patients taking 4 mg, 5% of patients taking 2 mg [25].

Table 1. *Cont.*

Drug Class	Specific Drug(s)	Associated Disease(s)	Infectious Risks	Reported Risk Estimates (HR, IRR, 95% CI)
Other Immuno-suppressants	Azathioprine (AZA)	ANCA-Associated Vasculitis (AAV)	Serious infection including respiratory, skin and soft tissue, urine and bloodstream infections.	Cumulative incidence of serious infection: 5.93% [13]. Cyclophosphamide + AZA: Cumulative incidence of serious infection: 20.81% [13]. Belimumab vs. AZA: HR 0.82 [16].
	Mycophenolate	Non-renal SLE	Higher risk of serious infection compared to Belimumab.	Belimumab vs. MMF: HR 0.69 [16].

HR: Hazard Ratio; IR: Incidence Rate; PY: person-years; IRR: Incidence Rate Ratio; CI: Confidence Interval; ANCA: Antineutrophil Cytoplasmic Antibody; GC: Glucocorticoids; aHR: Adjusted Hazard Ratio; AAV: ANCA-Associated Vasculitis; CMV: Cytomegalovirus; BK: BK Polyomavirus; AZA: Azathioprine; MMF: Mycophenolate Mofetil.

4. Discussion

The synthesized evidence reveals several patterns.

- Glucocorticoids: Still the Primary Driver of Infection Risk

Glucocorticoids are used across almost every autoimmune condition. They are used for induction therapy and flare management, but they are also the reason patients end up hospitalized with serious infections.

Clinical practice should prioritize the use of steroid-sparing agents to mitigate this risk. Starting them early allows a faster steroid taper. Tapering to the lowest effective dose and keeping them on steroids for the shortest time would decrease this infection risk [26].

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 [27]. Screening for latent TB, hepatitis B and C, and Strongyloides (if in endemic areas) is important [28].

Beyond absolute lymphopenia, novel risk stratification tools, such as the lymphocyte-to-monocyte ratio, may help predict severe infection risk in patients on depleting therapies, though validation in rheumatic populations is needed [29].

- B-Cell Therapies: Two Different Stories

How B-cells get targeted makes a difference in infection risk. Rituximab works by depleting CD20-positive B-cells. It is used in ANCA-associated vasculitis, rheumatoid arthritis, and off-label in SLE. A significant challenge is the profound B-cell depletion which leads to hypogammaglobulinemia in many patients [30].

With Rituximab, it is important to regularly check baseline IgG levels. In addition, vaccination before starting rituximab, especially against pneumococcus, influenza, hepatitis B, and COVID-19 2 to 4 weeks before the infusion [31]. 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 experience recurrent mild-to-moderate infections [32]. Except with concurrent high-dose steroid use, routine antimicrobial prophylaxis is not warranted [33].

- TNF Inhibitors: The Granuloma Problem

TNF-alpha inhibitors are used 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 [34].

Of real concern is reactivation of latent tuberculosis [35]. In addition, opportunistic infections with intracellular pathogens, like Histoplasma, Listeria, Legionella, and Salmonella, plus viral reactivations including hepatitis B and varicella zoster are not uncommon [36].

Before initiating TNF inhibitors, the patient should be screened for TB and checked for hepatitis B and C before starting therapy [36]. Patient education is important, as it is recommended to talk to patients about food safety and environmental exposures. They should also stay away from activities that disturb soil in areas where Histoplasma is common and avoid cleaning bird coops [36]. Basic food safety with poultry matters because of Salmonella risk. Ensure administration of the recombinant zoster vaccine (Shingrix) since VZV reactivation is a real concern [36].

- 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 [37]. 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 [37]. The recombinant zoster vaccine is thus essential before starting therapy, in addition to screening for latent TB and viral hepatitis [38].

- Disease Activity as an Independent Risk Factor

While agent-specific risks such as herpes zoster are well-defined, recent data underscores that the patient's inflammatory burden is a quantifiable driver of infection. Contextualizing the findings, a 2023 post hoc analysis of the ORAL Surveillance trial involving 4362 patients quantified this relationship. The study found that uncontrolled inflammation, measured by C-reactive protein (CRP) and the Clinical Disease Activity Index (CDAI), was a significant predictor of adverse events. Specifically, for every 5 mg/L increase in serum CRP, the hazard ratio for serious infection rose by 9% (HR 1.09) [39]. Furthermore, patients with high clinical disease activity had a 44% higher risk of non-serious infections compared to those in remission (HR 1.44). This suggests that tight control strategies to achieve remission also function as a primary infection prevention strategy [39].

The necessity of this dynamic monitoring is supported by the limitations of static risk assessment. A 2024 machine learning analysis of 8404 patients treated with tofacitinib attempted to predict serious infections using only baseline characteristics such as age, history of infection, and steroid use [40]. Despite using advanced modeling, the predictive accuracy was moderate (AUROC < 0.74), failing to meet the threshold for reliable clinical prediction. This confirms that infection risk is not a fixed baseline trait but a fluctuating probability driven by ongoing disease activity and treatment response, necessitating continuous rather than one-time risk stratification [40].

Table 2 shows the agent-specific recommendations to reduce infection risk.

Table 2. Agent-specific recommendations.

Drug Class	Screening and Risk Stratification	Vaccines	Prophylaxis
Glucocorticoids ≥ 20 mg/day	TB, Hep B, Strongyloides (if endemic) [28]	Influenza and pneumococcal [41]	TMP-SMX for PJP ≥ 4 weeks [27]
Rituximab	IgG levels, Hep B (core Ab) [12]	Give vaccines ≥ 2–4 w pre-infusion [31]	PCP prophylaxis if also on steroids [14]

Table 2. *Cont.*

Drug Class	Screening and Risk Stratification	Vaccines	Prophylaxis
TNF-α Inhibitors	TB (IGRA/TST), Hep B/C [36] Monitor CRP and disease activity [39]	Give Zoster shingles vaccine pre-therapy [38]	No routine antimicrobial prophylaxis [22]
JAK Inhibitors	TB, Hep B/C [39] Monitor disease activity [39]	Zoster shingles vaccine required [38]	No routine prophylaxis unless on steroids [25,30]

TB: Tuberculosis; Hep B: Hepatitis B; TMP-SMX: Trimethoprim/Sulfamethoxazole; PJP: *Pneumocystis jirovecii* Pneumonia; IgG: Immunoglobulin G; Ab: Antibodies; IGRA: Interferon-Gamma Release Assay; TST: Tuberculin Skin Test; TNF-α: Tumor Necrosis Factor-α; JAK: Janus kinase.

5. 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. The focus on literature from 2023 to 2025 ensures contemporary relevance and updates but may exclude earlier foundational studies of established therapies. In addition, while quantitative risk estimates were extracted where available, heterogeneity in outcome definitions remains a limitation. 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. Finally, this review focused on rheumatologic autoimmune diseases, hence findings may not generalize to other immune-mediated conditions.

6. Conclusions

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 [24], TNF-α inhibitors for opportunistic pathogens [23], while B-cell depletion requires vigilance for hypogammaglobulinemia [12].

Across RA-ILD, AAV, and SLE, infections remain a leading cause of death and hospitalization [8,10,19,42]. 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.

Beyond reaffirming established drug-specific risks, this review highlights emerging evidence linking disease activity to infection risk [40]. These insights support a dual strategy: agent-specific prophylaxis based on mechanistic vulnerabilities, coupled with tight disease control to mitigate inflammation-driven infection risk.

Therefore, infection risk mitigation must be individualized, based on cumulative immunosuppression, steroid exposure, comorbidities, disease control, and specific agent-associated pathogen profiles.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/rheumato6010004/s1, Table S1: Evaluation of Sources of Evidence. Table S2: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The author declares no conflicts of interest.

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