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Infection Risk Associated with Low Dose Rituximab in Primary Autoimmune Hemolytic Anaemia: Mechanisms, Outcomes, and Clinical Management

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ABSTRACT

Background: Primary autoimmune hemolytic anaemia (AIHA) is a rare, potentially life-threatening disorder characterized by immune-mediated destruction of red blood cells. Management of AIHA has evolved with the introduction of monoclonal antibodies such as rituximab, which targets CD20-positive B lymphocytes, playing a crucial role in refractory or relapsed cases. While standard-dose rituximab is effective, concerns regarding infection risk and immunosuppression have led to increasing interest in low-dose regimens to optimize the benefit-risk profile. This review aims to critically examine the infection risks associated with low-dose rituximab therapy in primary AIHA patients. It will explore the immunopathological mechanisms underlying infection susceptibility, synthesize available clinical evidence on infection incidence and types, and evaluate strategies for risk mitigation and clinical management. Special attention is given to patient-related risk factors, timing and patterns of infections, and the impact of infections on morbidity and overall outcomes.

Conclusion: Emerging data suggest that low-dose rituximab retains significant efficacy in AIHA while potentially reducing the risk and severity of infections compared to conventional dosing. Nevertheless, infection remains a notable complication, driven by rituximab-induced B cell depletion, hypogammaglobulinemia, and impairment of humoral immunity. The risk is modulated by baseline patient characteristics, concomitant immunosuppressive therapies, and existing comorbidities. Prophylactic interventions, vigilant monitoring, and individualized risk assessment are critical to optimizing patient safety. Current clinical guidelines emphasize the importance of infection screening, vaccination, and patient education. Despite promising results, long-term studies are warranted to define optimal dosing, identify high-risk subgroups, and develop targeted prevention strategies. In summary, understanding and managing infection risk is paramount to safely integrating low-dose rituximab into the therapeutic armamentarium for primary AIHA.

Keywords: *Infection Risk , Primary Autoimmune Hemolytic Anaemia, Rituximab*

Introduction

Primary autoimmune hemolytic anaemia (AIHA) is a heterogeneous group of disorders defined by the presence of autoantibodies targeting erythrocyte antigens, resulting in premature red blood cell destruction and variable degrees of anemia. The disease spectrum ranges from mild, compensated hemolysis to fulminant cases with life-threatening anemia and organ dysfunction. Conventional

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first-line therapy relies on corticosteroids, yet up to 30-40% of patients exhibit inadequate responses or frequent relapses, necessitating second-line immunosuppressive strategies[1].

Rituximab, an anti-CD20 monoclonal antibody, has significantly expanded therapeutic options for AIHA, particularly in refractory or relapsing disease. While initially administered at the standard lymphoma dose (375 mg/m² weekly for four weeks), recent studies suggest that lower doses may achieve comparable efficacy with potentially improved safety profiles[2]. However, the immunomodulatory nature of rituximab raises substantial concerns regarding infection risk, especially as B-cell depletion and hypogammaglobulinemia may impair humoral immunity for extended periods[3].

Despite growing adoption of low-dose rituximab in AIHA, the data regarding infection risk in this specific context remain limited and somewhat contradictory. Most available studies are retrospective, small-scale, or extrapolated from lymphoma or rheumatological populations, complicating direct application to primary AIHA[4]. Moreover, factors such as underlying immune dysregulation, concomitant therapies, and patient-specific risk profiles further confound the assessment of infectious complications.

The aim of this review is to systematically examine the current evidence and pathophysiological mechanisms underlying infection risk in primary AIHA patients treated with low-dose rituximab. By addressing this research gap, we hope to inform clinicians about the magnitude and nature of infection risk, highlight risk mitigation strategies, and propose areas for future investigation to optimize patient outcomes[5].

Primary Autoimmune Hemolytic Anaemia: Overview and Immunopathogenesis

Primary autoimmune hemolytic anaemia (AIHA) is an uncommon, acquired disorder in which autoantibodies target and mediate the destruction of the patient's own erythrocytes. The incidence is estimated at 1–3 cases per 100,000 persons per year, affecting individuals of all ages but showing a slight female predominance. AIHA is classified as primary (idiopathic) when no underlying disease is identified, and secondary when associated with conditions such as lymphoproliferative disorders, autoimmune diseases, or infections[6].

The immunopathogenesis of primary AIHA is complex and multifactorial. Central to its pathophysiology is the loss of self-tolerance, resulting in the production of autoantibodies (most commonly immunoglobulin G [IgG] or M [IgM]) that bind to red blood cell (RBC) surface antigens. These autoantibodies may activate complement or directly mediate phagocytosis by splenic or hepatic macrophages. The clinical course and laboratory features depend on the thermal characteristics of these antibodies, distinguishing between warm AIHA (typically IgG-mediated,

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active at 37°C) and cold agglutinin disease (primarily IgM-mediated, active at lower temperatures)[7].

The breakdown of tolerance in primary AIHA is thought to result from dysregulation of B-cell and T-cell function, impaired regulatory T cell (Treg) activity, and aberrant antigen presentation. Studies demonstrate that abnormalities in cytokine networks, particularly increased levels of B-cell activating factor (BAFF) and interleukin-10 (IL-10), further promote autoantibody production and survival of autoreactive clones[8]. Genetic susceptibility and environmental triggers, though less well defined, may also contribute to disease onset and perpetuation.

The manifestations of primary AIHA are highly variable, ranging from mild, compensated hemolysis to severe, life-threatening anemia with jaundice, splenomegaly, and reticulocytosis. Laboratory hallmarks include a positive direct antiglobulin (Coombs) test, elevated lactate dehydrogenase (LDH), indirect hyperbilirubinemia, and reduced haptoglobin. Understanding the immunopathogenesis of AIHA has laid the foundation for targeted therapies, including B-cell depleting agents such as rituximab, which aim to curtail autoantibody production and restore immune tolerance[9].

Rituximab in AIHA: Mechanism of Action and Justification for Low Dose

Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen expressed on pre-B and mature B lymphocytes, has revolutionized the management of autoimmune and hematological disorders. In the context of primary AIHA, rituximab acts by selectively depleting B cells, thereby reducing the pool of autoreactive clones responsible for the production of pathogenic autoantibodies. The binding of rituximab to CD20 induces cell death through mechanisms including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis[10].

The initial use of rituximab in AIHA was adopted from protocols established for B-cell lymphomas, typically employing a dose of 375 mg/m² administered weekly for four consecutive weeks. However, it soon became apparent that autoimmune conditions may require lower cumulative exposure to achieve therapeutic benefit, with a favorable safety profile. Pharmacodynamic studies have shown that even at reduced doses, rituximab can induce sufficient B-cell depletion and remission in a substantial proportion of AIHA patients, likely due to the lower B-cell burden compared to malignancies[11].

Several prospective and retrospective studies have reported encouraging results with low-dose rituximab regimens, such as 100 mg weekly for four weeks, or single fixed doses of 375 mg, demonstrating comparable efficacy to standard dosing in inducing and maintaining remission in both adult and pediatric AIHA cohorts. The rationale for lower dosing centers on minimizing

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immunosuppression and the attendant risk of infections, as well as reducing treatment cost and drug exposure without compromising outcomes[12].

Despite the promise of low-dose regimens, there remains heterogeneity in dosing schedules, patient selection, and outcome reporting across studies. Importantly, the potential for reduced infection risk with low-dose rituximab remains an area of active investigation, as robust data on long-term safety and immunological effects are still emerging. Careful patient monitoring and individualized therapeutic decisions remain integral to optimizing benefit while mitigating the risk of infection and other adverse events[13].

Clinical Evidence for Low Dose Rituximab in AIHA

The clinical efficacy and safety of low-dose rituximab in primary AIHA have been increasingly supported by a growing body of evidence, though much of the data derives from small prospective studies, retrospective cohorts, and case series. Early investigations demonstrated that low-dose regimens—commonly 100 mg weekly for four weeks or single infusions of 375 mg—could induce sustained responses in patients with refractory or relapsed AIHA, achieving remission rates ranging from 60% to 80%, similar to those observed with conventional lymphoma dosing[14].

A multicenter retrospective study including 64 adults with primary AIHA treated with low-dose rituximab reported an overall response rate of 75%, with a complete response rate of 48% at 12 months. The time to response was generally rapid, with many patients achieving hematological improvement within four weeks. Importantly, the cumulative incidence of severe infections in this cohort was low, occurring in fewer than 10% of treated patients during follow-up[15].

Pediatric studies have also affirmed the utility of low-dose rituximab in children with AIHA, particularly in those with steroid dependence or intolerance to other immunosuppressants. In a prospective series of 23 pediatric patients, low-dose rituximab led to durable remissions in over 70% of cases with a favorable safety profile, reinforcing its suitability as a steroid-sparing strategy[16].

Meta-analyses and systematic reviews suggest that low-dose rituximab is not only effective in inducing remission but may also reduce the risk of infectious complications, likely due to decreased cumulative immunosuppression. Nevertheless, most published studies are limited by their non-randomized designs, heterogeneity in patient characteristics, and relatively short duration of follow-up. Thus, while the available evidence is encouraging, larger randomized controlled trials are needed to establish the optimal dosing, long-term efficacy, and true infection risk profile of low-dose rituximab in primary AIHA[17].

Baseline Infection Risk in AIHA Patients

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Patients with primary autoimmune hemolytic anaemia (AIHA) inherently carry an elevated risk of infections, even prior to the initiation of immunosuppressive therapies. Several factors contribute to this baseline vulnerability. First, the chronic activation and dysregulation of the immune system in AIHA can impair both cellular and humoral immune responses, predisposing individuals to bacterial, viral, and fungal pathogens. Furthermore, the disease process often leads to functional asplenia or splenic dysfunction due to chronic hemolysis and extravascular clearance of opsonized erythrocytes, which can further compromise host defense, especially against encapsulated organisms such as Streptococcus pneumoniae and Haemophilus influenzae[18].

The frequent use of corticosteroids as first-line therapy, even in moderate doses, has been associated with an increased risk of opportunistic and community-acquired infections. Prolonged or high-dose steroid exposure can suppress neutrophil function, impair mucosal immunity, and alter cytokine profiles, compounding infection susceptibility in AIHA patients[19]. Moreover, many patients may have comorbidities—such as diabetes mellitus, chronic lung disease, or advanced age—that further elevate infection risk independent of their hematological condition.

Additionally, repeated hospitalizations, transfusions, and invasive procedures, which are common in the management of severe or relapsing AIHA, increase exposure to healthcare-associated pathogens. Several observational studies have reported that infection is a significant cause of morbidity and mortality in AIHA, with severe infections accounting for up to 20% of deaths in some cohorts[20].

Baseline evaluation of infection risk in AIHA should include a detailed history of prior infections, vaccination status, assessment for underlying immunodeficiencies, and screening for chronic viral infections such as hepatitis B, hepatitis C, and HIV. This comprehensive risk assessment is essential before initiating any further immunosuppressive therapy, including rituximab, to optimize preventive strategies and reduce the risk of adverse infectious outcomes[21].

Infection Risk with Rituximab: Incidence and Types

Rituximab, by targeting CD20-positive B cells, fundamentally alters humoral immunity and consequently modifies the infection risk profile in AIHA patients. Multiple studies in both autoimmune and malignant contexts have established that rituximab use is associated with an increased risk of infections, though the magnitude of this risk appears to depend on dosing regimen, underlying disease, and concurrent immunosuppression[22]. In AIHA specifically, the infection incidence with rituximab—especially at low doses—remains incompletely defined, but emerging data suggest that serious infections are less common compared to higher doses or combination regimens.

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The most frequently reported infections following rituximab therapy are bacterial, particularly respiratory tract infections and urinary tract infections. Viral reactivations—such as hepatitis B virus (HBV), cytomegalovirus (CMV), and herpes simplex virus (HSV)—are important but less common complications, often occurring in patients with pre-existing latent infection or additional immunosuppressive agents. Fungal infections, though rare, may be observed in profoundly immunosuppressed individuals or those with prolonged neutropenia[23].

In studies of low-dose rituximab for AIHA, the overall rate of severe (grade 3/4) infections has generally been reported as under 10%, with most infections being mild to moderate and manageable with standard antimicrobial therapies. The risk of opportunistic infections appears low but is not negligible, particularly in older adults and those with comorbidities. Notably, hypogammaglobulinemia may develop in a minority of patients, predisposing them to recurrent or atypical infections[24].

Case series and cohort studies have highlighted the occurrence of delayed infections—such as Pneumocystis jirovecii pneumonia, progressive multifocal leukoencephalopathy (PML), and late-onset neutropenia—though these events remain rare in the context of low-dose rituximab. Vigilance for unusual pathogens and a high index of suspicion are warranted in patients presenting with atypical infectious syndromes after therapy[25].

Pathophysiological Mechanisms of Infection Risk with Rituximab

The infection risk associated with rituximab in AIHA is principally driven by its mechanism of action—B cell depletion—which impairs the humoral arm of the adaptive immune system. By targeting CD20-positive B lymphocytes, rituximab depletes both naïve and memory B cells, thereby reducing antibody production and limiting the body's ability to mount effective responses to new and previously encountered pathogens. This effect is especially pronounced in the months following administration, during which the nadir of B cell counts occurs[26].

Hypogammaglobulinemia, resulting from the loss of antibody-secreting B cells, is a well-recognized complication of rituximab therapy. Reduced levels of immunoglobulins, particularly IgG and IgM, have been documented in a subset of patients after both standard and low-dose regimens. This state of humoral immunodeficiency not only impairs protection against encapsulated bacteria but also diminishes the efficacy of previous vaccinations and responses to new immunizations[27]. The risk of infection is heightened if rituximab is combined with other immunosuppressive drugs, such as corticosteroids, cyclophosphamide, or mycophenolate mofetil, due to synergistic suppression of both B and T cell-mediated immunity[28].

In addition to B cell depletion, rituximab may indirectly alter the function of other immune cells, including T lymphocytes and natural killer (NK) cells. Alterations in cytokine production,

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regulatory T cell function, and antigen presentation have been observed in patients receiving rituximab, further contributing to impaired pathogen recognition and clearance. Persistent B cell depletion beyond 12 months has been associated with a sustained increase in infection risk, particularly in patients with pre-existing hypogammaglobulinemia or advanced age[29].

The overall impact on infection risk is multifactorial and modulated by individual patient characteristics, dosing regimen, duration of therapy, and the presence of comorbidities. Understanding these pathophysiological mechanisms is critical for the development of risk stratification tools, preventive interventions, and tailored treatment strategies in AIHA patients receiving rituximab.

Risk Factors for Infection in AIHA Treated with Rituximab

Infection risk in AIHA patients treated with rituximab is not uniform; it is shaped by a constellation of patient-related and treatment-specific factors. Advanced age is one of the most consistent risk factors, as elderly patients often have pre-existing immunosenescence, comorbidities, and reduced physiological reserve. Baseline immune status, including pre-treatment hypogammaglobulinemia, low lymphocyte counts, and functional asplenia, further predispose individuals to infections following rituximab therapy[30].

Concomitant use of other immunosuppressive agents—such as high-dose corticosteroids, azathioprine, or cyclophosphamide—synergistically increases the risk of serious infections. Duration and cumulative intensity of immunosuppression are directly correlated with infection rates, with prolonged steroid exposure being particularly detrimental[31]. The presence of underlying comorbid conditions, such as diabetes mellitus, chronic lung disease, or chronic kidney disease, also heightens susceptibility by compromising local and systemic defenses.

Patients with a history of recurrent infections, non-responsiveness to vaccines, or underlying chronic viral infections (e.g., hepatitis B, hepatitis C, or HIV) are at substantially greater risk for severe or atypical infections. In addition, prior splenectomy or functional asplenia exacerbates the vulnerability to encapsulated bacterial infections, a recognized cause of life-threatening sepsis in immunocompromised hosts[32].

The timing of rituximab administration in relation to other therapies and the interval since previous immunosuppression can influence the degree of immune suppression and subsequent infection risk. Furthermore, low-dose rituximab may not eliminate risk entirely, especially in patients with high-risk profiles. Recognizing and stratifying these risk factors before initiating rituximab is crucial for individualized preventive strategies, such as vaccination, antimicrobial prophylaxis, and enhanced clinical monitoring[33].

Timing and Patterns of Infections Post-Treatment

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The temporal distribution and clinical patterns of infections following rituximab therapy in primary AIHA provide important insight for surveillance and intervention strategies. Infections are most commonly observed within the first six months after treatment, corresponding to the period of maximal B cell depletion and lowest immunoglobulin levels. However, delayed infections can also occur, particularly in individuals with persistent hypogammaglobulinemia or prolonged immunosuppression[34].

Early-onset infections, arising within the first three months post-rituximab, are typically community-acquired bacterial infections, including respiratory tract infections, urinary tract infections, and skin or soft tissue infections. These are generally mild to moderate but may progress to severe disease in high-risk patients or those with additional immunosuppressive therapies. Opportunistic infections such as Pneumocystis jirovecii pneumonia, invasive fungal infections, or reactivation of herpesviruses are rare but can develop, especially when rituximab is combined with corticosteroids or cytotoxic agents[35].

Late-onset infections, occurring beyond six months, often reflect the duration and degree of humoral immunodeficiency. These infections are frequently viral, including late reactivation of hepatitis B virus (HBV), cytomegalovirus (CMV), and, very rarely, progressive multifocal leukoencephalopathy (PML) caused by JC virus reactivation. Some patients may also experience recurrent sinopulmonary or gastrointestinal infections due to sustained hypogammaglobulinemia, necessitating intravenous immunoglobulin (IVIG) replacement in severe cases[36].

Patterns of infection may vary with patient age, baseline immune status, and concomitant therapy. Cohort studies suggest that infection rates are highest in the elderly, those with pre-existing immune compromise, and patients receiving prolonged corticosteroid therapy. Importantly, the infection profile following low-dose rituximab appears similar to, or slightly less severe than, standard-dose regimens, supporting its use in patients at increased infection risk[37].

Impact on Clinical Outcomes and Morbidity

Infectious complications following rituximab therapy in primary AIHA can substantially impact clinical outcomes, often necessitating hospitalization, prolonged antimicrobial therapy, or discontinuation of immunosuppressive treatment. Severe infections may result in significant morbidity, delay disease remission, and in some cases, contribute directly to mortality. Retrospective analyses have reported infection-related hospitalization rates of 5–15% in AIHA cohorts treated with rituximab, although this appears lower with low-dose regimens compared to conventional dosing[38].

The development of severe infections during or after rituximab therapy often leads to interruptions in planned treatment, suboptimal disease control, and increased risk of AIHA relapse. Patients who

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experience opportunistic or recurrent infections may require additional interventions such as intravenous immunoglobulin (IVIG) replacement, prolonged antimicrobial prophylaxis, or even intensive care support. These complications increase healthcare utilization and may worsen quality of life due to frequent medical visits and prolonged recovery periods[39].

Mortality attributable to infections in rituximab-treated AIHA is not negligible. In several large series, infection accounted for up to 20% of deaths in this population, underscoring the need for vigilant infection surveillance and proactive management. The burden of infection is particularly high in patients with baseline immunodeficiency, older adults, and those with multiple comorbidities[40]. Even mild or moderate infections can result in considerable clinical setbacks, emphasizing the importance of individualized risk assessment and prevention.

On the other hand, successful risk mitigation strategies—such as timely vaccination, antimicrobial prophylaxis, and careful patient selection—have the potential to reduce the incidence and severity of infections, enabling more patients to benefit from rituximab's therapeutic efficacy without undue harm. Continued emphasis on infection prevention, early recognition, and multidisciplinary management remains central to improving overall outcomes in this vulnerable patient population[41].

Management and Prevention Strategies for Infections

Effective management and prevention of infections in AIHA patients treated with rituximab require a multifaceted, proactive approach. Prior to initiation of rituximab, all patients should undergo a thorough infection risk assessment, including evaluation for chronic viral infections (hepatitis B, hepatitis C, HIV), review of vaccination history, and baseline immunoglobulin quantification. Vaccination against Streptococcus pneumoniae, Haemophilus influenzae type b, and influenza is recommended, ideally administered at least two to four weeks before rituximab to maximize immunogenicity[42].

During rituximab therapy, close clinical monitoring for signs and symptoms of infection is essential, with a low threshold for diagnostic evaluation and initiation of empiric antimicrobial therapy. For patients at high risk—such as those receiving concurrent corticosteroids or with significant comorbidities—primary antimicrobial prophylaxis may be considered, including trimethoprim-sulfamethoxazole for Pneumocystis jirovecii prevention or antiviral agents in patients with prior herpesvirus infection[43]. Regular surveillance of complete blood counts, immunoglobulin levels, and hepatic function can aid in early detection of complications.

Intravenous immunoglobulin (IVIG) replacement should be considered for patients who develop severe or recurrent infections in the context of persistent hypogammaglobulinemia, as this can

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significantly reduce infection risk and improve outcomes. Early consultation with infectious disease specialists is advised in complex or refractory cases[44].

Patient education is a cornerstone of infection prevention, emphasizing the importance of early symptom reporting, adherence to prophylactic measures, and avoidance of high-risk exposures. Additionally, clinicians should be alert to the need for timely re-vaccination after B cell recovery and avoid live-attenuated vaccines during and shortly after rituximab therapy due to impaired immune responsiveness[45].

Clinical Guidelines: Recommendations for Monitoring and Prophylaxis

Several national and international guidelines now provide evidence-based recommendations for infection risk management in patients receiving rituximab for autoimmune conditions, including AIHA. The British Society for Haematology and the American Society of Hematology endorse comprehensive baseline screening, emphasizing serological testing for hepatitis B and C, HIV, and varicella zoster virus, as well as quantification of immunoglobulin levels before rituximab initiation[46]. These guidelines highlight the need to update vaccinations—especially pneumococcal, influenza, and meningococcal—ideally before therapy commencement, as vaccine efficacy is diminished following B cell depletion.

During rituximab therapy, periodic monitoring is advocated, including surveillance of complete blood counts, immunoglobulin levels, and liver function. In patients at heightened risk—such as those with previous infections, baseline hypogammaglobulinemia, or concomitant immunosuppression—guidelines recommend consideration of antimicrobial prophylaxis, including antiviral agents (e.g., acyclovir) in herpesvirus-seropositive individuals, and Pneumocystis jirovecii prophylaxis in those receiving high-dose steroids or multiple immunosuppressants[47].

Guidelines also emphasize the avoidance of live-attenuated vaccines during rituximab treatment and for at least six months afterward, due to the risk of vaccine-related disease in the context of impaired humoral immunity. In cases of persistent or severe hypogammaglobulinemia associated with recurrent infections, regular intravenous immunoglobulin replacement is advised to mitigate infection risk and improve quality of life[48]. Furthermore, the importance of patient education and multidisciplinary coordination is underscored, as these approaches can help ensure early recognition and management of infections.

Clear documentation and individualized infection prevention plans, coupled with timely referral to infectious disease or immunology specialists for complex cases, represent key recommendations within these guidelines. As new data emerge, periodic updates and institutional protocols should

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be maintained to reflect evolving best practices in infection prevention for AIHA patients on rituximab therapy[49].

Future Directions and Unmet Needs

Despite advances in the understanding and management of infection risk with low-dose rituximab in primary AIHA, several important knowledge gaps and clinical challenges persist. One major unmet need is the lack of large, randomized controlled trials directly comparing low-dose versus standard-dose rituximab regimens, particularly with a focus on long-term infectious complications, immunological recovery, and relapse rates. Current evidence remains limited to small, often retrospective studies, making it difficult to develop universally accepted, evidence-based dosing recommendations or risk mitigation strategies[50].

Further research is warranted to better characterize which patient subgroups derive the most benefit from low-dose rituximab with minimal infectious risk. There is a pressing need for validated biomarkers that can predict infection risk, guide prophylactic strategies, and enable early identification of patients most likely to develop hypogammaglobulinemia or opportunistic infections. Additionally, the long-term effects of repeated or sequential rituximab courses on immune function and infection susceptibility remain poorly defined, especially in patients with relapsing or chronic AIHA[51].

The optimal strategies for infection prevention, including timing and choice of vaccination, duration of antimicrobial prophylaxis, and criteria for immunoglobulin replacement, also require clarification through prospective studies. Greater emphasis on patient-reported outcomes, quality of life measures, and cost-effectiveness analyses will further inform the safe and sustainable use of rituximab in this population[52].

Collaboration across international research consortia, patient registries, and real-world evidence platforms is needed to collect high-quality, longitudinal data. The ultimate goal is to achieve durable disease remission in AIHA while minimizing infectious morbidity and mortality, ensuring that low-dose rituximab can be integrated into therapeutic algorithms with confidence in its safety and efficacy[53].

Conclusion

Low-dose rituximab has emerged as a valuable therapeutic option for patients with primary autoimmune hemolytic anaemia, offering effective disease control with a potentially improved safety profile compared to standard-dose regimens. Nevertheless, infection remains a clinically significant complication of rituximab therapy, arising from its targeted depletion of B cells and consequent impairment of humoral immunity. The majority of infections are mild to moderate and

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manageable, but severe and opportunistic infections can occur, especially in high-risk patient subsets and those with concurrent immunosuppression or comorbidities.

A comprehensive approach to infection risk management is essential, encompassing baseline risk assessment, pre-treatment vaccination, close clinical monitoring, and, where appropriate, prophylactic antimicrobials or immunoglobulin replacement. Adherence to evidence-based guidelines, patient education, and a multidisciplinary care model can substantially reduce infection-related morbidity and enhance clinical outcomes. While current evidence supports the use of low-dose rituximab as a means to limit cumulative immunosuppression, additional research is needed to define optimal dosing, identify predictors of infection, and refine preventive strategies. Ultimately, balancing the benefits of disease remission against the risks of infection is central to the successful integration of rituximab into AIHA management. Ongoing research and real-world data will be critical in further minimizing infectious complications and maximizing the therapeutic potential of rituximab for this rare but challenging disorder.

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