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Balancing Efficacy and Infection Risk: Low Dose Rituximab in Primary Autoimmune Hemolytic Anaemia

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ABSTRACT

***Background*:** Primary autoimmune hemolytic anaemia (AIHA) is a rare hematologic disorder marked by the immune-mediated destruction of red blood cells, leading to variable degrees of anemia and hemolysis. While corticosteroids remain the mainstay of first-line therapy, a significant proportion of patients experience refractory or relapsing disease, prompting the use of second-line immunosuppressive agents. Rituximab, a monoclonal antibody targeting CD20-positive B cells, has become an established therapeutic option, with increasing interest in low-dose regimens aimed at balancing efficacy with infection risk.

Aim: This review provides a comprehensive analysis of the efficacy and infection risk associated with low-dose rituximab therapy in primary AIHA. The objective is to synthesize current evidence on pharmacokinetics, clinical outcomes, and immune modulation, as well as to identify infection patterns and predictors, preventive strategies, and research priorities. Special focus is given to comparing low-dose with standard-dose rituximab, examining vaccination and long-term immune recovery, and discussing approaches for patient selection and risk stratification.

Conclusion: Available data indicate that low-dose rituximab is effective in inducing and sustaining remission in primary AIHA, with response rates comparable to standard dosing in many studies. Importantly, low-dose regimens may reduce cumulative immunosuppression and thereby lower the risk of serious and opportunistic infections. However, infection risk is not eliminated, and can be modulated by patient-related factors such as age, baseline immune status, comorbidities, and concurrent therapies. Preventive strategies, including vaccination, infection surveillance, and selective use of antimicrobial prophylaxis, are critical to minimizing infectious complications. Comparative studies and real-world registry data are needed to clarify the optimal dosing, long-term safety, and cost-effectiveness of low-dose rituximab. Continued research should prioritize patient-centered outcomes, individualized risk assessment, and the development of validated biomarkers to guide therapy. In summary, low-dose rituximab represents a promising strategy for balancing disease control and infection risk in primary AIHA, but requires ongoing vigilance and research to ensure optimal patient outcomes.

Keywords: Infection Risk, Rituximab ,Autoimmune Hemolytic Anaemia

INTRODUCTION

Primary autoimmune hemolytic anaemia (AIHA) remains a therapeutic challenge due to its unpredictable course, heterogeneous presentation, and potential for life-threatening hemolysis. While initial management with corticosteroids leads to remission in many patients, up to 40% may relapse or become steroid-dependent, necessitating alternative immunosuppressive strategies[1]. The introduction of rituximab, a monoclonal antibody targeting CD20-expressing B lymphocytes, has expanded second-line treatment options and demonstrated significant efficacy in inducing durable remission in both adults and children with primary AIHA[2].

However, the immunosuppressive effects of rituximab—particularly its capacity to cause B cell depletion and hypogammaglobulinemia—raise important concerns regarding infection risk. Severe infections remain a leading cause of morbidity and, in some cases, mortality in rituximab-treated patients, especially when combined with corticosteroids or other immunosuppressants[3]. Recent studies and real-world experience suggest that low-dose rituximab regimens may retain therapeutic benefit while limiting immune suppression and infection risk, prompting a shift toward tailored dosing strategies in AIHA management[4].

Despite the growing utilization of low-dose rituximab, there remains a significant research gap concerning its long-term safety, optimal patient selection, and the best practices for infection prevention. Much of the available evidence is derived from small cohorts, retrospective analyses, or extrapolation from lymphoma or rheumatologic populations, complicating direct application to primary AIHA. There is a need for systematic synthesis of available data to inform clinical decision-making and guide future research priorities[5].

The aim of this review is to critically evaluate the balance between efficacy and infection risk in the use of low-dose rituximab for primary AIHA. This article will address pharmacokinetics, immunological effects, infection patterns, comparative risk data, preventive strategies, and knowledge gaps, with the goal of supporting informed and individualized therapeutic choices.

Low Dose Rituximab: Pharmacokinetics and Rationale in AIHA

Low-dose rituximab regimens have gained attention in primary AIHA based on pharmacokinetic and pharmacodynamic considerations that differentiate autoimmune disease from malignant lymphoproliferative disorders. Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen present on the surface of pre-B and mature B lymphocytes, inducing B cell lysis through complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and direct apoptosis[6]. In the context of lymphoma, a standard dose of 375 mg/m² weekly for four weeks is required to achieve sufficient tissue and tumor penetration. However, in AIHA, the target cell burden is significantly lower, suggesting that lower doses may achieve adequate B cell depletion without unnecessary exposure[7].

Pharmacokinetic studies in autoimmune diseases indicate that even single fixed doses as low as 100 mg weekly for four weeks or a single dose of 375 mg can achieve peripheral B cell depletion similar to standard regimens. Serum half-life and clearance of rituximab are influenced by total B cell mass, immune activation, and patient-specific factors, supporting the rationale for individualized, lower dosing in AIHA[8]. Importantly, low-dose approaches may minimize cumulative immunosuppression, reduce treatment costs, and potentially lower the risk of infectious complications compared to traditional lymphoma dosing.

Initial clinical experiences and small-scale studies have demonstrated that low-dose rituximab is not only feasible but also associated with favorable efficacy and safety profiles. The immune modulation achieved with lower doses appears sufficient to interrupt pathogenic autoantibody production in most AIHA patients, particularly when administered early in the disease course or in the absence of significant comorbidities[9]. This tailored approach aligns with the broader movement toward personalized medicine in hematology and has led to increasing adoption of low-dose protocols in clinical practice.

Despite these advantages, optimal dosing regimens have not yet been universally defined, and further research is needed to delineate the lowest effective dose, optimal schedule, and long-term outcomes specific to AIHA. Comparative studies with standard-dose rituximab remain a critical unmet need in this evolving field[10].

Efficacy Outcomes: Remission and Relapse Data

The clinical efficacy of low-dose rituximab in primary AIHA has been investigated in a variety of prospective and retrospective studies, which collectively support its use as a viable alternative to standard dosing. Remission rates reported in the literature for low-dose regimens—such as 100 mg weekly for four weeks or a single dose of 375 mg—range from 60% to 80%, closely mirroring outcomes observed with conventional lymphoma-based dosing[11]. These responses include both complete and partial remissions, often achieved within several weeks of treatment initiation.

Long-term follow-up studies demonstrate that remissions achieved with low-dose rituximab are generally durable, with relapse-free survival rates at one and two years that are comparable to those of higher-dose protocols. Notably, the time to relapse does not appear to be significantly shortened by the use of lower doses, suggesting that therapeutic efficacy is maintained when cumulative drug exposure is reduced[12]. In steroid-dependent or refractory patients, low-dose rituximab has also been shown to facilitate steroid tapering and discontinuation, minimizing steroid-related adverse effects and improving overall quality of life.

Pediatric data, though more limited, are also encouraging. Several case series and cohort studies report that low-dose rituximab induces sustained responses in children with primary AIHA who have failed conventional therapies, with few treatment-related infections or significant adverse events[13]. These findings underscore the potential utility of low-dose rituximab as a steroid-sparing and immunosuppressive-sparing agent in both adults and children.

Despite these promising results, most available data derive from single-arm or observational studies, and few head-to-head trials have directly compared low-dose to standard-dose rituximab in AIHA. Furthermore, heterogeneity in dosing schedules, response criteria, and patient selection complicates direct comparisons. Ongoing randomized studies and real-world registry data are expected to provide greater clarity regarding the relative efficacy and optimal use of low-dose rituximab in the management of primary AIHA[14].

Immune Modulation: Effects on B Cells and Immunoglobulins

The therapeutic benefit of rituximab in primary AIHA is closely linked to its profound effects on B lymphocyte populations and, consequently, on humoral immunity. Low-dose rituximab achieves near-complete depletion of circulating CD20-positive B cells within days of administration, a pharmacodynamic effect comparable to standard-dose protocols in most patients[15]. This rapid B cell clearance underlies the reduction in autoantibody production and amelioration of hemolysis in responsive patients.

Despite the lower cumulative exposure, low-dose rituximab is associated with transient hypogammaglobulinemia, most notably reductions in immunoglobulin M (IgM) and, to a lesser extent, immunoglobulin G (IgG) levels. The degree and duration of hypogammaglobulinemia are variable, influenced by patient age, baseline immunoglobulin levels, and concurrent immunosuppressive therapies. Most patients experience a gradual recovery of B cell numbers and immunoglobulin concentrations within six to twelve months after therapy, though a minority—particularly those receiving repeated courses—may develop more prolonged or clinically significant immunodeficiency[16].

The risk of hypogammaglobulinemia is generally lower with low-dose compared to standard-dose regimens, which may contribute to the observed reduction in severe infection rates in published cohorts. Nevertheless, monitoring of immunoglobulin levels is recommended before and after rituximab administration, especially in patients with a history of recurrent infections or other risk factors for immunodeficiency[17]. Re-vaccination following B cell recovery may be necessary, as rituximab impairs both the primary and secondary immune response to polysaccharide and protein-based vaccines.

In addition to effects on B cells and antibodies, rituximab may modulate T cell function and regulatory networks, though the clinical relevance of these changes in AIHA is still under investigation. Overall, the immunomodulatory profile of low-dose rituximab supports its role in AIHA therapy, but necessitates ongoing vigilance for infectious complications, particularly in high-risk subgroups[18].

Baseline Infection Risk in AIHA: Clinical and Laboratory Predictors

Patients with primary autoimmune hemolytic anaemia are at heightened baseline risk for infections, even before the introduction of immunosuppressive therapies. Several clinical and laboratory factors contribute to this vulnerability. Chronic hemolysis, with the resultant release of free hemoglobin and iron, impairs innate immunity and enhances bacterial proliferation. Functional asplenia or splenic dysfunction—a frequent complication of chronic hemolytic states—compromises clearance of encapsulated

bacteria such as *Streptococcus pneumoniae* and *Neisseria meningitidis*[19].

Clinically, the presence of comorbid conditions such as diabetes mellitus, chronic lung disease, advanced age, or malnutrition independently increases susceptibility to both community-acquired and opportunistic infections. A history of frequent hospitalizations or prior severe infections is a recognized predictor of future infectious complications[20]. Laboratory findings, including baseline lymphopenia, low serum immunoglobulin levels, or markers of systemic inflammation (such as elevated C-reactive protein), are associated with higher infection rates in AIHA cohorts.

First-line therapy with corticosteroids remains a major contributor to infection risk, with the magnitude depending on dose and duration. Patients with prolonged or high-dose steroid exposure are particularly susceptible to reactivation of latent infections, such as herpesviruses, tuberculosis, or hepatitis B, as well as fungal and bacterial pathogens. Pre-existing immune dysregulation in AIHA—manifested by impaired T-cell and B-cell function and abnormal cytokine profiles—further compounds the risk[21].

Thorough assessment of these clinical and laboratory risk factors prior to initiating rituximab therapy is essential for identifying patients at highest risk of infection. Early intervention strategies, including vaccination, infection screening, and prophylactic antimicrobials, can then be targeted more effectively, reducing morbidity and optimizing outcomes in this complex patient population[22].

Infection Patterns After Low Dose Rituximab: Evidence Synthesis

Clinical data from observational studies, case series, and small prospective cohorts have helped define the infection patterns seen in primary AIHA patients treated with low-dose rituximab. The overall incidence of serious infections appears lower than that reported with standard lymphoma-dose regimens, though infections remain a notable complication. Most infections occur within the first six months after treatment, aligning with the period of greatest B cell depletion and hypogammaglobulinemia[23].

The majority of reported infections are mild to moderate in severity and include upper and lower respiratory tract infections, urinary tract infections, and soft tissue infections. Bacterial pathogens, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli*, predominate. Viral reactivations, including herpes simplex virus (HSV), varicella zoster virus (VZV), and hepatitis B, have been observed but are less common with low-dose than standard-dose rituximab, particularly when appropriate screening and prophylaxis are employed[24]. Opportunistic infections, such as *Pneumocystis jirovecii* pneumonia, are rare but may occur in patients receiving concurrent corticosteroids or with additional immunodeficiency.

Several cohort studies have found that the overall rate of grade 3–4 (severe) infections is generally less than 10% with low-dose rituximab, and infection-related mortality is uncommon. Most infections respond to standard antimicrobial therapies, and hospitalization is infrequently required. However, cases of delayed-onset infections, such as late viral reactivation or recurrent sinopulmonary infections, have been described in patients with persistent hypogammaglobulinemia or those receiving repeated courses of rituximab[25].

Long-term safety data are still emerging, and the risk of infection may be higher in elderly or frail patients, those with comorbidities, or those receiving multiple immunosuppressive agents. Continued surveillance and reporting are needed to fully characterize the infectious risk associated with low-dose rituximab in real-world settings[26].

Opportunistic and Severe Infections: Case Reports and Series

Although most infections in primary AIHA patients receiving low-dose rituximab are mild and self-limited, rare cases of opportunistic and severe infections have been reported in the literature. Published case reports and small series highlight that the risk, while reduced compared to higher-dose regimens, is not eliminated, particularly in individuals with additional immunosuppressive therapy, underlying immunodeficiency, or pre-existing comorbidities[27].

Documented opportunistic infections include *Pneumocystis jirovecii* pneumonia (PJP), cytomegalovirus (CMV) reactivation, progressive multifocal leukoencephalopathy (PML) due to JC virus, and invasive fungal infections such as aspergillosis. These events have been most commonly described in patients with persistent or profound hypogammaglobulinemia, or those treated with a combination of rituximab and corticosteroids or cytotoxic agents. Several reports also note severe bacterial sepsis—often due to encapsulated organisms—in patients with functional asplenia or baseline immune compromise[28].

Severe viral reactivation, particularly of hepatitis B virus (HBV), remains a critical concern in endemic areas or in those with serological evidence of prior infection. Reactivation can occur months after rituximab administration, underlining the importance

of rigorous pre-treatment screening and antiviral prophylaxis. Delayed-onset neutropenia, another complication of rituximab, may further contribute to infectious risk, necessitating close hematological monitoring and prompt intervention if febrile episodes occur[29].

Most published case series stress the need for individualized infection risk assessment and highlight the importance of early recognition and aggressive management of severe infections. Despite their rarity, opportunistic and life-threatening infections should remain on the clinician's differential diagnosis, particularly when evaluating unexplained symptoms or new organ dysfunction in rituximab-treated AIHA patients[30].

Prophylaxis and Preventive Strategies

Prevention of infections is a cornerstone of safe and effective use of low-dose rituximab in primary AIHA. A comprehensive, individualized approach is recommended for all patients prior to and during rituximab therapy. This includes baseline screening for chronic viral infections—especially hepatitis B and C, HIV, and, when indicated, tuberculosis—as well as assessment of vaccination status and baseline immunoglobulin levels[31].

Vaccination should ideally be completed prior to rituximab administration, as antibody responses are blunted for at least six months after B cell depletion. Recommended vaccines include those targeting *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis*, and annual influenza. Live-attenuated vaccines should be avoided during and for several months following rituximab therapy due to impaired cellular and humoral immunity[32]. Booster vaccinations may be required once immune reconstitution is documented.

Antimicrobial prophylaxis is indicated in select high-risk patients—such as those on concomitant high-dose steroids or with known hypogammaglobulinemia. Prophylaxis against *Pneumocystis jirovecii* pneumonia with trimethoprim-sulfamethoxazole is recommended in these cases, and antiviral agents (e.g., acyclovir or valacyclovir) may be considered in patients with prior herpesvirus infections. In those with serological evidence of resolved or chronic hepatitis B, prophylactic antiviral therapy should be initiated to prevent reactivation, as per guideline recommendations[33].

Close monitoring for clinical signs and laboratory evidence of infection is critical throughout and after therapy. Regular evaluation of complete blood count, immunoglobulin levels, and liver function tests aids early detection of complications. In patients who develop persistent or severe hypogammaglobulinemia, intravenous immunoglobulin (IVIG) replacement may reduce the risk of recurrent infections. Patient education regarding infection symptoms, hygiene measures, and the importance of early medical attention is essential to reduce infection-related morbidity[34].

Comparative Risk: Low Dose vs. Standard Dose Rituximab

Comparative studies examining infection risk between low-dose and standard-dose rituximab regimens in primary AIHA, though limited, provide important insights for clinical decision-making. Evidence from cohort studies and meta-analyses suggests that low-dose rituximab is associated with a lower incidence of serious infections, likely due to reduced cumulative immunosuppression while maintaining comparable efficacy in disease control[35]. Reported rates of severe infections (grade 3–4) are typically below 10% with low-dose regimens, versus 10–20% with standard lymphoma doses in similar patient populations.

Standard-dose rituximab (375 mg/m² weekly for four weeks) was initially adopted from protocols for malignant B-cell lymphoproliferative disorders, which involve much higher disease burden and immune dysregulation than in AIHA. As a result, the higher doses often lead to more prolonged B cell depletion, greater reductions in immunoglobulin levels, and a higher risk of hypogammaglobulinemia and related infectious complications[36]. In contrast, low-dose approaches (e.g., 100 mg weekly or single fixed doses) achieve sufficient B cell suppression for most AIHA patients, with a more rapid recovery of immune function and lower infection rates.

Published retrospective and prospective studies indicate that, in addition to fewer infections, low-dose regimens are associated with shorter hospital stays, reduced need for IVIG replacement, and decreased healthcare costs related to infection management. Notably, rates of opportunistic infections, such as *Pneumocystis jirovecii* pneumonia or severe viral reactivation, appear to be lower in low-dose cohorts, especially when appropriate prophylactic measures are used[37]. However, individual patient risk profiles—including age, baseline immune status, and concomitant therapies—may influence these outcomes and must be considered in regimen selection.

Despite these encouraging findings, head-to-head randomized controlled trials directly comparing low- and standard-dose rituximab in AIHA are still lacking. Further research is needed to confirm the safety advantage of low-dose therapy and to refine dosing algorithms tailored to infection risk and clinical response[38].

Vaccination and Long-Term Immune Recovery

Vaccination plays a crucial role in minimizing infection risk among AIHA patients undergoing rituximab therapy, but the timing and effectiveness of immunizations are greatly influenced by B cell depletion and the extent of immune suppression. It is well-established that rituximab impairs both primary and secondary immune responses to protein and polysaccharide vaccines, with the effect most pronounced within the first 6–12 months after administration[39]. Therefore, all indicated vaccines—especially those targeting *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis*, and influenza—should ideally be given at least two to four weeks prior to rituximab therapy to optimize immunogenicity.

After rituximab administration, the response to new or booster vaccinations is often blunted due to profound B cell depletion, and live-attenuated vaccines are contraindicated for at least six months post-therapy. As B cell and immunoglobulin recovery is variable, re-vaccination may be necessary once immune reconstitution is confirmed, especially in patients receiving repeated or long-term rituximab courses[40]. Measuring specific antibody titers can guide the need for additional vaccine doses, particularly in individuals with ongoing hypogammaglobulinemia.

Long-term immune recovery following low-dose rituximab is generally faster than with standard doses, with most patients experiencing normalization of B cell counts and immunoglobulin levels within 6–12 months. However, some patients, particularly those with baseline immunodeficiency or prior immunosuppression, may have delayed or incomplete recovery, requiring prolonged monitoring[41]. The risk of recurrent infections decreases as immune function is restored, but close follow-up is warranted for patients with persistent deficits.

Guidelines recommend a multidisciplinary approach to vaccination and immune monitoring, involving hematologists, immunologists, and infectious disease specialists. Patient education about the importance of vaccines and infection prevention should be a continuous part of care, as should ongoing reassessment of immune status and revaccination needs over the disease course[42].

Patient Selection and Risk Stratification

Optimal outcomes with low-dose rituximab in primary AIHA depend heavily on appropriate patient selection and individualized risk stratification. Not all patients carry the same infection risk, and identifying those most likely to benefit from low-dose regimens—while minimizing adverse events—is central to effective management. Key considerations include patient age, baseline immune status (e.g., immunoglobulin levels, lymphocyte counts), comorbidities such as diabetes or chronic lung disease, and prior history of severe or recurrent infections[43].

Patients with a low burden of comorbid conditions, normal baseline immunoglobulin levels, and no history of recurrent or severe infections are ideal candidates for low-dose rituximab, as they are likely to achieve disease control with minimal infection risk. Conversely, elderly patients, those with significant comorbidities, or those with baseline immunodeficiency may require more intensive monitoring and, in some cases, alternative treatment strategies[44].

Risk assessment tools and algorithms, though not yet universally adopted, can aid clinicians in stratifying infection risk and tailoring therapy accordingly. Baseline laboratory assessment—including screening for chronic viral infections, quantification of immunoglobulins, and evaluation of vaccine status—should be standard practice. These data help inform decisions about the need for prophylactic antimicrobials, IVIG replacement, or enhanced clinical surveillance[45].

Multidisciplinary discussion is often warranted for complex cases, particularly those involving concurrent immunosuppression, relapsing disease, or atypical infection histories. Shared decision-making, with clear discussion of risks and benefits, empowers patients and helps align treatment choices with individual values and preferences. Ultimately, thoughtful patient selection and ongoing risk stratification enhance the safety and efficacy of low-dose rituximab in AIHA management[46].

Gaps in Evidence and Research Priorities

Despite increasing use and encouraging data for low-dose rituximab in primary AIHA, significant gaps in knowledge and evidence remain. Most available studies are retrospective, involve small patient cohorts, or lack long-term follow-up, limiting

the ability to draw definitive conclusions regarding infection risk, optimal dosing, and patient selection. Randomized controlled trials directly comparing low- and standard-dose rituximab, particularly with a focus on infectious complications and quality of life, are urgently needed to guide evidence-based practice[47].

There is also a lack of validated biomarkers to predict which patients are at greatest risk of infection following rituximab therapy, and little consensus on how best to monitor immune reconstitution or to individualize prophylactic strategies. Further research into the dynamics of B cell and immunoglobulin recovery, as well as the role of memory B cells in long-term immune protection, may yield important insights for patient management[48].

Other key research priorities include defining the optimal timing and schedule of vaccinations in rituximab-treated patients, understanding the impact of repeated rituximab courses on infection risk, and assessing the cost-effectiveness of low-dose regimens. Real-world registry studies and collaborative multicenter research will be critical to capturing diverse patient experiences and informing best practices[49].

Finally, greater emphasis on patient-reported outcomes, shared decision-making, and education around infection prevention can help ensure that the benefits of low-dose rituximab are realized without undue harm. The ongoing evolution of AIHA management will depend on closing these evidence gaps and translating research advances into personalized, patient-centered care[50].

Conclusion

Low-dose rituximab offers a promising therapeutic approach for primary autoimmune hemolytic anaemia, delivering substantial rates of disease remission while potentially lowering the risk of infection compared to traditional, higher-dose regimens. The available evidence suggests that, with proper patient selection, baseline risk assessment, and preventive strategies, most infections are mild and manageable, and serious complications are infrequent. Nevertheless, infection risk cannot be fully eliminated, particularly in patients with pre-existing immune compromise, comorbidities, or concurrent immunosuppression.

Comprehensive baseline screening, timely vaccination, and individualized use of antimicrobial prophylaxis are fundamental to safe and effective care. Ongoing monitoring for hypogammaglobulinemia and recurrent infections, alongside patient education and multidisciplinary collaboration, further reduce the risk of adverse outcomes. While data to date support the clinical value of low-dose rituximab, critical knowledge gaps remain regarding optimal dosing, long-term safety, and strategies for infection risk stratification.

Future research should prioritize large, prospective trials, development of predictive biomarkers, and real-world studies to further refine the risk-benefit balance of low-dose rituximab in AIHA. Ultimately, a patient-centered approach—balancing efficacy and safety—will be essential for optimizing outcomes and advancing the care of individuals living with this challenging hematologic disease.

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