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Age, Low Immunoglobulin G, and M Serum Levels Predict Infections in People With AQP4-IgG+ NMOSD Treated With Rituximab—A Multicenter Cohort Study From the German Neuromyelitis Optica Study Group (NEMOS)

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ABSTRACT

Introduction: Rituximab is effective and widely used as long-term treatment in aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder (AQP4-IgG+ NMOSD). However, infections remain a significant concern during rituximab treatment.

Methods: We conducted a retrospective multicenter cohort study within the NMO Study Group (NEMOS) in Germany, analyzing demographic and clinical data from people with AQP4-IgG+ NMOSD receiving rituximab or azathioprine by retrospective chart, and compared infection occurrence and severity. For rituximab-treated patients, we collected laboratory data (blood lymphocytes, B-cell counts, serum IgG, IgM, and IgA levels), assessed risk factors for infections, and determined the probability of infection within a 3-month window before and after the laboratory assessment.

Daniel Engels and Mariella Herfurth contributed equally.

Florian Then Bergh and Tania Kümpfel supervised equally.

Results: In 92/170 rituximab and in 12/33 azathioprine treatment episodes, one or more infections were documented. Rituximab and azathioprine showed comparable types and risk of infection (HR = 1.24, 95% CI: 0.68–2.25). Rituximab-treated individuals older than 60 years had a higher risk of infection (HR = 1.62, 95% CI: 1.02–2.57). Hypogammaglobulinemia (IgG < 6.0 g/L: OR = 2.27, 95% CI: 1.15–4.48; IgM < 0.3 g/L: OR = 2.08, 95% CI: 1.05–4.09) predicted infections and the occurrence of both low IgG and IgM serum levels further increased the risk of infection (OR = 2.77, 95% CI: 1.10–6.98) during rituximab treatment. Low IgG and IgA serum levels as well as lymphopenia predicted infection-related hospitalizations.
Conclusion: Age > 60 years and immunoglobulin serum levels during rituximab treatment may serve as predictors for infection and help to individualize treatment decisions in NMOSD.

1 | Introduction

Aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder (AQP4-IgG+ NMOSD) is a severe neuroimmunological disease characterized by attacks, predominantly manifesting as either optic neuritis or myelitis [1, 2]. Attacks often result in permanent physical impairment. Preventing attacks is the fundamental principle in the treatment of AQP4-IgG+ NMOSD [3].

Classical immunosuppressants such as azathioprine, and specifically the monoclonal anti-CD20 antibody rituximab have been the mainstay of immunotherapy to reduce attack frequency in people with AQP4-IgG+ NMOSD [4–7]. Patients with stable disease usually do not switch or stop immunotherapy, and recently approved monoclonal antibodies for the treatment of AQP4-IgG+ NMOSD (eculizumab, inebilizumab, satralizumab, ravulizumab) are not available worldwide. Thus, many patients are still on long-term rituximab treatment [3, 5].

Among numerous considerations, the risk of infection during immunotherapy plays a crucial role in treatment selection. Therefore, assessing the infection risk before and during therapy can significantly influence patient counseling, prompting the initiation of preventive measures such as prophylactic antibiotics or immunoglobulin supplementation, and possibly necessitating therapy adjustment. Rituximab can carry an increased risk of infections [8]. However, many patients tolerate it well in this respect [7, 9]. To date, it is not well understood which patient subgroups are at increased risk of infection and whether the type and risk of infection differ between rituximab and other classical immunosuppressants such as azathioprine. There is evidence that hypogammaglobulinemia, lymphopenia, and higher cumulative rituximab dose may be associated with higher infection risk [10–15]. However, not all studies have confirmed these variables as risk factors for infection in individuals with AQP4-IgG+ NMOSD undergoing rituximab therapy, and in most cases, the timing of immunoglobulin measurements is not considered. Moreover, it remains unclear if there is a causal relationship between serum immunoglobulin concentrations and infections, since they often occur independently [14].

In this retrospective multicenter cohort study conducted by the German Neuromyelitis Optica Study Group (NEMOS), we aimed to investigate three key hypotheses: We examined whether the risk of infection differs between patients treated with rituximab and those receiving azathioprine (1), explored whether demographic and disease-related factors are associated with an altered risk of infection during rituximab treatment (2), and assessed whether laboratory parameters—including blood cell counts and serum immunoglobulin concentrations—could serve as predictors of infection in rituximab-treated patients within a 3-month window before and after the date of the laboratory assessment (3).

2 | Methods

2.1 | Study Cohort and Data Collection

For this retrospective cohort study, clinical data from patients with AQP4-IgG+ NMOSD were obtained from the German NEMOS registry (www.nemos-net.de), which includes contributions from university and regional hospitals as well as specialized outpatient clinics involved in the clinical care of NMOSD patients. We reviewed and extracted demographic and clinical data, which were retrieved during routine outpatient visits or inpatient treatment. We included individuals with AQP4-IgG+ NMOSD according to the International Panel for NMO Diagnosis (IPND) criteria [16], who received either monotherapy with azathioprine or rituximab. A treatment episode was defined as the period during which continuous therapy with rituximab or azathioprine was applied. Overlapping treatment episodes (two or more drugs for more than 60 days simultaneously) were excluded from analysis. We included (1) treatment episodes of patients who received rituximab, and (2) treatment episodes of patients who received azathioprine (but who have never been treated with rituximab) for at least 6 months. All patients provided informed consent in accordance with local ethical regulations.

2.2 | Outcome Parameters

We collected data on infections (date, type, and severity) by retrospective chart review. Infection severity was scored according to the following criteria: no clinical signs or symptoms (asymptomatic, 0), infectious disease without hospitalization (1), infectious disease with hospitalization (2), death due to infection (3). Clinical data included type of initial manifestation, year of diagnosis, Expanded Disability Status Scale (EDSS) values (EDSS value at treatment start: assessed within 6 months before to 6 months after therapy initiation; EDSS value for regression models: assessed not more than 12 months before or after an infection or, if there was no recorded infection, 12 months before or after the discontinuation of therapy, and time/duration of attack preventing immunotherapy with rituximab and azathioprine). In addition, for rituximab-treated patients, laboratory data, including serum immunoglobulin levels (IgG, IgM, and IgA), peripheral blood B-cell counts, and leukocyte counts, were collected from each center where available, either at single timepoints or longitudinally. The association between lab values and

infections was defined if an infection occurred within 3 months before or after a lab value measurement.

2.3 | Statistical Analysis

Demographic variables were expressed with point estimates (median) and measures of dispersion (interquartile range, IQR, spanning from the 25th to the 75th quantile). We applied the Mann–Whitney *U* test to analyze whether there is a difference in the distribution of a non-parametric variable between two groups. The association between two categorical variables was estimated by chi-squared test. Infection and infection-related hospitalization rates (per 100 patient-years [PY]) with 95% confidence intervals were estimated using a negative binomial regression model with an offset for patient-years of follow-up. To compare the risk of infection during rituximab and azathioprine treatment episodes and simultaneously account for individual infection susceptibility, we computed mixed-effects Cox proportional hazards regression models for recurring events with study subject as a random effect and type of therapy (rituximab vs. azathioprine) or clinical variables as fixed effects. Hazard ratios with 95% confidence intervals were reported as results of the models. To assess whether laboratory variables influence the probability of infection in rituximab-treated patients, we employed generalized linear mixed-effects models with a binomial link function. The binary outcome variable indicated whether an infection occurred within a 3-month window before or after the corresponding laboratory measurement (or not). Study participant was included as a random effect, while various cutoff values for immunoglobulin serum levels (IgG, IgM, IgA), along with B-cell, lymphocyte, and leukocyte counts, were included as fixed effects. B-cell depletion was defined as the absence of detectable B-cells. We included only laboratory values that were obtained at least 6 months after the initiation of rituximab therapy. To assess whether laboratory variables influence the probability of infection-related hospitalizations, we fitted generalized linear models with a binomial link function, excluding random effects. This choice was made because a model with random effects would have been too unstable due to the limited number of infection-related hospitalizations. Due to potential multicollinearity among the variables (immunoglobulin serum levels, cell counts), independent (univariable) models were calculated for each. Observations with missing data were excluded from the respective model. We performed a sensitivity analysis for unmeasured confounding by calculating *E*-values for the estimated hazard and odds ratios. The *E*-value quantifies the minimum strength of association, on the risk-ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain the observed association [17].

3 | Results

3.1 | Demography

Our study cohort encompassed 203 patients with AQP4-IgG+ NMOSD taken care of at a total of 15 neuroimmunology centers in Germany. Of those, 170 patients were treated with rituximab, and 33 were treated with azathioprine (and never with rituximab, Table 1). The median rituximab treatment episode duration was 3.9 years (IQR: 2.2–7.5 years), and the median azathioprine treatment episode duration was 4.1 years (IQR: 1.6–9.7 years). There was a strong female preponderance in both treatment groups. Myelitis was the most frequent phenotype at onset, followed by optic neuritis. Seventy-three percent of azathioprine treatment episodes were administered as first-line therapy, whereas approximately half of the rituximab treatment episodes were preceded by other treatments. There was no statistically significant difference in the fraction of females, symptom at onset, age at diagnosis, age at start of the treatment episode, treatment episode duration, or EDSS value before treatment.

TABLE 1 | Demography of study subjects.

	Rituximab	Azathioprine	*p*
Number of patients/ treatment episodes	170	33	—
Rituximab/ azathioprine as first-line treatment, proportion	49%	73%	0.02[#]
Females, proportion	92%	82%	0.15[#]
Myelitis/optic neuritis/ other at onset, proportion	47/34/19%	39/30/31%	0.33[#]
Age (years) at diagnosis, median (IQR)	46 (39–58)	44 (34–57)	0.50[‡]
Age (years) at rituximab/ azathioprine start, median (IQR)	49 (39–59)	44 (32–53)	0.07[‡]
Treatment episode duration (years), median (IQR)	3.9 (2.2–7.5)	4.1 (1.6–9.7)	0.90[‡]
EDSS value at treatment start, median (IQR)	3.0 (2.0–5.0)	3.5 (2.5–6.0)	0.80[‡]

Note: Patients with AQP4-IgG+ NMOSD who received rituximab or azathioprine. *p*-values result from chi-squared test ([#]) or Mann–Whitney *U* test ([‡] EDSS: Expanded Disability Status Scale, IQR: interquartile range).

3.2 | Infections Under Therapy

In 92/170 rituximab treatment episodes, one or more infections were documented (54%, Figure 1A). At least one infection-related hospitalization occurred in 27/170 treatment episodes (16%). The infection rate per 100 PY was 32.87 (95% CI: 26.86–40.22), and the infection-related hospitalization rate per 100 PY was 5.32 (95% CI: 3.79–7.45). The most frequent infections were upper respiratory infections (36% of all documented infections), followed by urinary tract infections (27%), and skin and soft tissue infections (9%). Infection-related hospitalizations (18% of all documented infections) were mostly due to urinary tract infections (33%) and pneumonia (28% of all hospitalizations during rituximab treatment).

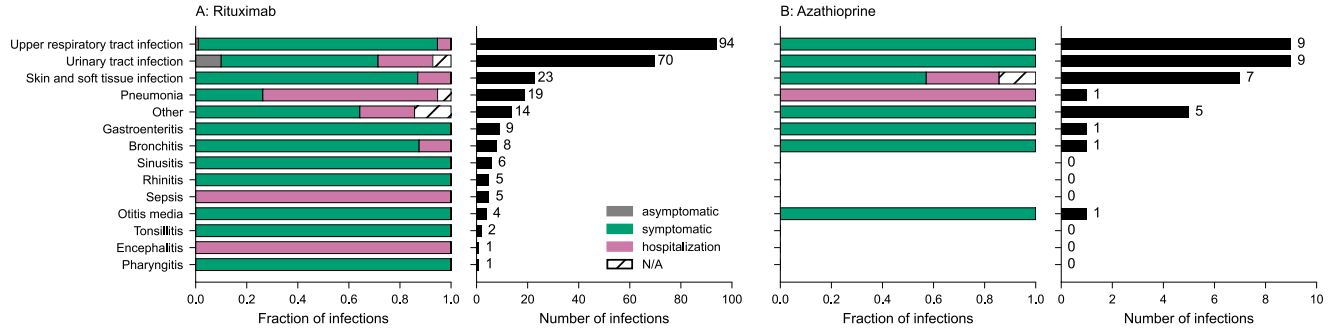

FIGURE 1 | Infections under rituximab and azathioprine treatment episodes. Absolute number of infections in black (right) and fraction of asymptomatic infections (gray), symptomatic infections without hospitalization (green), and infection-related hospitalizations (purple, left) during rituximab (A, $N = 170$) and azathioprine (B, $N = 33$) treatment episodes in AQP4-IgG+ NMOSD patients. Missing severity information is represented by white striped hatch bars.

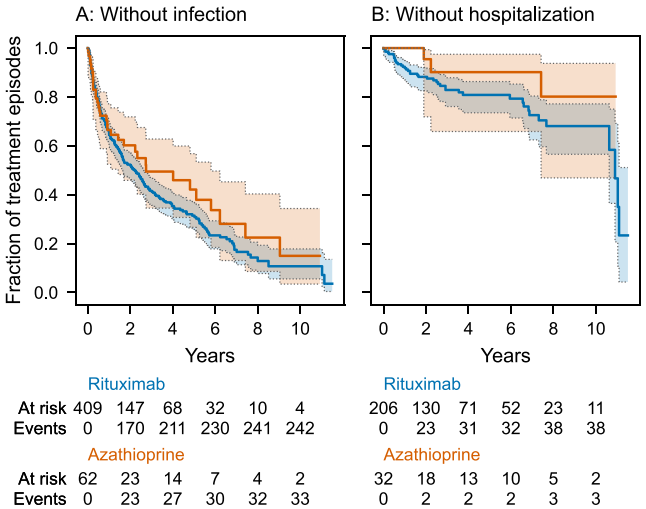

FIGURE 2 | Risk of infection during rituximab and azathioprine treatment episodes. Fraction of treatment episodes without infection (A) or without infection-related hospitalizations (B) from recurring time-to-event analysis (rituximab: $N = 170$ patients, azathioprine: $N = 33$ patients).

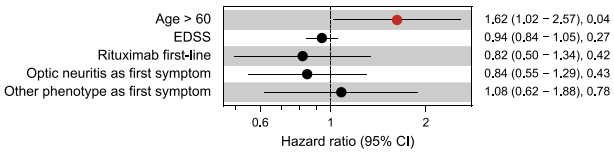

FIGURE 3 | Clinical variables predicting the risk of infection during rituximab treatment episodes of AQP4-IgG+ NMOSD patients. Recurring time-to-event multivariable mixed-effects Cox proportional hazards model with study subject as random effect and age > 60 years (at infection or end of observation), EDSS value (close to infection or end of observation), rituximab as first-line (versus escalation) treatment and phenotype (optic neuritis and other manifestations) at first disease manifestation (referenced to myelitis) as fixed effects. Hazard ratios (HR, dots) with 95% confidence intervals (95% CI, horizontal lines) are shown. Red dot indicates a HR whose 95% CI excludes 1. Right: HR with 95% CI and *p-value* for H_0: HR = 1 (observations: $N = 246$; patients: $N = 80$).

In 12/33 azathioprine treatment episodes (36%, Figure 1B), at least one infection was documented. The infection rate per 100 PY was 19.70 (95% CI: 11.84–32.80), and the infection-related hospitalization rate per 100 PY was 1.46 (95% CI: 0.44–4.81). The nature of infections was similar to rituximab: Urinary tract infections and upper respiratory infections occurred most frequently (both 26%), followed by skin and soft tissue infections (21%). 3/34 (9%) documented infections required hospitalization. There were no deaths due to infection in either group.

3.3 | Risk of Infections (Rituximab vs. Azathioprine)

The median time to first infection was 2.04 years (IQR: 0.83–4.14 years) after start of rituximab, and 2.28 years (IQR: 0.83–4.88 years) after start of azathioprine ($p = 0.27$, log-rank test). Rituximab and azathioprine treatment were associated with similar hazards for infections (HR = 1.24, 95% CI: 0.68–2.25, observations/events: $n = 471/277$, Figure 2A). An independent model, with treatment episodes for which at least one infection was documented, likewise demonstrated similar hazards for infections (HR = 1.07, 95% CI: 0.65–1.76, observations/events: $n = 277/277$). The risk of infection-related hospitalizations did not differ between rituximab and azathioprine treatment episodes (HR = 2.29, 95% CI: 0.74–7.04, Figure 2B, mixed-effects Cox proportional hazards model).

3.4 | Variables Predicting Infections in Individuals Treated With Rituximab

We next tested if clinical variables could predict infections under rituximab treatment. We analyzed 246 rituximab treatment episodes (between infections or without any infection) from 80 patients. Individuals older than 60 years (at infection or at treatment discontinuation) had an approximately 60% higher risk of infection (HR = 1.62, 95% CI: 1.02–2.57, $p = 0.04$, $E = 2.14$, Figure 3). In contrast, phenotype at first disease manifestation such as optic neuritis or other symptoms (e.g., multiple symptoms, myelitis with optic neuritis, brainstem syndrome) did not alter the risk for infections (referenced to myelitis). Likewise, rituximab administered as first-line treatment (vs. escalation) and EDSS value (at infection or treatment discontinuation) showed no effect.

We tested if laboratory parameters could predict infections during rituximab treatment (Figure 4). Hypogammaglobulinemia (low

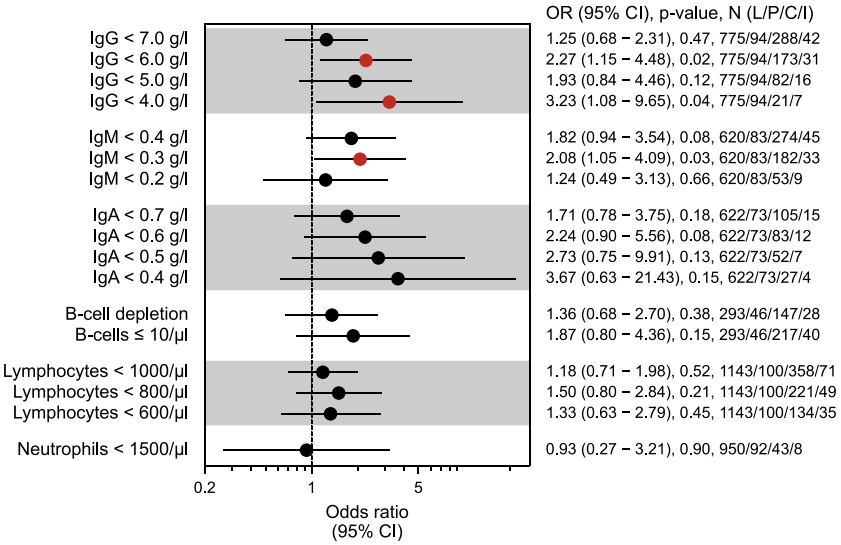

FIGURE 4 | Laboratory parameters predicting probability of infections in rituximab treatment episodes from AQP4-IgG+ NMOSD patients. Univariable generalized linear mixed-effects models with binomial linker function. The occurrence of infection (yes/no) was defined as target variable, study subject was defined as random effect, immunoglobulin serum levels and cell counts as fixed effects. Odds ratio (OR, dots) with 95% confidence interval (95% CI, horizontal line) are shown. *p*-values result from testing for H_0: OR = 1. Number of included laboratory values (L), patients (P), laboratory values meeting the cutoff criteria (C), and infections not more than 3 months before or after laboratory values meeting the cutoff criteria (I) are shown.

IgG and IgM, as per definition) was associated with a higher probability for infection (IgG < 6.0 g/L: OR = 2.27, 95% CI: 1.15–4.48, $p = 0.02$, $E = 2.38$; IgM < 0.3 g/L: OR = 2.08, 95% CI: 1.05–4.09, $p = 0.03$, $E = 2.24$). If IgG serum levels were below 6.0 g/L, the probability of infection within 3 months before or after the measurement was 0.20, compared to 0.10 for measurements with normal IgG serum levels (≥ 6.0 g/L). Similarly, infection probability was 0.18 if IgM serum levels were below 0.3 g/L, compared to 0.09 with IgM serum levels ≥ 0.3 g/L. Low IgA serum levels did not predict infections. The simultaneous occurrence of IgG serum levels < 6 g/L and IgM serum levels < 0.4 g/L increased the risk of infection compared to isolated IgG or IgM hypogammaglobulinemia (OR = 2.77, 95% CI: 1.10–6.98, $p = 0.03$, $E = 2.72$, interaction analysis). There was no interaction of age > 60 years (at the time of the lab value assessment) and either IgG serum levels < 6.0 g/L or IgM serum levels < 0.3 g/L (IgG: OR = 1.85, 95% CI: 0.80–4.25, $p = 0.15$; IgM: OR = 1.58, 95% CI: 0.62–3.99, $p = 0.33$). (Low) B-cell, leukocyte, or lymphocyte counts could not predict the probability of infection. When looking at the prediction of infection-related hospitalizations in rituximab-treated patients, low IgG and IgA serum levels showed an even stronger effect (Figure S1). Additionally, lymphopenia predicted infection-related hospitalizations.

4 | Discussion

We identified higher age (> 60 years) and hypogammaglobulinemia (IgG < 6 g/L and IgM < 0.3 g/L) as risk factors for the occurrence of infections in people with AQP4-IgG+ NMOSD treated with rituximab monotherapy. The most frequent types of infection and the risk of infection were similar between individuals treated with rituximab and azathioprine.

Currently, four monoclonal antibodies with different mechanisms of action are approved in Germany for the treatment of AQP4-IgG+ NMOSD (eculizumab, inebilizumab, ravulizumab, and satralizumab) [3]. Nevertheless, rituximab and azathioprine as classical immunosuppressants are still available and widely used as off-label therapy, especially in patients who remain stable on these therapies, and in countries where the above-mentioned novel monoclonal antibodies are not available due to health economic regulations and restrictions. Thus, it is important to gain further insights into the safety profiles of these drugs to advise patients and physicians. Usually, the decision on which immunotherapy to use and when to switch the treatment of AQP4-IgG+ NMOSD depends, among other factors, on comorbidities, previous therapies, safety profiles, and the mode and frequency of administration [3]. To date, there are no controlled trials that directly compare the risk of infection between these different drugs. Hence, registry-based cohort studies like the present study are needed to gain deeper insights into the benefits and risks of different immunotherapies and, eventually, optimize the choice of immunotherapy. Regarding infections, real-world data are essential, as they also include patients with (infection-relevant) comorbidities and elderly patients [18]. For instance, a recent retrospective real-world study revealed (severe) infections during treatment with eculizumab in the context of AQP4-IgG+ NMOSD [19]. These infection risks may be underestimated in randomized controlled trials, which tend to include primarily younger individuals with fewer comorbidities and often exhibit shorter observation time.

4.1 | Age > 60 Predicts Infections

Among the clinical and demographic variables examined, only age (> 60 years) was associated with an increased risk of infection during rituximab treatment. The *E*-value for this association was 2.14, indicating that an unmeasured confounder would need to be associated with both age and infection risk by risk ratios

of at least 2.14 each, above and beyond the measured covariates, to fully explain away the observed effect. This suggests that the association is moderately robust to unmeasured confounding. Furthermore, this finding is in line with a large Japanese study that identified age ≥ 75 years as a risk factor for serious infections [20]. Moreover, a Swedish registry-based study on MS and risk of serious infections with a matched reference cohort found that the hazard ratio for infection decreased with age, whereas absolute rate differences between MS patients and the general population increased in individuals over 60 years [21]. Implying an increased infection risk in the general population beyond this age the higher infection risk observed in NMOSD patients older than 60 years in our study may partly reflect an age-related effect rather than purely disease- or treatment-specific factors. When selecting treatment for older AQP4-IgG+ NMOSD patients, a risk–benefit assessment must be conducted, taking into consideration the higher risk of infection, but on the other hand, a poorer recovery after possible disease-related attacks. Interestingly, the degree of impairment, as measured by the EDSS, was no risk factor for infections in rituximab-treated AQP4-IgG+ NMOSD patients in our study, in contrast to previous (MS) studies [21, 22]. The median EDSS value of individuals treated with rituximab in our cohort was 3.0, with an IQR extending up to 5.0. It is suspected that individuals with high EDSS values are underrepresented. Those with higher EDSS values (e.g., with immobility and severe bladder dysfunction) may have an increased risk of infections. In line with this consideration, a French study reported an increased risk of infection among patients with NMOSD or MOGAD who had urinary tract dysfunction [10]. Further studies with a greater proportion of patients with higher EDSS values as well as evaluation of functional systems scores and larger sample sizes are needed to identify disability-related predictors for infection in people with AQP4-IgG+ NMOSD. Thus, the infection risk and risk factors for infection in our cohort only apply to the studied EDSS value range.

4.2 | Low IgG and IgM Serum Levels Predict Infections

There are conflicting results concerning the increased risk of infection in rituximab-treated patients with hypogammaglobulinemia, which is partially due to different study populations (rheumatological diseases, MS, NMOSD), but also due to methodological factors. In a previous Korean study with 169 people with NMOSD, duration of rituximab treatment, annual rituximab dose and prolonged memory B-cell depletion after rituximab, previous mitoxantrone treatment, IgG hypogammaglobulinemia at baseline, or obesity were identified as risk factors for developing rituximab-induced hypogammaglobulinemia. However, they observed no association between hypogammaglobulinemia and the incidence of severe infections [12], which is also supported by a small single-center Swedish study [23]. In contrast, our results imply that low IgG and IgM serum levels may serve as predictors for infections. While in our model, neutrophil, and B-cell counts, or other demographic and disease-related variables showed no effect considering all infections, lymphopenia was associated with infection-related hospitalizations. In addition, the risk of severe infection seems to increase with increasing hypogammaglobulinemia. Lymphopenia and longer exposure to anti-CD20 therapy were reported as risk factors for infections in a cohort of people with MS and NMOSD treated with ocrelizumab and rituximab [24]. Likewise, anti-CD19 therapy with inebilizumab in people with AQP4-IgG+ NMOSD decreased IgG serum levels; however, no association between low IgG serum levels and the risk of infection was observed so far during an observation time up to 5.5 years [25]. Importantly, we did not consider individual comorbidities or previous immunotherapies, especially corticosteroids, that could additionally contribute to an increased risk of infection and hypogammaglobulinemia, which is a limitation of this study [26, 27]. At the same time, the E-values of roughly 2 indicate that a moderately strong unmeasured confounder could still explain the association, underscoring the need for cautious interpretation. However, a strength of our study and major difference to previous studies is the consideration of the temporal component in determining laboratory parameters concerning the occurrence of infections (infections within 3 months before or after the measurement) and, furthermore, the definition of clear cutoff values for (reduced) IgG and IgM serum levels. In most previous studies, the timepoint of immunoglobulin serum concentration measurements in association with infections was not respected and usually determined at baseline and/or the end of specific observation periods.

Furthermore, combined hypogammaglobulinemia (IgG < 6 g/L and IgM < 0.3 g/L) may act as a predictor for infections during rituximab treatment. In those patients, switch of therapy and/or early intravenous immunoglobulin (IVIG) substitution might be beneficial. However, currently, IVIG substitution, which can decrease the risk of infection in patients with hypogammaglobulinemia, is only approved in Germany when the IgG serum level is below 4 g/L. Moreover, low IgA and lymphopenia predicted infection-related hospitalizations. Thus, our findings clearly underscore the importance of regular serum immunoglobulin and differential white blood cell count monitoring during B-cell depletion therapy.

4.3 | No Difference in Infection Type or Risk Between Rituximab and Azathioprine

In a model controlled for observation time, age, and individual infection propensity (allowing recurring events), we showed that the hazard for infection during rituximab and azathioprine treatment episodes was comparable in our cohort. However, due to relatively small and unbalanced sample sizes, the model might be underpowered. It also remains unclear to what extent treatment availability, individual treatment decision (for azathioprine vs. rituximab)—for example, due to comorbidities—as well as timing of therapy have an influence. Thus, conclusions regarding the comparative risk of infection between azathioprine and rituximab should be drawn with caution. Nevertheless, our finding aligns with observations by Kim et al., who found no difference in the incidence rates of severe infections among patients receiving rituximab, azathioprine, or mycophenolate mofetil in a cohort of elderly NMOSD patients [28]. Furthermore, a meta-analysis by Wang et al. suggested that the risk of any infections is comparable during rituximab and azathioprine treatment [29]. In addition to the (comparable) frequency of infections under rituximab and azathioprine, we also observed similar types of infection. The fraction of treatment episodes in which severe infections occurred (17%) matches a previously reported incidence of 15% [30]. Likewise, the distribution

of types of infections in our study was also similar to previous observations: In a cohort of 37 AQP4-IgG+ and seronegative NMOSD patients, urinary tract infections (19%) and pneumonia (11% of all observed infections) were reported as the most common infections [31]. Another study reported a much higher incidence (46%) of severe infections in a smaller, single-center cohort including 24 people with AQP4-IgG+ NMOSD [23]. The infection-related hospitalization rate per 100 PY of individuals treated with rituximab (5.32, 95% CI: 3.79–7.45) was comparable to the serious infection event rate of 3.76 (95% CI: 3.46–4.09) reported in a large pooled case analysis from long-term safety data of rituximab in rheumatoid arthritis (RA) cohorts (from randomized clinical trials, open-label extension, and open-label prospective studies), and to the serious infection rate of 5.77 (95% CI: 5.23–6.35) reported in a large registry-based study from Japan [20, 32]. However, the overall infection rate per 100 PY in our study (32.87, 95% CI: 26.86–40.22) was lower than what they reported (75.70, 95% CI: 74.31–77.11). This difference is likely attributable to observation bias, specifically due to the standardized recording of infections compared to the retrospective assessment through chart review (in our study). Nevertheless, given the similar infection-related hospitalization rate, the findings of our study can be considered reliable. Methodological differences (e.g., single-center, multicenter, and registry-based studies) as well as differences in the underlying diseases (e.g., NMOSD, MS, and RA) should be considered when comparing studies on rituximab-associated infection risk.

Another limitation of our study is the potential for observation bias in comparing infection risk between rituximab and azathioprine. Patients treated with rituximab are likely to be seen more frequently at specialized neuroimmunology centers (due to the need for infusion administration), while azathioprine therapy is often managed by outpatient neurologists, with visits at specialized centers every 1 to 2 years. Consequently, the threshold for documenting infections may be lower for patients on rituximab, potentially leading to a seemingly higher infection incidence in these patients. Standardized and patient-reported outcome measures for infections may improve data collection on infection risk in real-world settings.

5 | Conclusion

Our study underscores the importance of regular clinical monitoring and standardized recording of infections during any immunomodulatory treatment. It supports the recommendation for regular serum immunoglobulin monitoring during B-cell depleting therapies and high vigilance in older patients and those with lymphopenia. Particularly, in the context of new therapies with different mechanisms of action, the insights from this study could help stratify individual infection risk, optimizing therapy monitoring and informing the selection of appropriate immunotherapy.

Author Contributions

Daniel Engels: conceptualization, investigation, writing – original draft, methodology, validation, visualization, writing – review and editing, software, formal analysis, project administration, data curation, supervision, resources. **Patrick Schindler:** investigation. **Mariella Herfurth:** writing – review and editing, investigation, data curation. **Joachim Havla:** investigation. **Klemens Ruprecht:** investigation. **Florian Then Bergh:** investigation. **Tania Kümpfel:** conceptualization, investigation, writing – original draft, writing – review and editing, data curation, supervision, resources. **Marius Ringelstein:** investigation. **Martin W. Hümmert:** investigation. **Thorleif Etgen:** investigation. **Charlotte Schubert:** investigation. **Ioannis Vardakas:** investigation. **Katrin Giglhuber:** investigation. **Sven Jarius:** investigation. **Jasmin Naumann:** investigation. **Insa Schiffmann:** investigation. **Matthias Grothe:** investigation. **Makbule Senel:** investigation. **Carolin Schwake:** investigation. **Brigitte Wildemann:** investigation. **Vivien Häußler:** investigation. **Orhan Aktas:** investigation. **Corinna Trebst:** investigation. **Frank Hoffmann:** investigation. **Achim Berthele:** investigation. **Katinka Fischer:** investigation. **Judith Bellmann-Strobl:** investigation. **Ilya Ayzenberg:** investigation. **Clemens Warnke:** investigation.

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Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. S. Jarius, O. Aktas, I. Ayzenberg, et al., "Update on the Diagnosis and Treatment of Neuromyelits Optica Spectrum Disorders (NMOSD)—Revised Recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part I: Diagnosis and Differential Diagnosis," *Journal of Neurology* 270, no. 7 (2023): 3341–3368, https://doi.org/10.1007/S00415-023-11634-0.

2. S. Jarius, F. Paul, B. G. Weinshenker, M. Levy, H. J. Kim, and B. Wildemann, "Neuromyelitis Optica," *Nature Reviews. Disease Primers* 6, no. 1 (2020), https://doi.org/10.1038/S41572-020-0214-9.

3. T. Kümpfel, K. Giglhuber, O. Aktas, et al., "Update on the Diagnosis and Treatment of Neuromyelitis Optica Spectrum Disorders (NMOSD)—Revised Recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack Therapy and Long-Term Management," *Journal of Neurology* 271, no. 1 (2024): 141–176, https://doi.org/10.1007/S00415-023-11910-Z.

4. B. A. C. Cree, S. Lamb, K. Morgan, A. Chen, E. Waubant, and C. Genain, "An Open Label Study of the Effects of Rituximab in Neuromyelitis Optica," *Neurology* 64, no. 7 (2005): 1270–1272, https://doi.org/10.1212/01.WNL.0000159399.81861.D5.

5. V. Häußler, C. Trebst, D. Engels, et al., "Real-World Multicentre Cohort Study on Choices and Effectiveness of Immunotherapies in NMOSD and MOGAD," *Journal of Neurology, Neurosurgery, and Psychiatry* (2024), https://doi.org/10.1136/JNNP-2024-334764.

6. H. L. Pellkofer, M. Krumbholz, A. Berthele, et al., "Long-Term Follow-Up of Patients With Neuromyelitis Optica After Repeated Therapy With Rituximab," *Neurology* 76, no. 15 (2011): 1310–1315, https://doi.org/10.1212/WNL.0B013E3182152881.

7. M. Tahara, T. Oeda, K. Okada, et al., "Safety and Efficacy of Rituximab in Neuromyelitis Optica Spectrum Disorders (RIN-1 Study): A Multicentre, Randomised, Double-Blind, Placebo-Controlled Trial," *Lancet Neurology* 19, no. 4 (2020): 298–306, https://doi.org/10.1016/S1474-4422(20)30066-1.

8. E. Gkrania-Klotsas and D. S. Kumararatne, "Serious Infectious Complications After Rituximab Therapy in Patients With Autoimmunity: Is This the Final Word?," *Clinical Infectious Diseases* 72, no. 5 (2021): 738–742, https://doi.org/10.1093/CID/CIAA131.

9. V. Shaygannejad, E. Fayyazi, S. Badihian, et al., "Long-Term Tolerability, Safety and Efficacy of Rituximab in Neuromyelitis Optica Spectrum Disorder: A Prospective Study," *Journal of Neurology* 266, no. 3 (2019): 642–650, https://doi.org/10.1007/S00415-019-09180-9.

10. A. Avouac, A. Maarouf, J.-P. Stellmann, et al., "Rituximab-Induced Hypogammaglobulinemia and Infections in AQP4 and MOG Antibody-Associated Diseases," *Neurology Neuroimmunology & Neuroinflammation* 8, no. 3 (2021): 977, https://doi.org/10.1212/NXI.0000000000000977.

11. J. R. Karlowicz, M. Klakegg, J. H. Aarseth, et al., "Predictors of Hospitalization due to Infection in Rituximab-Treated MS Patients," *Multiple Sclerosis and Related Disorders* 71 (2023): 104556, https://doi.org/10.1016/j.msard.2023.104556.

12. S. H. Kim, N. Y. Park, K. H. Kim, J. W. Hyun, and H. J. Kim, "Rituximab-Induced Hypogammaglobulinemia and Risk of Infection in Neuromyelitis Optica Spectrum Disorders: A 14-Year Real-Life Experience," *Neurology Neuroimmunology & Neuroinflammation* 9, no. 5 (2022): 1179, https://doi.org/10.1212/NXI.0000000000001179.

13. R. Labrosse, S. Barmettler, B. Derfalvi, et al., "Rituximab-Induced Hypogammaglobulinemia and Infection Risk in Pediatric Patients," *Journal of Allergy and Clinical Immunology* 148, no. 2 (2021): 523–532.e8, https://doi.org/10.1016/j.jaci.2021.03.041.

14. A. Langer-Gould, B. H. Li, J. B. Smith, and S. Xu, "Multiple Sclerosis, Rituximab, Hypogammaglobulinemia, and Risk of Infections," *Neurology Neuroimmunology & Neuroinflammation* 11, no. 3 (2024): e200211, https://doi.org/10.1212/NXI.0000000000200211.

15. K. Smolik, F. Camilli, I. Panzera, et al., "Hypogammaglobulinemia and Severe Infections in Multiple Sclerosis Patients on Anti-CD20 Agents: A Multicentre Study," *Multiple Sclerosis and Related Disorders* 93 (2025): 106191, https://doi.org/10.1016/J.MSARD.2024.106191.

16. D. M. Wingerchuk, B. Banwell, J. L. Bennett, et al., "International Consensus Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorders," *Neurology* 85, no. 2 (2015): 177–189, https://doi.org/10.1212/WNL.0000000000001729.

17. T. J. VanderWeele and P. Ding, "Sensitivity Analysis in Observational Research: Introducing the E-Value," *Annals of Internal Medicine* 167, no. 4 (2017): 268–274, https://doi.org/10.7326/M16-2607.

18. G. Cerono, B. A. C. Cree, S. L. Hauser, and S. E. Baranzini, "Comparative Safety Profiles of Ocrelizumab and Rituximab in Multiple Sclerosis Treatment Using Real-World Evidence," *Annals of Neurology* 2025 (2025): 78033, https://doi.org/10.1002/ana.78033.

19. M. Ringelstein, S. Asseyer, G. Lindenblatt, et al., "Eculizumab Use in Neuromyelitis Optica Spectrum Disorders: Routine Clinical Care Data From a European Cohort," *Neurology* 103, no. 9 (2024), https://doi.org/10.1212/WNL.0000000000209888.

20. N. Isobe, T. Oda, T. Yamaguchi, et al., "Incidence and Risk Factors for Serious Infections in Patients With Neuromyelitis Optica Spectrum Disorder: A Claims Database Study in Japan," *Neurology and Therapy* 14, no. 5 (2025): 1993–2009, https://doi.org/10.1007/s40120-025-00794-y.

21. J. S. Brand, K. A. Smith, F. Piehl, T. Olsson, and S. Montgomery, "Risk of Serious Infections in Multiple Sclerosis Patients by Disease Course and Disability Status: Results From a Swedish Register-Based Study," *Brain, Behavior, & Immunity - Health* 22 (2022): 100470, https://doi.org/10.1016/j.bbih.2022.100470.

22. T. Derfuss, R. Bermel, C.-J. Lin, et al., "Long-Term Analysis of Infections and Associated Risk Factors in Patients With Multiple Sclerosis Treated With Ocrelizumab: Pooled Analysis of 13 Interventional Clinical Trials," *Therapeutic Advances in Neurological Disorders* 17 (2024): 17562864241277736, https://doi.org/10.1177/17562864241277736.

23. O. Carlsson, D. I. Jonsson, L. Brundin, and E. Iacobaeus, "Relapses and Serious Infections in Patients With Neuromyelitis Optica Spectrum Disorder Treated With Rituximab: A Swedish Single-Center Study," *Journal of Clinical Medicine* 13 (2024): 355, https://doi.org/10.3390/jcm13020355.

24. V. Mears, C. Jakubecz, C. Seeco, S. Woodson, A. Serra, and H. Abboud, "Predictors of Hypogammaglobulinemia and Serious Infections Among Patients Receiving Ocrelizumab or Rituximab for Treatment of MS and NMOSD," *Journal of Neuroimmunology* 377 (2023): 578066, https://doi.org/10.1016/j.jneuroim.2023.578066.

25. M. Rensel, A. Zabeti, M. A. Mealy, et al., "Long-Term Efficacy and Safety of Inebilizumab in Neuromyelitis Optica Spectrum Disorder: Analysis of Aquaporin-4–Immunoglobulin G–Seropositive Participants Taking Inebilizumab for ⩾4 Years in the N-MOmentum Trial," *Multiple Sclerosis* 28, no. 6 (2022): 925–932, https://doi.org/10.1177/13524585211047223.

26. S. Samadzadeh, F. C. Oertel, H. Salih, et al., "Comorbidities Are Associated With Unfavorable Outcome in Aquaporin-4 Antibody Positive Neuromyelitis Optica Spectrum Disorders and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease: Exploratory Study From the CROCTINO Cohort," *European Journal of Neurology* 32, no. 6 (2025): 70214, https://doi.org/10.1111/ENE.70214.

27. S. Virtanen, F. Piehl, and T. Frisell, "Impact of Previous Treatment History and B-Cell Depletion Treatment Duration on Infection Risk in Relapsing-Remitting Multiple Sclerosis: A Nationwide Cohort Study," *Journal of Neurology, Neurosurgery, and Psychiatry* 95, no. 12 (2024): 1150–1157, https://doi.org/10.1136/jnnp-2023-333206.

28. K. H. Kim, Y. H. Chung, J.-H. Min, et al., "Immunosuppressive Therapy in Elderly Patients With Neuromyelitis Optica Spectrum Disorder: A Retrospective Multicentre Study," *Journal of Neurology, Neurosurgery & Psychiatry* 95 (2024): 333644, https://doi.org/10.1136/JNNP-2024-333644.

29. H. Wang, J. Zhou, Y. Li, et al., "Adverse Events of Rituximab in Neuromyelitis Optica Spectrum Disorder: A Systematic Review and Meta-Analysis," *Therapeutic Advances in Neurological Disorders* 14 (2021): 17562864211056710, https://doi.org/10.1177/17562864211056710.

30. P. Barreras, E. S. Vasileiou, A. G. Filippatou, et al., "Long-Term Effectiveness and Safety of Rituximab in Neuromyelitis Optica Spectrum Disorder and MOG Antibody Disease," *Neurology* 99, no. 22 (2022): e2504, https://doi.org/10.1212/WNL.0000000000201260.

31. M. T. G. Hayes, R. J. Adam, P. A. McCombe, M. Walsh, and S. Blum, "Long-Term Efficacy and Safety of Rituximab in the Treatment of Neuromyelitis Optica Spectrum Disorder," *Multiple Sclerosis Journal - Experimental, Translational and Clinical* 10, no. 2 (2024): 7876, https://doi.org/10.1177/20552173241257876.

32. R. F. Van Vollenhoven, R. M. Fleischmann, D. E. Furst, S. Lacey, and P. B. Lehane, "Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program Over 11 Years," *Journal of Rheumatology* 42, no. 10 (2015): 1761–1766, https://doi.org/10.3899/JRHEUM.150051.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ene70520-sup-0001-DataS1.zip.