JPPT | Single-Center Retrospective Study

A Systematic Review and Meta-analysis of Rituximab-Associated Infections Among Children and Adolescents With Glomerular Disease: Focus on the Risk of Infections

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OBJECTIVE This systematic review and meta-analysis aimed to explore rituximab (RTX) associated infectious complications in children with glomerular disease.

METHODS We performed an electronic search of PubMed, International Scientific Information (ISI), Scopus, and EMBASE between January 2010 and July 2021. Infection rates and total drug-related adverse events were the outcomes. Statistical heterogeneity was evaluated by using the I^2 statistic. When there was statistical evidence of heterogeneity (I^2 > 50%, p > 0.1), a random-effect model was adopted. Data analysis was performed with Stata17.0 software.

RESULTS A total of 7 studies with 668 patients (136 with lupus nephritis [LN] and 532 with nephrotic syndrome were included in the meta-analysis. The pooled risk ratio showed that the administration of RTX was significantly associated with lower risk of infectious complications in patients with LN and nephrotic syndrome (0.72 [95% CI 0.58, 0.85]) when compared with population data of patients without glomerular disease (p = 0.2). There was no significant difference between the LN and nephrotic syndrome groups in terms of total serious adverse events or the occurrence of infections. There was significant heterogeneity among the reported studies (Q = 42.39, p < 0.001, I^2 = 81%).

CONCLUSION Administration of RTX in children with glomerular disease is associated with a lower rate of infections when compared with population data of patients without LN or nephrotic syndrome. Additional high-quality randomized controlled trials with long-term follow-up are needed to identify the long-term potential complications. Trial registration PROPERO ID: CRD42021274869 (https://www.crd.york.ac/prospero/display_record.php?)

ABBREVIATIONS CYC, cyclophosphamide; FRNS, frequently relapsing nephrotic syndrome; FSGS, focal segmental glomeulosclerosis; HBV, hepatitis virus; IgG, immunoglobulin G; LN, lupus nephritis; MMF, mycophenolate mofetil; PRISMA, Preferred Reporting Items for Systematic r\Reviews and Meta-Analyses; RTX, rituximab; SRNS, Steroid-Resistant Nephrotic Syndrome; LN, lupus nephritis.

KEYWORDS children; glomerular disease; infectious complications; lupus nephritis; nephrotic syndrome; rituximab

J Pediatr Pharmacol Ther 2023;28(4):308–315

DOI: 10.5863/1551-6776-28.4.308

Introduction

Rituximab (RTX) is a monoclonal anti CD-20 antibody that induces B-cell apoptosis with significant efficacy in the treatment of a variety of autoimmune kidney diseases including lupus nephritis (LN), steroid-resistant nephrotic syndrome (SRNS), steroid-dependent glomerulonephritis, frequently relapsing nephrotic syndrome (FRNS), and focal segmental glomeulosclerosis (FSGS).[1–5]

The use of RTX, however, is known to be associated with serious infections including Pneumocystis jiroveci pneumonia and reactivation of hepatitis B virus (HBV) and tuberculosis. Rituximab treatment can lower a patient's immune response and this can increase the risk of serious infectious complications, particularly in patients with pre-existing hypogammaglobulinemia.[4–6] Estimates of the infectious complications rate after RTX administration range from 6.6 to 16.6 per 100 patient-years for patients with LN[7] Minimizing the risk of infections during RTX therapy is, therefore, crucial. Thus, monitoring B-cell counts, serum immunoglobulin concentrations, prophylaxis and vaccinations against bacterial and viral infections

are essential to reducing the risk of infections during RTX therapy.

Given the increasing use of RTX in glomerular diseases, this systematic review and meta-analysis study was designed to investigate the incidence of infectious complications after RTX therapy in children and adolescents with glomerular disease, to consider the potential risk factors for infections after RTX use, and to determine the outcome of theses patients.

Materials and Methods

Search Strategies. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] We searched EMBASE (n = 67), International Scientific Information [ISI] (n = 26), Scopus (n = 120), and PubMed (n = 38) for publication between January 2001 and July 2021, in the English language using the following MeSH terms or their combinations: "rituximab", "CD-20 antibody," glomerular disease," "infections," "risk factors," "immunization status," "serum immunoglobulin G (IgG)," "B-cell count," "use of prophylaxis antibiotics," and "children." The type of infections (bacterial, viral, fungal), blood B-cell count, level of serum IgG, glomerular filtration rate, the status of vaccination, use of prophylactic antibiotic, and the site of infection (respiratory tract or urinary tract) varied among study outcomes. Similarly, serious life-threatening infection from RTX use (sepsis, bacteremia, pneumonia, and BK viremia, and urinary and respiratory tracts) also varied among the study outcomes.

Data Collection. Two independent reviewers extracted data from all eligible studies after removing duplicates from the search results. The third reviewer resolved any disagreements about the inclusion or exclusion of a study. Reviewers performed data extraction and quality assessment of all screened articles. Data extraction was as follows: first author's name; publication date; study country; mean age of participants; sample size; "infectious complications"; "infection site"; "type of infection" (bacterial, viral, or fungal); "B-cell count"; "serum IgG concentration"; "glomerular filtration rate", "disease activity"; "the status of vaccination; and "the use of prophylactic antibiotic. Multiple infections were defined as multiple sites of infection involving 2 or more organs simultaneously. Outcomes including serious infections, site, and type of infections were abstracted and recorded.

Statistical Analysis. Meta-analyses were conducted for all outcomes for which there were study quality scores of 7 or 8 for reporting useable data, using The Newcastle-Ottawa Scale (NOS).[9] The relative risks [RRs] were calculated from the data reported in the articles and hazard ratios (HR) were considered approximations of relative risk ratio RR in our meta-analysis and adjusted for confounders. Any discrepancies in data extraction were discussed and assessed by a third reviewer for resolution from November 2, 2021 to January 23, 2022.

Statistical heterogeneity was evaluated by using the I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $p > 0.1$), a fixed effects model was adopted. Otherwise, the random-effects model of Borenstein and Hedges was used[11] to calculate the summary RR and 95% confidential interval (CI). Subgroup analysis was performed from the type and site of infections. Statistical heterogeneity was tested with the Cochran's Q statistic and also the calculation of the I^2 statistic. Possible publication bias was evaluated by using visual inspection of Begg's funnel plot and Egger's regression test. If publication bias was detected (correlation coefficient from Begg's test was close to 1 or the slope parameter from Egger's regression test was high), the trim-and-fill analysis was performed to estimate the potential influence of the bias on the pooled summary estimates. All tests were performed with Stata software version 17 (Stata Corp, College Station, Texas 77845 USA). All reported data are 2-sided and p values less than 0.05 were considered statistically significant for all included data.

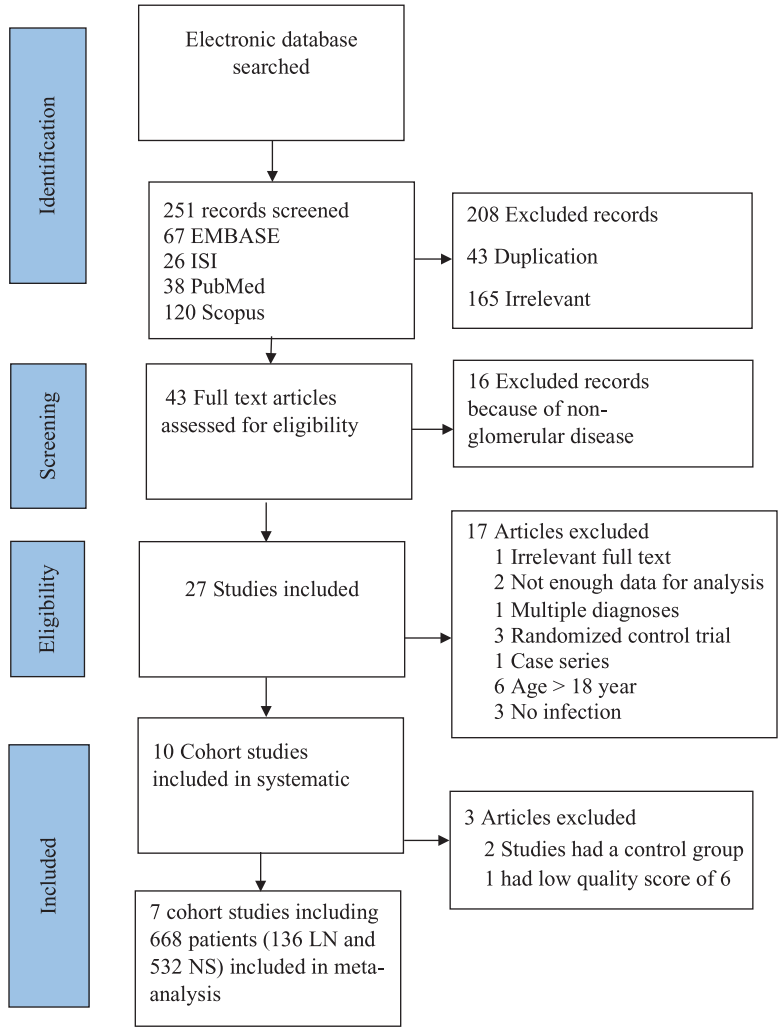
Results

Literature Search. Study flow diagram of the included studies is shown in Figure 1. In the initial search, 251 studies were screened from the electronic databases. After removing patients with non-glomerular disease and duplicate articles, an additional 17 studies were excluded because they did not meet the inclusion criteria at the title or abstract levels because of irrelevant full text (n = 1), insufficient data for computation of RR, CI, and/or standard error (SE) (n = 2), multiple diagnoses (n = 1), case report tabulation (CRT) (n = 3), case series (n = 1), age younger than 2 or older than 18 years (n = 6) and no infection (n = 3).

Inclusion Criteria. Children diagnosed with nephrotic syndrome, steroid-resistance nephrotic syndrome (SRNS); steroid-dependent nephrotic syndrome (SDNS); frequent-relapsing nephrotic syndrome (FRNS); LN, focal segmental glomerulosclerosis (FSGS); drug-related adverse events; and the occurrence of infections. We included the full publication of cohort studies and analysis (hospital records/database) that evaluated the risk of infections in children and adolescent patients with SDNS, FRNS, and LN and compared data with population data (patients without LN, SDNS, FRNS, or SRNS). All patients were treated with RTX alone or in combination with other immunosuppressive agents (glucocorticoid, cyclosporine, azathioprine or mycophenolate mofetil [MMF]). The infectious complications and RTX administration did not lead to life-threatening events in any study patients.

Of the 10 studies that were analyzed, 3 were removed, 2 had a control group (RTX vs. conventional immunosuppressive agents) and 1 had a low-quality score of 6. Ultimately, 7 studies with 668 patients (136 patients with LN and 532 with nephrotic syndrome) were included in the qualitative synthesis.[11–17] (Figure 1). Overall, there were 5 retrospective cohort studies

Figure 1. PRISMA flow diagram of the literature search and study selection process.



Twenty-seven studies were excluded because of non-glomerular diseases (n = 10); irrelevant full text (n = 1); insufficient data for computation of RR, CI, SE (n = 2); multiple diagnoses (n = 1); case report tabulation (n = 3); case series (n = 1); age <2 years or >18 years (n = 6) and no infection (n = 3). ISI, international Science information; LN, lupus nephritis; NS, nephrotic syndrome

(n = 501)[11,13–15,17] and 2 prospective cohort studies (n = 167).[12,16] Two studies were multicenter (68 and 5 hospitals)[13,17] (n = 167).

Study Characteristics. The general characteristics of the included studies are summarized in the Table 1. Two studies included different races (African American, Asian, Caucasian, Hispanic, Latino, and White).[12,13] Most of the studies included males and females in the population data and only 2 studies discussed different outcomes with sex.[16] The percentage of female patients ranged from 0.29%[11] to 81%.[12] The age of patients ranged from 2.2 to18.7 years. The follow-up duration ranged from 3 to 41 months.[14–18]

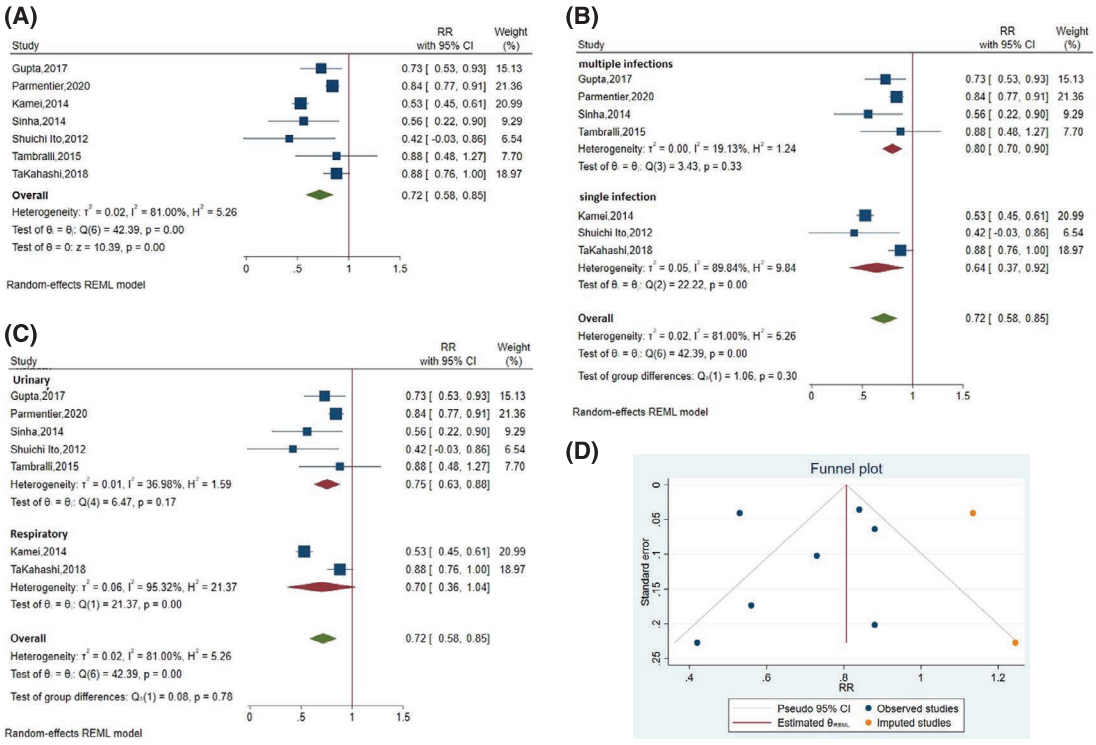
Risk of RTX- Related Infections. Two studies showed a positive association of infection associated with RTX therapy and decreased risk of infection in patients with nephrotic syndrome and LN which, was not statistically significant.[15,17] Pooled RR ratio using a random-effects model for all the 7 cohort studies (single and multiple infections) was 0.72 (95% CI 0.58, 0.85). The meta-analysis showed that RTX treatment was significantly associated with a decreased risk of infection in patients with glomerular disease (p = 0.03). The pooled meta-analysis indicated that there was large statistical heterogeneity among the included studies (Q = 42.39, p < 0.001, I^2 = 81%), (Figure 2A).

Table 1. Study Characteristics: Risk of Rituximab-Associated Infection Among Children and Adolescents With Glomerular Disease

Primary Diagnosis	Study Design	Author, Publication Year, and Country of Origin	Total Number of Participant (Number of Cases)	Age, Mean±SD, yr	Sex, Race, Ethnicity	Source of Comparison	Outcome, Site and Type of Infection	RTX Treatment Regimen, Median (Range)	Treatment Follow-up, Mean (Range), mo
LN	Prospective	Gupta 2017 USA[13]	32 (22)	13–16	M (n = 6), F (n = 26), AA (n = 9), W (n = 12), H (n = 11)	Same as LN population	Viuria BKV viremia (n = 16)	375 mg/m^2 4–6 wk apart Cumulative dose (g) 5.0 (1.8–9.9) RTX alone	16 (3–41) Mean 41.9
LN	Retrospective	Tambralli 2015 USA[17]	104 (50)	12.3±4.8	M (n = 23), F (n = 81), AA (n = 61), W (n = 31), H (n = 5)	Population data	Pneumonia Bacteremia (n = 12)	750 mg/m^2 (maximum 1g/dose) 2 wk apart 2 doses RTX alone	12
NS	Retrospective Multicenter	Takahashi 2019 Japan[18]	25 (22)	Median 11.2 (9–13)	M (n = 8), F (n = 14)	Same as NS population	Tonsilitis (n = 12)	375 mg/m^2 Single dose maximum 500 mg/ dose RTX alone	6
NS	Retrospective	Kamei 2015 Japan[15]	114 (99)	Median 12.5 (4.3–10.2)	M (n = 76), F (n = 38), Asian	Population data	Sinusitis, tonsillitis, URI (n = 9)	375 mg/m^2 Maximum 500 mg/dose every 2 wk 2–4 doses RTX alone	1–6
NS	Prospective	Sinha 2014 India[16]	135 (101)	Median 10.9 (2.2–18.7)	Asian	Same as NS population	Peritonitis (n = 1) Varicella (n = 1).\, Malaria (n = 1)	375 mg/m^2 Weekly for 2–4 doses, Combination therapy	6
NS	Retrospective Multicenter	Ito 2013 Japan[14]	74 (55)	5.9±4.0	M (n = 44), F (n = 30), Asian	Same as NS population	Sepsis (n = 1) Granulocytosis (n = 1), Severe adverse events (n = 1)	375 mg/m^2 single dose Once weekly, RTX alone	24 (8–51), Mean ± SD, 24.2±19.8
NS	Retrospective	Parmentier 2020 France[12]	126 (107)	3.1 (2.2–5.4)	M (n = 70), F (n = 37), W (n = 107)	Population data	Pneumonia Meningitis Viral myocarditis, varicella, EBV (n = 9)	375 mg/m^2 11 patients received single dose and 96 required repeated infusions Combination therapy	6

AA, African American; H, BKV, BK virus; EBV, Ebstein Barr virus; F, Female; H, Hispanic; LN, lupus nephritis; M, male; NS, nephrotic syndrome; URI, upper respiratory infection; UTI, urinary tract infection; W, white.

Figure 2. Forrest plots showing the risk of RTX infection in glomerular disease. (A) Overall risk of infection. (B) Subgroup analysis by type of infections. (C) Subgroup analysis by site of infections. (D) Begg funnel plot.



REML, restriction maximum likelihood; RR, relative risk; RTX, rituximab.

Type of RTX-Associated Infection. Infections occurred in all studies. Of these, 3 were single and 4 were multiple infections.[13,14,17] Forest plots displaying the multiple infections and single infection (Figure 2B). For single infection, RR for each study ranged from –0.03 to 1.0. For multiple infections, RR for each study ranged from 0.22 to 1.27, and pooled RR was 0.80 (95% CI 0.70, 0.90) (Figure. 2B). The pooled RR for both single and multiple infections was 0.72 (95% CI 0.58,0.85) and the pooled RR for just single infection was 0.64 (95% CI, 0.37,0.92), Figure 2B). The findings suggest that RTX therapy is associated with a statistically significant decreased risk of infections (p = 0.02) (Figure 2B).

Site of RTX-Associated Infection. Respiratory infections were the most frequent sites of infection. Relative risk for each study ranged from 0.36 to 1.04. For the 5 urinary infections, RR for each study ranged from –0.03 to 1.27, and pooled RR was 0.75 (95% CI, 0.63, 0.88). The pooled RR results of respiratory and urinary infections were 0.72 (95% CI, 0.58,0.85) (Figure 2C).

Overall adverse drug events [ADEs] were lower in the MMF group (59.3%) than in the cyclophosphamide [CYC] group (76.4%) (p = 0.03). Grade 3 adverse events occurred in 7 patients (20.5%) in the CYC group and in 4 patients (12.5%) in the MMF group (p = 0.04). Grade IV, infection-related adverse events, were observed in 3 (9%) patients receiving MMF and 5 patients (15%) receiving CYC ($p < 0.05$). The treatment-related ADEs was defined and graded according to the International Conference on Harmonization Guideline for Clinical Study Data Management (https://cte.cancer.gov/protocoledevelopment/electronic_applications.docs.ctcaev3.pdf). These patients were treated with intravenous immunoglobulin and antibiotic therapy and were subsequently withdrawn from the study and considered as treatment failures and included in the final analysis.

Sensitivity Analysis and Publication Bias. The risk of bias summary is shown in Figure 2D. Sensitivity analysis indicated that the study designs, methods, dose of RTX administration, and participant ethnicity excessively influenced the pooled association between RTX-related infections. The publication bias was not detected from the Begg's test (p value = 0.54), Egger's test (p value = 0.37), and visual inspection of the funnel plot (Figure 2D). According to the trim-and-fill analysis, 2 potential missing studies were required on the right side of the funnel plot to make it symmetric.

Discussion

Our meta-analysis showed that the administration of RTX was significantly associated with a lower risk of infections in children with LN and nephrotic syndrome when compared with the population data of patients without systemic lupus erythematosus [SLE] or nephrotic syndrome. This is the first meta-analysis examining RTX associated infectious complications in children with glomerular diseases. Further, our meta-analysis showed fewer life-threatening infections in patients with LN and nephrotic syndrome than in the population without glomerular disease. There were also no significant differences in serious life-threatening infections or the occurrence of infectious complication between LN and nephrotic syndrome. The study also showed that administration of a smaller dose of RTX was associated with a lower incidence of infection than a larger dose of RTX.

Rituximab is highly effective in a variety of autoimmune kidney diseases. Several factors appear to contribute to the risk of severe infections, including larger RTX doses, (375 mg/m^2) concomitant use of prednisone or other immunosuppressive agents, renal impairment, prolonged B cell depletion, neutropenia, and hypogammaglobulinemia.[18,19]

Ruggenenti *et al*.[20] described no treatment-related serious adverse events when treating 100 cases of idiopathic membranous nephropathy with RTX. Similarly, Cravedi *et al*.[21] observed no infectious complications after RTX administration in a smaller cohort of patients with resistant idiopathic membranous nephropathy. Additionally, Inoki et al.[22] in a retrospective observational study of 140 children with nephrotic syndrome showed no statistically significant association between hypogammaglobulinemia severity and infection rate. Finally, a recent systematic review of RTX therapy for frequently relapsing/steroid-dependent minimal change disease [MCD] and FSGS also described RTX as being well tolerated.[23]

Tambralli, et al.[17] in a retrospective study of 50 patients with LN evaluated the safety and efficacy of RTX and showed that RTX treatment was significantly associated with a lower rate of infection, compared with other treatment. In a more recent study, Takahashi et al.[18] reported that a periodical administration of small-dose RTX is safer and more efficacious than a single high dose in maintaining disease-free survival rate in patients with nephrotic syndrome.

Assadi, et al.[24] in a recent randomized controlled trial treated 63 children with steroid-resistant nephrotic syndrome (SRNS) using 2 to 3 doses of RTX in combination with CYC or mycophenolate mofetil (MMF), and found that the overall incidence of severe adverse drug events was lower in the MMF group (59.3%) than the CYC group (76.4%) (p = 0.03). Grade 3 adverse events occurred in 7 patients (20.5%) in the CYC group and in 4 patients (12.5%) in the MMF group (p = 0.04). Grade IV, infection-related adverse events, were observed in 3 (9%) patients receiving RTX plus MMF and 5 patients (15%) receiving RTX plus CYC (p < 0.05%).

Unlike the previous studies, Odler et al,[25] in a retrospective cohort study of 140 adult patients with autoimmune kidney diseases treated at least with 1 course of RTX, found a high incidence of respiratory infections (40%) followed by urinary infections (12%) and gastrointestinal infections (8%).

A prospective study by *Terrier* et al.[26] came to the same conclusion. These investigators described severe infections in 9% of patients treated with RTX for systematic lupus erythematosus [SLE], mostly occurring in the first 3 months, and reported that 79% of all infections were of bacterial origin. Additional studies are needed to determine RTX's safety profile in this patient group.

The Lower rate of infectious complications with RTX in the present review and studies reported by others is likely the result of diversity in the study designs and methodologies used by the different investigators. The timing of RTX administration, variability in different numbers and doses of RTX used for treatment, histological variability among patients with initial or late resistance to medications, and the heterogeneity of nephrotic syndrome itself may explain some of the conflicting reports.[16]

Additional studies are needed to determine RTX's safety profile in patients with LN and nephrotic syndrome

Limitations

Our meta-analysis has several potential limitations. First, only 7 cohort studies were included, and their sample sizes were relatively small, which may result in a certain level of bias in the conclusions. Second, for the safety assessment of RTX in patients with glomerular diseases, relative short-term follow-ups can underestimate the rate of infections. Third, the doses and duration of RTX treatment were different in the included studies. Fourth, there was a large heterogeneity between the outcomes, which can affect the final results; fifth, several factors appear to increase the risk of infections during RTX therapy. These include large dose of RTX, concomitant use of prednisone or other immunosuppressive agents, renal impairment[18], prolonged B-cell depletion.[20] neutropenia,[27] hypogammaglobulinemia,[27–31] and impaired immune response after vaccination, which can introduce bias that affects the results and makes the interpretation of data rather difficult.[29,32,33] Last, only English articles were included and important studies published in other languages may have been overlooked.

Conclusions

Based on the current evidence, the present meta-analysis documents that administration of RTX in children with glomerular disease is associated with a lower rate of infections when compared with population data of

patients without lupus nephritis or nephrotic syndrome. The safety of RTX in children with glomerular diseases is yet to be established. Additional high-quality randomized controlled trials with long-term follow-up are needed to further examine the infectious complications associated with RTX therapy in patients with glomerular diseases.

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Author contributions. Z.P. searched the literature, contributed in data acquisition, data analysis, provided critical discussion regarding the research question at hand, and executed the project. F.A. designed the study, drafted the initial project proposal, contributed in the data analysis and interpretation, wrote, and revised the manuscript. M.M. performed data extraction and quality assessment of all screened articles and resolved any disagreements about the inclusion or exclusion of a study. NH wrote the research proposal and registered the study in Prospero. Z.R. performed statistical analyses of extracted data from all eligible studies after removing duplicates from the search results, and prepared table and figures. M.M., A.Z. and F.G.S searched the literature and contributed in data acquisition. All authors reviewed and approved the final manuscript version for publication in the journal.

Ethical Approval and Informed Consent. Not applicable

Acknowledgments. Authors are grateful to Mrs. Sepideh Alibeyk for her help in collecting and extracting data of the all the included studies.

Submitted. May 16, 2022

Accepted. September 21, 2022

Supplemental Material. DOI: 10.5863/xxxx-xxxx-xx.x.xx.S1

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