



Immunosuppression Exposure and Risk of Infection-Related Acute Care Events in Patients With Glomerular Disease: An Observational Cohort Study

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Rationale & Objective: Infections cause morbidity and mortality in patients with glomerular disease. The relative contributions from immunosuppression exposure and glomerular disease activity to infection risk are not well characterized. To address this unmet need, we characterized the relationship between time-varying combinations of immunosuppressant exposure and infection-related acute care events while controlling for disease activity, among individuals with glomerular disease.

Study Design: Prospective, multicenter, observational cohort study.

Setting & Participants: Adults and children with biopsy-proven minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, or immunoglobulin A nephropathy/vasculitis were enrolled at 71 clinical sites in North America and Europe. A total of 2,388 Cure Glomerulonephropathy Network participants (36% aged <18 years) had at least 1 follow-up visit and were included in the analysis.

Exposures: Immunosuppression exposure modeled on a weekly basis.

Outcome: Infections leading to an emergency department visit or hospitalization.

Analytical Approach: Marginal structural models were used to estimate the effect of time-varying immunosuppression exposure on hazard of first infection-related acute care event while accounting for baseline sociodemographic and clinical factors, and time-varying disease activity.

Results: A total of 2,388 participants were followed for a median of 3.2 years (interquartile range, 1.6-4.6), and 15% experienced at least 1 infection-related emergency department visit or hospitalization. Compared to no immunosuppression exposure, steroid exposure, steroid with any other immunosuppressant, and nonsteroid immunosuppressant exposure were associated with a 2.65-fold (95% CI, 1.83-3.86), 2.68-fold (95% CI, 1.95-3.68), and 1.7-fold (95% CI, 1.29-2.24) higher risk of first infection, respectively.

Limitations: Absence of medication dosing data, lack of a control group, and potential bias in ascertainment of outcome events secondary to the coronavirus 2 pandemic.

Conclusions: Corticosteroids with or without concomitant additional immunosuppression significantly increased risk of infection leading to acute care utilization in adults and children with glomerular disease.

Visual Abstract included

Complete author and article information provided before references.

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Infections contribute to morbidity and mortality in chronic kidney disease and end-stage kidney disease, and are considered an important clinical outcomes by stakeholders in the glomerular disease community, including patients, care partners, and health care professionals.¹⁻⁸ Putative risk factors for infection in patients with glomerular disease include exposure to immunosuppressive medications, systemic inflammation, altered immune cell function, and urinary loss of immunoglobulin and complement factors.^{9,10} However, measuring the contribution to infection risk from individual factors is challenging because glomerular diseases can relapse and remit, in turn resulting in intermittent exposures to multiple immunosuppressive agents, alone and in combination, over the disease course. Previous estimates of infectious risk in patients with glomerular disease have been limited by small sample size, short follow-up duration, and restriction to baseline

measurements of disease activity and immunosuppression exposure.¹¹ There remains uncertainty regarding estimates of infection risk, particularly with respect to the confounding effect of disease activity on the association between immunosuppressant exposure and risk of infection.

Using data from participants enrolled in the Cure Glomerulonephropathy Network (CureGN), we sought to develop marginal structural models (MSMs) to characterize the relationship between time-varying combinations of immunosuppressant exposure and infection-related acute care events while accounting for baseline sociodemographic and clinical characteristics as well as time-dependent markers of disease activity (ie, proteinuria and serum albumin). We hypothesized that corticosteroid exposure, both when used alone and in combination with other immunosuppressive medications, would be associated with risk of infection.

PLAIN-LANGUAGE SUMMARY

Infections are an important cause of morbidity and mortality in patients with glomerular disease. In the present study, marginal structural models were used to estimate the effect of immunosuppression exposure on risk of infection while accounting for sociodemographic and clinical factors, such as disease activity. Adults and children with biopsy-proven glomerular disease were followed over time as part of the Cure Glomerulonephropathy Network. Across multiple drug classes, immunosuppression exposure that included corticosteroids was associated with a higher risk of infection. Purine inhibitor exposure alone did not appear to significantly increase infection risk. These findings provide important information to clinicians, patients, and the research community that will guide treatment decisions, mitigation strategies, and areas for future research in infection risk in immunosuppressed populations.

METHODS

Participant Population and Data Collection

CureGN is a prospective, multicenter observational cohort study of children (aged <18 years) and adults (aged ≥18 years) with biopsy-proven minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), or immunoglobulin A nephropathy/vasculitis (IgAN/IgAV) enrolled at 71 clinical sites in North America, Italy, and Poland (Item S1). Inclusion criteria include a biopsy-based diagnosis of MCD, FSGS, MN, or IgAN/IgAV within 5 years of enrollment without a history of chronic dialysis, kidney transplant, diabetes mellitus, lupus erythematosus, human immunodeficiency virus, active malignancy, or hepatitis B or C at time of first kidney biopsy. The CureGN study protocol was approved by the Institutional Review Board at each participating study site (18-0032) and was conducted in adherence with the Declaration of Helsinki. All participants provided written informed consent or assent if appropriate at enrollment.

This present study includes CureGN participants enrolled between December 2014 and September 2021 with at least 1 completed follow-up visit. Demographics and baseline clinical characteristics were collected at enrollment. Updated clinical data including medication changes, local laboratory test results, such as serum albumin and urinary protein-creatinine ratio (UPCR), and details of intercurrent emergency department visits or hospitalizations were collected every 4-6 months at in-person or remote study visits. Race and ethnicity were self-reported or reported by parents of children. Reporting race in the CureGN study was mandated by the US National Institutes of Health, consistent with the Inclusion of

Women, Minorities, and children policy. Participant exposure time was censored at first infection, receipt of a kidney transplant, cancer diagnosis, or last completed study visit. Detailed methods for the CureGN study, including approaches to ensuring data quality, have been previously published.^{12,13}

Definitions

Exposure: Baseline and Time-varying Variables

The Chronic Kidney Disease Epidemiology Collaboration 2021 formula (race agnostic) and the U25 formula were used to determine estimated glomerular filtration rate (eGFR) for subjects aged ≥25 and <25 years, respectively.^{14,15} eGFR was capped at 130 mL/min/1.73 m² to account for decreased precision of estimating formulas at low serum creatinine values. UPCR was calculated from a 24-hour urine collection, first morning void, or random spot urine. If UPCR was missing but a negative urine dipstick was reported, UPCR was assigned a value of 0.2 mg/mg.

Time-varying variables (immunosuppression, serum albumin, UPCR) collected at study visits were modeled on a weekly basis. Immunosuppression exposure was defined using start/stop dates identified by study coordinators. Medication exposure time was extended beyond medication stop dates to account for residual physiologic immunosuppressive activity (Table S1). For each week of follow-up, participants were considered to be exposed to an immunosuppressive medication if their exposure time during that week lasted at least 4 days. Participants with missing medication start dates were excluded from the analysis. Medications without stop dates were assumed to continue until end of follow-up unless the duration exceeded the 75th percentile duration of those with non-missing stop dates for each medication.

The number of comorbid conditions at enrollment was defined as the summation of hypertension, coronary artery disease, heart failure, arrhythmia, stroke, peripheral vascular disease, aortic aneurysm, valvular heart disease, celiac disease, inflammatory bowel disease, gastrointestinal bleed, cirrhosis, chronic obstructive pulmonary disease, asthma, sleep apnea, sickle cell disease, seizure disorder, solitary kidney, deep vein thrombosis, pulmonary embolism, renal vascular thrombosis, diabetes, human immunodeficiency virus, hepatitis B, hepatitis C, malignancy, or psychiatric disease. Participants were considered exposed to tobacco if they smoked at or within 1 year of enrollment.

Outcome: Infection-Related Acute Care Events

Study coordinators at each clinical site collected data regarding all ED visits or hospitalizations, including discharge International Classification of Diseases, Tenth Revision codes, hospital length of stay and intensive care unit admission. An International Classification of Diseases, Tenth Revision code-based algorithm was utilized to identify infection-related acute care

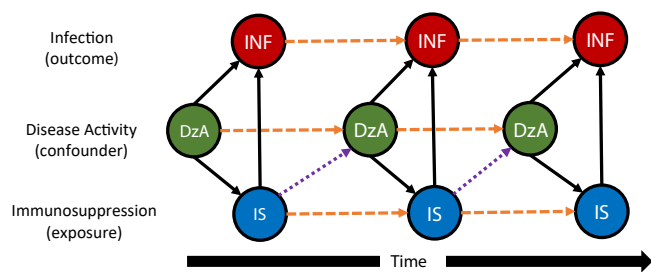


Figure 1. Illustration of time-dependent confounding by Disease Activity (DzA) of the relationship between Immunosuppression Exposure (IS) and Infection (INF) over longitudinal follow-up. Solid arrows demonstrate effects of interest and standard confounding typically found in observational studies, dashed arrows represent correlations within a variable over time, and dotted arrows represent time-dependent confounding affected by previous exposure.

events. Development and validation of this algorithm within CureGN has been previously described and demonstrated positive and negative predictive values of 87% (95% CI, 75%-99%) and 83% (95% CI, 72%-93%), respectively.¹⁶ Infection-related acute care events occurring within 2 weeks of a prior infection of the same type were considered as 1 event. ED visits leading to hospitalization were categorized as hospitalization events. Severe infections were defined as acute care events requiring hospitalization.

Statistical Methods

Demographics and clinical characteristics at the time of study enrollment were summarized using median and interquartile range (IQR) for continuous variables and frequency for categorical variables. Immunosuppressant use at study enrollment and infection-related acute care events were summarized using frequency for categorical variables and the number of events per 100 person-years for outcome event rates. To assess whether the incidence rates of infection-related acute care events changed after the start of the coronavirus disease 2019 (COVID-19) pandemic, a linear regression model with an interaction between calendar time and a COVID-19 era indicator was used to create a piecewise regression and compare regression slopes before versus during the COVID-19 pandemic. For subsequent statistical analyses, missing baseline demographic and clinical characteristics as well as missing UPCR and serum albumin values over follow-up were multiply imputed. Ten imputed data sets were created using the sequential regression technique implemented by IVEware 2.0.^{17,18}

MSMs were used to estimate the effect of time-varying immunosuppression exposure on hazard of first infection-related acute care event while accounting for the effects of presumed time-dependent confounding due to serum albumin and UPCR (Fig 1).¹⁹ MSMs account for confounding variables over time, in this case changes in

disease activity, by weighting each time point for each participant by the inverse probability of that participant's observed treatment status. For example, participants who receive treatment due to having greater disease activity would be down-weighted and participants who do not receive treatment despite having greater disease activity would be up-weighted. The weights therefore create a pseudo-population of participants with balanced confounder values. The main advantage of MSM models over Cox regression models is the ability to adjust for time-dependent confounding. See Xie et al¹⁹ for a comprehensive review.

In the current study, we estimated the unconditional probability of treatment for each participant-week of follow-up using a logistic regression model that included the previous week's treatment status and clinically meaningful baseline demographic and clinical characteristics as covariates. The conditional probability of treatment was then calculated using the same covariates with the addition of the time-dependent confounding variables of UPCR and serum albumin. For the first week of follow-up when previous treatment status was not available, separate models were run to estimate the unconditional and conditional probabilities omitting the previous week's treatment as a covariate. Stabilized inverse probability of treatment (or nontreatment) weights were then calculated as the ratio of the unconditional to conditional probabilities of treatment (or nontreatment).

Similarly, logistic regression models were used to calculate unconditional and conditional probabilities of censoring for all participant-weeks of follow-up after week 1. All participants were assigned a censoring probability of 0 for week 1 because there were no censoring events at this time. Stabilized inverse probability of censoring (or noncensoring) weights were then calculated as the ratio of these 2 probabilities (unconditional/conditional) of censoring (or noncensoring). Each participant's final weight at each week was then calculated as the product of their stabilized inverse probability of treatment (or nontreatment) weight and their stabilized inverse probability of censoring (or noncensoring) weight.

To approximate a discrete failure time model, we estimated the time to first infection using a pooled logistic regression model with time-updated weights, as described above, and an independent correlation structure. Odds ratios from this model approximate hazard ratios traditionally obtained from a Cox survival model. Three MSMs were estimated based on different categorizations of immunosuppression types and combinations: (1) any immunosuppression versus no immunosuppression, (2) steroids alone versus steroid with any other immunosuppressant versus nonsteroid immunosuppressant only versus no immunosuppression, and (3) 9 categories that included each of calcineurin inhibitors, antimetabolites, and rituximab alone and with steroids, steroids alone, other nonsteroid immunosuppressant combination, and no immunosuppression. Post hoc pairwise comparisons

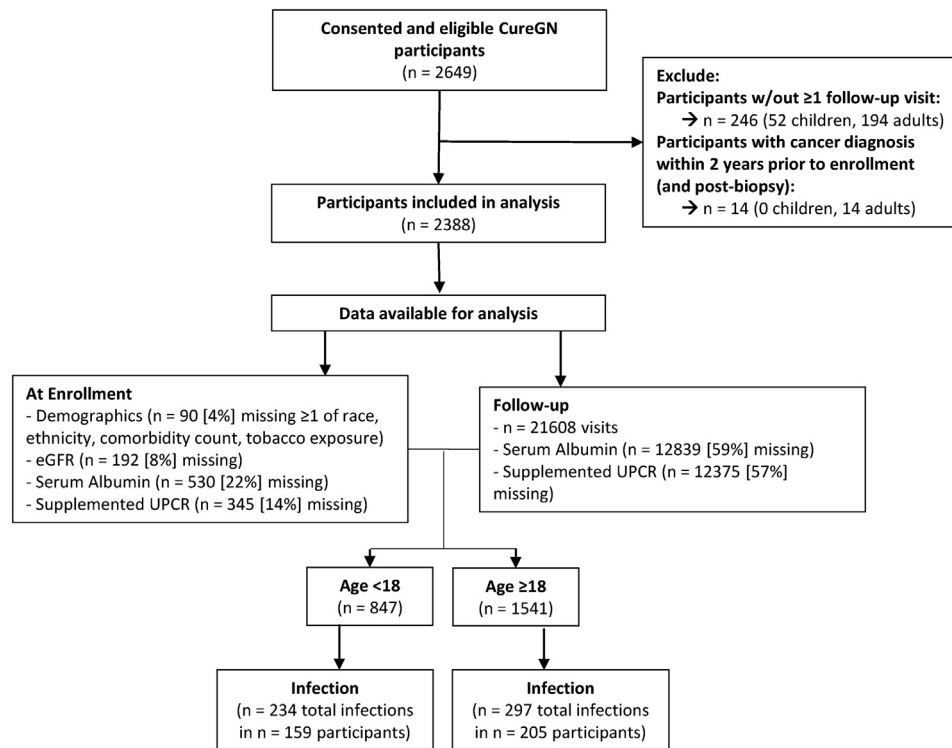


Figure 2. Cohort assembly. Abbreviations: eGFR, estimated glomerular filtration rate; UPCR, urinary protein-creatinine ratio.

between select categories of immunosuppression exposure from models 2 and 3 were conducted to answer the specific research question about the effect of including steroids with other immunosuppressants. Models 1 and 2 were also estimated separately for children and adults, but model 3 was not estimated in subgroups due to concerns about violating the positivity assumption of MSMs within the small subgroup sample sizes. SAS v9.4 (SAS Institute) was used for all statistical analyses.

RESULTS

Participant Characteristics at Baseline

Baseline characteristics stratified by age <18 or ≥18 years are shown in Table 1. A total of 2,388 participants were included in this study, 847 of whom were aged <18 years at CureGN enrollment (Fig 2). At enrollment, 17% of the cohort were aged <10 years, 18% were 11–17 years, 49% were 18–60 years, and 15% were ≥60 years. Females accounted for 43% (n = 1,030) of the cohort, and 16% (n = 373) of the cohort was of Black race. Glomerular disease subtype was based on study pathologist review of a diagnostic kidney biopsy obtained a median of 11.7 months (IQR, 3.7–30.2) before study enrollment. The cohort was comprised of 558 (23%) individuals with MCD, 605 (25%) individuals with FSGS, 537 (22%) individuals with MN, and 688 (29%) individuals with IgAN/IgAV. A greater proportion of

children had MCD (39% vs 15%), whereas MN was more common in adults (32% vs 6%). Of those participants without missing data at enrollment, 71% had an eGFR >60 mL/min/1.73 m² and 42% had an eGFR >90 mL/min/1.73 m². Seventy-eight percent had a UPCR >0.2 mg/mg, 53% had a UPCR >1 mg/mg, and 27% had a UPCR >3.5 mg/mg. Additionally, 41% had a serum albumin ≤3.5 mg/dL and 15% had a serum albumin ≤2.5 mg/dL at enrollment. Low eGFR at enrollment (<60 mL/min/1.73 m²) was more common among adult participants (41% vs 9%). Adult participants were also enrolled with a greater number of comorbid health conditions.

Immunosuppression Exposure

Table 2 summarizes participant immunosuppression exposure at enrollment stratified by age category. At enrollment, 46%, 33.4%, 18%, 2.5%, and 0.1% of the complete cohort were currently exposed to 0, 1, 2, 3, and 4 immunosuppressive medications, respectively. The proportion of follow-up time with exposure to multiple combinations of immunosuppressants is summarized in Table 3. Over a median follow-up of 3.2 years (IQR, 1.6–4.6), 69% of follow-up exposure time was free of any immunosuppressant exposure. The proportion of immunosuppression free exposure time increased with age from 50% for those aged 0–10 years to 75% for those aged ≥60 years.

Table 1. Enrollment Characteristics of N = 2,388 Participants in the CureGN Network

	Total (N = 2,388)	Age <18 y (N = 847)	Age ≥18 y (N = 1,541)
Age (y), median (IQR)	31 (14-51)	11 (7-14)	46 (32-59)
≤10	412 (17%)	412 (49%)	0 (0%)
11-17	435 (18%)	435 (51%)	0 (0%)
18-59	1,180 (49%)	0 (0%)	1,180 (77%)
≥60	361 (15%)	0 (0%)	361 (23%)
Female sex	1,030 (43%)	355 (42%)	675 (44%)
Race^a			
Black	373 (16%)	141 (17%)	232 (16%)
Multiracial/other ^b	294 (13%)	101 (12%)	193 (13%)
White	1,639 (71%)	577 (70%)	1,062 (71%)
Hispanic/Latino^c	307 (13%)	111 (13%)	196 (13%)
Glomerular disease type			
MCD	558 (23%)	334 (39%)	224 (15%)
FSGS	605 (25%)	202 (24%)	403 (26%)
MN	537 (22%)	48 (6%)	489 (32%)
IgAN/IgAV	688 (29%)	263 (31%)	425 (28%)
Corticosteroids at enrollment	889 (37%)	415 (49%)	474 (31%)
Other immunosuppression^d at enrollment	877 (37%)	424 (50%)	453 (29%)
eGFR (mL/min/1.73m²),^e median (IQR)	83 (54-103)	97 (81-114)	71 (44-97)
<60	646 (29%)	70 (9%)	576 (41%)
60-90	631 (29%)	244 (31%)	387 (27%)
>90	919 (42%)	472 (60%)	447 (32%)
UPCR (mg/mg),^{f,g} median (IQR)	1.0 (0.2-3.7)	0.4 (0.1-2.2)	1.5 (0.4-4.2)
≤0.2	556 (27%)	306 (40%)	250 (20%)
0.2-1	460 (23%)	176 (23%)	284 (22%)
1-3.5	501 (25%)	130 (17%)	371 (29%)
>3.5	526 (26%)	149 (20%)	377 (29%)
Serum albumin (g/dL),^h median (IQR)	3.8 (3.0-4.2)	3.8 (2.9-4.2)	3.7 (3.0-4.1)
≤2.5	294 (16%)	126 (18%)	168 (14%)
2.5-3.5	467 (25%)	144 (21%)	323 (27%)
>3.5	1097 (59%)	412 (60%)	685 (58%)
Tobacco exposure^c	330 (14%)	13 (2%)	317 (21%)
Number of comorbidities,^{g,i} median (IQR)	1 (0-2)	0 (0-1)	2 (1-3)
0	801 (34%)	493 (58%)	308 (20%)
1-3	1385 (58%)	343 (41%)	1042 (68%)
>3	201 (8%)	10 (1%)	191 (12%)
Months from kidney biopsy to enrollment, median (IQR)	11.7 (3.7-30.2)	10.5 (2.9-28.1)	12.8 (4.3-32.2)

Note: Values for categorical variables are presented as count (percentage among nonmissing values) and values for continuous variables are presented as median (interquartile range [IQR]) where noted.

Abbreviations: eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; MCD, minimal change disease; MN, membranous nephropathy; UPCR, urinary protein-creatinine ratio.

^aIncludes participants who self-identified as multiracial. "Other" race includes Alaskan Native/First Nations/Native American, Asian, Native Hawaiian/other Pacific Islanders

^bMissing 3%

^cMissing <1%

^dOther immunosuppression includes adrenocorticotropic hormone, azathioprine, calcineurin inhibitor, cyclophosphamide, mycophenolic acid, and rituximab

^eMissing 8%

^fMissing 14%

^gIf UPCR was missing but a negative urine dipstick was reported, UPCR was assigned a value of 0.2 mg/mg

^hMissing 22%

ⁱComorbid conditions include deep vein thrombosis, pulmonary embolism, renal vein or artery thrombosis, diabetes, human immunodeficiency virus, hepatitis B, hepatitis C, hypertension, coronary artery disease, heart failure, arrhythmia, stroke, peripheral vascular disease, aortic aneurysm, valvular heart disease, celiac disease, inflammatory bowel disease, gastrointestinal bleed, cirrhosis, chronic obstructive pulmonary disease, asthma, sleep apnea, attention-deficit/hyperactivity disorder, psychiatric disorder, seizure/epilepsy, solitary kidney, sickle cell, and cancer.

Missing data

At enrollment, 22% of participants were missing serum albumin, 14% were missing UPCR (supplemented with negative urine dipstick), 8% were missing eGFR, 3% were missing race, and <1% were missing ethnicity, tobacco

exposure, and comorbid condition information. Over follow-up, serum albumin and supplemented UPCR were missing at 59% and 57% of the study visits, respectively. Data from urine dipsticks were available for 20% of visits with missing UPCR values, and unadjusted logistic

Table 2. Immunosuppression Exposure at Enrollment,^a n (%)

	Total (N = 2,388)	0-10 y (N = 412)	11-17 y (N = 435)	18-59 y (N = 1,180)	60+ y (N = 361)
0 medications	1,089 (46%)	70 (17%)	190 (44%)	625 (53%)	204 (57%)
1 medication					
Steroids only	427 (18%)	88 (21%)	75 (17%)	202 (17%)	62 (17%)
CNI only	222 (9%)	53 (13%)	49 (11%)	95 (8%)	25 (7%)
MMF only	68 (3%)	19 (5%)	16 (4%)	28 (2%)	5 (1%)
Rituximab only	58 (2%)	6 (1%)	5 (1%)	33 (3%)	14 (4%)
Azathioprine only	12 (1%)	1 (0.2%)	3 (1%)	8 (1%)	0 (0%)
Cyclophosphamide only	10 (0.4%)	1 (0.2%)	0 (0%)	5 (0.4%)	4 (1%)
2 medications					
Steroids + CNI	224 (9%)	83 (20%)	39 (9%)	81 (7%)	21 (6%)
Steroids + MMF	91 (4%)	31 (8%)	22 (5%)	32 (3%)	6 (2%)
Steroids + rituximab	41 (2%)	11 (3%)	4 (1%)	23 (2%)	3 (1%)
Steroids + cyclophosphamide	35 (1%)	7 (2%)	5 (1%)	18 (2%)	5 (1%)
Other 2 drug combinations	58 (2%)	16 (4%)	19 (4%)	16 (1%)	7 (2%)
3 medications					
Steroids + CNI + rituximab	23 (1%)	12 (3%)	3 (1%)	4 (0.3%)	4 (1%)
Steroids + CNI + MMF	17 (1%)	9 (2%)	2 (0.5%)	5 (0.4%)	1 (0.3%)
Other 3 drug combinations	11 (0.5%)	4 (1%)	2 (0.5%)	5 (0.4%)	0 (0%)
4 drug combinations	2 (0.1%)	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)

Abbreviations: CNI, calcineurin inhibitor; MMF, mycophenolic acid.

^aCurrent exposure, see Table S1 for exposure windows by drug class.

regression models showed that participants with a lower UPCR or a higher serum albumin were more likely to have a missing UPCR or albumin, respectively, at their next visit (UPCR: OR, 0.97, $P < 0.001$; albumin: OR, 1.22,

$P < 0.001$). Therefore, missing data were imputed using sequential regression multiple imputation techniques that incorporated each participant's observed lab values and urine dipstick data.

Table 3. Immunosuppression Exposure Over Follow-up,^a Percent Follow-up Time^b

	Total (N = 2,388)	0-10 y (N = 412)	11-17 y (N = 435)	18-59 y (N = 1,180)	≥60 y (N = 361)
Follow-up time (y), median (IQR)	3.2 (1.6-4.6)	3.3 (1.4-4.6)	3.4 (1.7-4.6)	3.1 (1.5-4.6)	3.2 (1.8-4.5)
0 medications	69.0%	49.5%	69.5%	73.8%	75.1%
1 medication					
Steroids only	5.1%	6.5%	4.5%	4.9%	4.8%
CNI only	9.1%	14.0%	10.1%	7.5%	7.8%
MMF only	3.9%	7.7%	5.1%	2.9%	1.1%
Rituximab only	2.7%	3.1%	0.9%	2.7%	4.6%
Azathioprine only	0.7%	0.6%	1.3%	0.6%	0.1%
Cyclophosphamide only	0.1%	0%	0%	0.2%	0.3%
2 medications					
Steroids + CNI	3.5%	7.1%	3.4%	2.7%	2.2%
Steroids + MMF	1.4%	2.7%	1.8%	1.1%	0.6%
Steroids + rituximab	1.0%	1.9%	0.4%	0.9%	1.1%
Steroids + cyclophosphamide	0.3%	0.2%	0.1%	0.3%	0.2%
Other 2 drug combinations	1.9%	3.3%	1.9%	1.6%	1.6%
3 medications					
Steroids + CNI + rituximab	0.4%	1.1%	0.3%	0.3%	0.1%
Steroids + CNI + MMF	0.4%	1.2%	0.5%	0.2%	0%
Other 3 drug combinations	0.3%	0.8%	0.2%	0.2%	0.2%
4 drug combinations	0.1%	0.3%	0.1%	0%	0%

Abbreviations: CNI, calcineurin inhibitor; IQR, interquartile range; MMF, mycophenolic acid.

^aTime from enrollment until first infection, cancer diagnosis, or transplant, else until last completed study visit.

^bEach column total adds to 100%, with individual values representing the proportion of follow-up time exposed to the relevant medication(s). See Table S1 for exposure windows by drug class.

Table 4. Infection-Related Acute Care Events, by Age at Enrollment

	All participants (N = 2,388)	Age at enrollment			
		0-10 y (N = 412)	11-17 y (N = 435)	18-59 y (N = 1,180)	≥60 y (N = 361)
All-cause acute care utilization events, n	2,934	847	523	1,222	342
Infection-related events, n (% of all acute care events)	531 (18%)	175 (21%)	59 (11%)	228 (19%)	69 (20%)
Hospitalizations, n (% of all infection events)	302 (57%)	103 (59%)	24 (41%)	119 (52%)	56 (81%)
ED visits, n (% of all infection events)	229 (43%)	72 (41%)	35 (59%)	109 (48%)	13 (19%)
Participants with ≥1 infection-related event, n (% of participants)	364 (15%)	108 (26%)	51 (12%)	156 (13%)	49 (14%)
Infection-related events per participant, n (% of participants)					
1	264 (11%)	71 (17%)	45 (10%)	114 (10%)	34 (9%)
2	62 (3%)	22 (5%)	5 (1%)	24 (2%)	11 (3%)
≥3	38 (2%)	15 (4%)	1 (0.2%)	18 (2%)	4 (1%)
Infection-related acute care events/100 person-years	6.1	10.6	3.8	5.5	5.3
Length of stay (d), median (IQR)	3 (1-5)	3 (1-5)	3 (2-5)	3 (2-6)	4 (2-6)
ICU stay due to infection, n (% of all infection events)	24 (8%)	11 (11%)	5 (21%)	7 (6%)	1 (2%)
Infections by body system [more than one can apply], n (% of all infection events)					
Pulmonary/lower respiratory	161 (30%)	46 (26%)	15 (25%)	61 (27%)	39 (57%)
Multisystem infection/site unspecified	123 (23%)	54 (31%)	11 (19%)	51 (22%)	7 (10%)
Upper respiratory tract/throat	101 (19%)	45 (26%)	17 (29%)	32 (14%)	7 (10%)
Genitourinary	59 (11%)	9 (5%)	5 (8%)	41 (18%)	4 (6%)
Gastrointestinal	57 (11%)	14 (8%)	7 (12%)	29 (13%)	7 (10%)
Skin and soft tissue	46 (9%)	13 (7%)	7 (12%)	21 (9%)	5 (7%)
Bacteremia and septicemia	39 (7%)	11 (6%)	3 (5%)	14 (6%)	11 (16%)
Ear and nose	15 (3%)	9 (5%)	3 (5%)	2 (1%)	1 (1%)
Eye	11 (2%)	6 (3%)	1 (2%)	3 (1%)	1 (1%)
Bone and joint	2 (0.4%)	1 (1%)	0 (0%)	1 (0.4%)	0 (0%)
Central nervous system	1 (0.2%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)

Abbreviations: ED, emergency department; ICU, intensive care unit; IQR, interquartile range.

For noninfusion immunosuppressants, the 75th percentile duration of courses with nonmissing stop dates was used to approximate the stop date for 16% of records due to missing stop dates.

Infection-Related Acute Care Events

Table 4 summarizes characteristics of infection-related acute care events stratified by age at enrollment. Of 2,388 participants, 364 (15%) experienced at least 1 infection-related acute care event over a median follow-up of 3.2 years (IQR, 1.6-4.6). During this time, a total of 2,934 all-cause ED visits and hospitalizations were reported. Of these, 531 (18%) were determined to be infection related. A total of 302 (57%) infection-related events required hospitalization, and of these, 24 (8%) included an intensive care admission. Pulmonary/lower respiratory tract infections were the most common infection in the full cohort (30%). Table 4 summarizes type of infection by age at enrollment. A heatmap of

immunosuppression use at time of infection, by body system, is shown in Fig S1.

Figure 3 shows the incidence of infections over time, with regression lines indicating trends before and after COVID-19-related quarantine began in most regions in the United States.

Regression slopes prior to- versus during the COVID-19 pandemic were -0.004 and -0.02 per month, respectively but were not found to be significantly different in this sample ($P = 0.08$).

MSM Models

Figure 4 shows adjusted hazard ratios for first infection-related acute care event by immunosuppressant category for the complete cohort. Hazard ratios for models restricted to severe infections (ie, hospitalized infections) are also shown. All models adjusted for baseline demographics (age, sex, race, ethnicity) and clinical characteristics (disease subtype, eGFR, number of comorbid

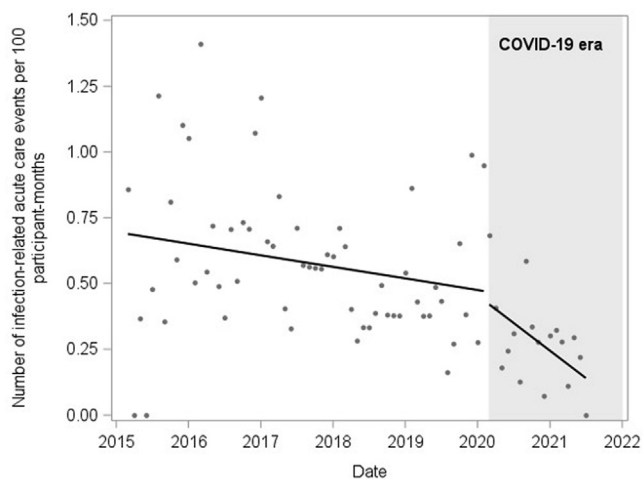


Figure 3. Scatterplot of infection-related acute care events by year. Linear regression model using the interaction between time and coronavirus disease 2019 (COVID-19) era indicator was used to compare regression slopes before vs during the COVID-19 pandemic ($P = 0.08$).

conditions, tobacco use, time from biopsy to enrollment), and accounted for time-varying markers of disease activity (UPCR and serum albumin) via model weights. In model 1, any immunosuppression exposure during follow-up was associated with a 2.1-fold (95% CI, 1.67-2.64) higher risk of first infection-related acute care event compared to no immunosuppression exposure. Table S2 shows similar results when this model was estimated separately in children and adults. In model 2, compared to no immunosuppression exposure, steroid exposure, steroid and any other immunosuppressant, and all other (nonsteroid) immunosuppressant exposure were associated with a 2.65-fold (95% CI, 1.83-3.86), 2.68-fold (95% CI, 1.95-3.68), and 1.7-fold (95% CI, 1.29-2.24) higher risk of infection-related acute care event, respectively. The effects of steroid exposure and steroid with any other immunosuppressant were similar among children and adults, whereas there was a smaller effect of other (nonsteroid) immunosuppressants among adults (Table S3). Risks of infection with exposure to immunosuppression with versus without concomitant corticosteroid exposure were also significantly different overall ($P = 0.008$) and among adults ($P = 0.02$). Similarly, multiple classes of individual and combined immunosuppression exposures were associated with higher hazards of infection compared with no immunosuppression exposure in model 3 (Fig 4). Risks of infection with exposure to mycophenolic acid with versus without concomitant corticosteroids were significantly different ($P = 0.006$), but there was not sufficient evidence of a significant difference between calcineurin inhibitor with versus without concomitant corticosteroids ($P = 0.52$) or between rituximab with versus without concomitant corticosteroids ($P = 0.16$). In model 3, direct effects (as opposed to total

effects) of age at enrollment, Black race, number of comorbid conditions, and shorter time from biopsy to enrollment also demonstrated associations with higher risk of first infection, whereas higher eGFR at enrollment was associated with a lower risk of first infection (Table S4). Results from models restricted to severe infections were similar to analyses using all infections across all 3 models. The distribution of model weights for MSM models 1-3 are summarized in Table S5.

DISCUSSION

In this multicenter cohort of adults and children with glomerular disease, we determined that corticosteroid exposure, with or without concomitant exposure to nonsteroid immunosuppressive medications, was associated with a greater than 2-fold increased risk for infection-related acute care events after adjusting for confounding by disease activity. This finding represents an important step forward in understanding infection risks posed by current immunosuppression regimens in patients with glomerular disease. Purine inhibitors (mycophenolate and azathioprine) alone did not appear to significantly increase the risk of infections leading to acute care use in this cohort, whereas corticosteroids alone or in combination with additional immunosuppressants were associated with a significantly increased risk. As stated by Steiger et al,²⁰ rigorous study of the “secondary immunodeficiency related to chronic kidney disease” is an unmet need in the

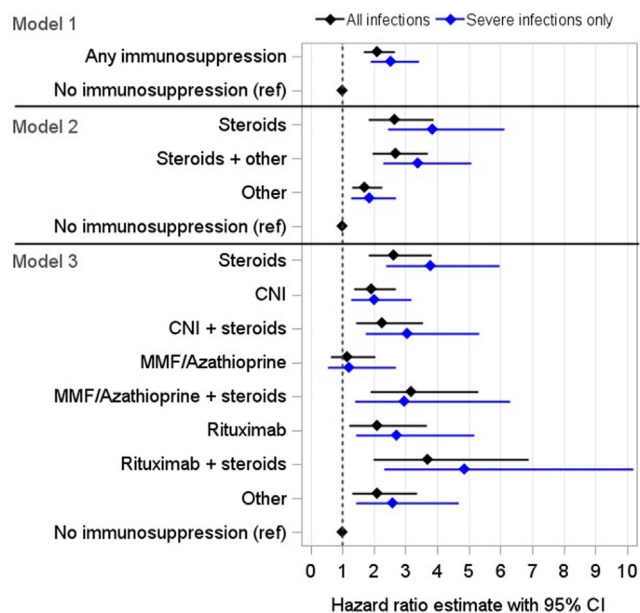


Figure 4. Marginal structural Cox models assessing the relationship between immunosuppression exposure and risk of first infection. Hazard ratio estimates and corresponding 95% CIs depicted as diamonds and horizontal bars, respectively. Full model results are provided in Tables S2-S4. Abbreviations: CNI, calcineurin inhibitor; MMF, mycophenolic acid; ref, reference.

nephrology research community; this study helps to address this unmet need. Further, the coronavirus 2 pandemic has reinvigorated interest in understanding and minimizing infection risk among immunosuppressed populations, and this study is therefore timely. We expect our findings to inform treatment-related discussion and decisions for patients and providers as they weigh the risks and benefits of various treatment regimens, both at disease presentation and over time.

In a prior analysis of infection-related acute care events occurring in CureGN from 2014–2017, corticosteroid exposure, younger age, hypoalbuminemia, and nephrotic-range proteinuria were all associated with time to first infection.¹¹ Sample size limitations prevented a granular analysis of the effect of concomitant nonsteroid immunosuppression exposures on infection risk, and only baseline immunosuppression exposure was considered. In the current analysis, leveraging a larger cohort with longer follow-up, we demonstrate that over time and independent of disease activity, corticosteroid exposure remains a strong risk factor for the development of infections serious enough to lead to acute care events. Across multiple drug classes, immunosuppression exposure that included corticosteroids was associated with higher risk of first infection. These findings strongly support efforts to develop novel, and refine existing, treatment strategies that minimize or altogether forgo use of corticosteroids for patients with MCD,²¹ FSGS,²² MN,²³ and IgAN.²⁴

Identifying which patients are at greatest risk for infection has important clinical utility. In our analysis, age <10 years and Black race were also associated with higher risk of infection even after adjusting for potential mediating factors of disease activity and immunosuppression exposure over time. There are multiple reasons why young age could be associated with infection risk as defined in our study. Caregivers and health care providers may be more conservative when making decisions on having young children evaluated in the ED or admitted to the hospital. Young children may require central lines, a significant infection risk, due to poor vascular access or decreased tolerance of frequent blood draws.²⁵ MCD in this age group is known to be associated with an increased risk of serious infection, presumably due to severe immunodeficiency from massive losses of protein in the urine and profound edema that predisposes patients to peritonitis, cellulitis, and other infections.²⁶ Moreover, young children are more likely to have a genetic cause of their glomerular disease, and most genetic causes are resistant to therapy.²⁷ Hence, these children may have more infections due to persistent, severe nephrotic syndrome.

Evidence continues to accumulate linking social determinants of health with chronic kidney disease outcomes and disparities.²⁸ The association between infection and Black race in our study may be due to decreased access to health care secondary to disparities that are not explored in our analysis. Disparities may decrease access to immunizations or prophylactic medications or lead to more ED

visits for health care.^{29,30} More severe glomerular disease activity and lower socioeconomic status, as measured by health insurance status, education level, and employment status, have previously been shown to explain lower health-related quality of life among Black participants in CureGN.³¹ Further study is needed to explore how these and other social determinants of health contribute to infection risk.

Results from the present study are generally consistent with the existing literature describing the epidemiology of infections among patients with nephrotic syndrome, most notably, that steroids confer an increased risk of severe infection in adults and children with nephrotic syndrome when used alone or in combination with other immunosuppressive medications.^{32–34} An analysis of steroid-associated side effects identified in electronic medical records from 884 adults and children with primary proteinuric kidney disease found a 2-fold increased risk of infection in those treated with corticosteroids.³⁵ The rate of severe infections in this cohort was 4.61 infections per 100 person-years, a finding similar to the rate in our study (6.1 infections/100 person-years). The discrepancy is likely explained by a broader definition of infection in our analysis. The previous study was also limited by a lack of granular longitudinal data on medication exposure and disease activity, precluding an exploration of infection risk as a function of intermittent immunosuppression exposure over time.

Our findings are also consistent with results of a large meta-analysis of patients with systemic lupus erythematosus, in whom calcineurin inhibitors, mycophenolic acid, or azathioprine exposure was associated with lower rates of serious infection compared to glucocorticoids and other immunosuppressive drugs.³⁶ Our study broadens and strengthens these findings through its large prospective multicenter design and inclusion of both children and adults with multiple glomerular disease subtypes. Specifically, we found that corticosteroid exposure, with or without concomitant exposure to nonsteroid immunosuppressive medications, was associated with infection-related acute care events. These data support the importance of ongoing efforts to reduce corticosteroid exposure in trials of novel therapeutic agents for glomerular diseases.³⁷

The principal strength of our study is its use of a large multinational cohort of well phenotyped and racially and geographically diverse participants. Additionally, our analysis used a time-varying MSM model designed to reduce time-dependent confounding by disease activity, allowing for a more accurate estimate of the effect of immunosuppression exposure on infection. Limitations include absence of dosing data in the present analysis, lack of a nonglomerular disease control group, and potential bias in ascertainment of outcome events secondary to the coronavirus 2 pandemic³⁸. Although we did not find a statistically significant difference in the trend in infection-related acute care event incidence before vs. during the pandemic, the COVID-19 era trend appeared to decline

more steeply. We hypothesize that this decline may be a result of multiple factors, including a reduction in patients seeking acute care out of fear of acquiring coronavirus 2 or potentially a reluctance to prescribe immunosuppressive medication in the setting of active glomerular disease. Decreased transmission of infectious agents due to social distancing, masking, and other public health interventions has been well documented for influenza and other respiratory pathogens.^{39,40} and may have contributed to reduction in infection incidence. Last, we recognize the higher-than-expected rate of missing values for serum albumin and UPCR in the cohort. Logistic regression models support the hypothesis that participants with less disease activity (higher albumin and lower UPCR) are more likely to have subsequent missing data. We feel confident that the most likely factors driving missing data (ie, previous assessment of disease activity or proteinuria evaluation by urine dipstick) are observed in the data such that missingness can be assumed to be at random. Rather than carry forward data from prior visits until the next measurement, we used the more rigorous approach of multiple imputation to account for missing data.

In summary, our findings provide important information to clinicians, patients, and the research community that will guide treatment decisions, mitigation strategies and areas for future research of infection risk in immunosuppressed populations. Although our findings represent a critical step forward, gaps persist in our understanding of the risk for infection in patients with glomerular disease. These include individual and disease-specific factors such as dysregulated innate and acquired immunity, persistent chronic inflammation, malnutrition, dysbiosis, and impaired initial and sustained response to vaccination for influenza, pneumococcus, and coronavirus 2.²⁰ Optimized treatment protocols that minimize infection risk are critical to improving patient-centered outcomes and reducing morbidity and mortality.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Heatmap of immunosuppression use at time of infection, by body system

Item S1: CureGN Collaborators

Table S1: Rules Used to Determine Immunosuppression Exposure

Table S2: Marginal Structural Cox Model With Binary Immunosuppression Exposure (Model 1), Hazard Ratio (95% Confidence Interval)

Table S3: Marginal Structural Cox Model With 4-Level Immunosuppression Exposure (Model 2), Hazard Ratio (95% Confidence Interval)

Table S4: Marginal Structural Cox Model With 9-Level Immunosuppression Exposure (Model 3), Hazard Ratio (95% Confidence Interval)

Table S5: Distribution of Weights for Marginal Structural Cox Models 1-3

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Immunosuppression Exposure and Risk of Infection-related Acute Care Events in Patients with Glomerular Disease



Methods

CureGN: prospective observational study

71 clinical sites in North America & Europe

Adults & Children (N = 2388)

Biopsy proven glomerular disorders (MCD, FSGS, IgAN, MN)

Exposures



Steroids
CNI
MMF
Rituximab
Azathioprine
Cyclophosphamide

Immunosuppression (IS) exposure modelled on a weekly basis

Median Period of exposure: 3.2 Years

Outcomes

Infections leading to an ER visit or hospitalisation

At least 15% experienced outcome defining infection

Results	Agent	HR (95% CI)
	Steroids	→ 2.65 (1.83 to 3.86)
	Steroids with other IS agents	→ 2.68 (1.95 to 3.68)
	Non-steroid IS agents	→ 1.7 (1.29 to 2.24)

Conclusion: Corticosteroids with or without concomitant additional immunosuppression significantly increased risk of infection leading to acute care utilization in adults and children with glomerular disease.

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