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Steroid-Associated Side Effects in Patients With Primary Proteinuric Kidney Disease

Gia J. Oh[1], Anne Waldo[2], Francisco Paez-Cruz[2], Patrick E. Gipson[2], Anne Pesenson[3], David T. Selewski[4], Elaine S. Kamil[5], Susan F. Massengill[6], Richard A. Lafayette[1], Meg Modes[7], Sharon G. Adler[8], Hailey Desmond[2], Richard Eikstadt[2], Samara Attalla[2], Zubin J. Modi[2,9], Jonathan P. Troost[2] and Debbie S. Gipson[2]

[1]Division of Nephrology, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA; [2]Division of Nephrology, Department of Pediatrics and Communicable Diseases, University of Michigan Medical School, Ann Arbor, Michigan, USA; [3]The Polyclinic, Seattle, Washington, USA; [4]Division of Nephrology, Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina, USA; [5]Division of Pediatric Nephrology, Department of Pediatrics, Cedars-Sinai Medical Center, David Geffen School of Medicine at the University of California, Los Angeles, California, USA; [6]Division of Pediatric Nephrology, Department of Pediatrics, Levine Children's Hospital, Charlotte, North Carolina, USA; [7]Livonia, Michigan, USA; [8]Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles, California, USA; and [9]Susan B. Meister Child Health Evaluation and Research (CHEAR) Center, University of Michigan, Ann Arbor, Michigan, USA

Introduction: The goal of this study was to assess the occurrence of steroid-associated adverse events (SAAE) in patients with primary proteinuric kidney disease.

Methods: The Kidney Research Network Registry consists of children and adults with primary proteinuric kidney disease. SAAEs of interest were hypertension, hyperglycemia and diabetes, overweight and obesity, short stature, ophthalmologic complications, bone disorders, infections, and psychosis. Events were identified using *International Classification of Diseases, Ninth Revision/Tenth Revision* codes, blood pressures, growth parameters, laboratory values, and medications. Poisson generalized estimating equations tested the association between steroid onset and dose on SAAE risk.

Results: A total of 884 participants were included in the analysis; 534 (60%) were treated with steroids. Of these, 62% had at least one SAAE. The frequency of any SAAE after initiation of steroids was 293 per 1000 person-years. The most common SAAEs were hypertension (173.7 per 1000 person-years), diabetes (78.7 per 1000 person-years), obesity (66.8 per 1000 person-years), and infections (46.1 per 1000 person-years). After adjustment for demographics, duration of kidney disease, estimated glomerular filtration rate (eGFR), proteinuria, and other therapies, steroid exposure was associated with a 40% increase in risk of any SAAE (Relative risk [RR]: 1.4; 95% confidence interval [CI]: 1.3–1.6). A 1-mg/kg per day increase in steroid dose was associated with a 2.5-fold increase in risk of any SAAE.

Conclusion: Most patients with primary proteinuric kidney disease treated with steroids experienced at least one SAAE. Steroid therapy increased risk of hypertension, diabetes, weight gain, short stature, fractures, and infections after adjusting for disease-related factors. This study highlights the importance of surveillance and management of SAAE and provides rationale for the development of steroid minimization protocols.

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Patients with proteinuric kidney disease are predisposed to comorbidities that are multifactorial in nature that may result from the disease itself, progression of chronic kidney disease, or the treatment of the underlying disease. The acute complications associated with nephrotic syndrome are well described and contribute significantly to this burden. To improve outcomes in these patients, it is important to understand the full impact of corticosteroid therapy on patients with proteinuric kidney disease.

Corticosteroid therapy is widely used in the treatment of patients with primary proteinuric kidney diseases such as minimal change disease, focal segmental glomerulosclerosis, and IgA nephropathy.

Correspondence: Jonathan P. Troost, University of Michigan School of Medicine, Med Sci 1, ARF #2511A, 1150 West Medical Center Drive, Ann Arbor, Michigan 48109, USA. E-mail: troostj@med.umich.edu

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These patients often have prolonged or multiple exposures to steroid therapy throughout the disease course, and thus are at risk for the development of SAAEs. The adverse effects of corticosteroids on the cardiovascular system, glucose and lipid metabolism, immune system, and central nervous system are well described in literature, but little is known about their burden in patients with proteinuric kidney disease.[1–4] To date there has not been a report of sufficient size to account for multiple disease characteristics (e.g., chronic kidney disease stage, proteinuria) in evaluating the independent association of corticosteroids on adverse events in primary proteinuric kidney disease. This study used electronic health record (EHR) data to systematically characterize the risk of SAAEs observed in patients with proteinuric kidney disease. We postulate that SAAEs will occur commonly in this population and there will be disease characteristics that will predispose individuals to SAAEs. This study represents a critical first step to elucidate the epidemiology of SAAEs in proteinuric kidney disease and providing practitioners information to improve patient monitoring and clinical trial development.

METHODS

Participants and Data Source

The Kidney Research Network (formerly the NephCure Accelerating Cures Institute) is an ongoing study of patients with primary proteinuric kidney disease from 7 centers that began enrollment in November 2015. The goal of this network is to improve the treatment options and health outcomes of patients with glomerular disease.[5] Patients enrolled in the Kidney Research Network provided consent to share both retrospective and prospective data from their EHRs, including demographics, diagnosis, kidney biopsy report, laboratory values, vital signs, medication data, and hospitalizations. Patients could consent to join the registry at any point in their disease course, but retrospective data were available from the time patients entered their current nephrology care environment. Renal diagnoses are confirmed by the enrolling site's nephrology principal investigator. The study protocol was reviewed and approved by the University of Michigan Institutional Review Board.

As of July 2018, there were 1145 patients enrolled in the Kidney Research Network Registry (Figure 1). For this analysis, we excluded patients with end-stage kidney disease before their first EHR in the Kidney Research Network data registry, and patients with secondary forms of disease (e.g., lupus, diabetic nephropathy). Patients were also censored at the time of end-stage kidney disease.

SAAE Definitions

Specific events analyzed were hypertension, hyperglycemia, diabetes, overweight, obesity, short stature, cataracts, glaucoma, osteoporosis, osteonecrosis, psychosis,

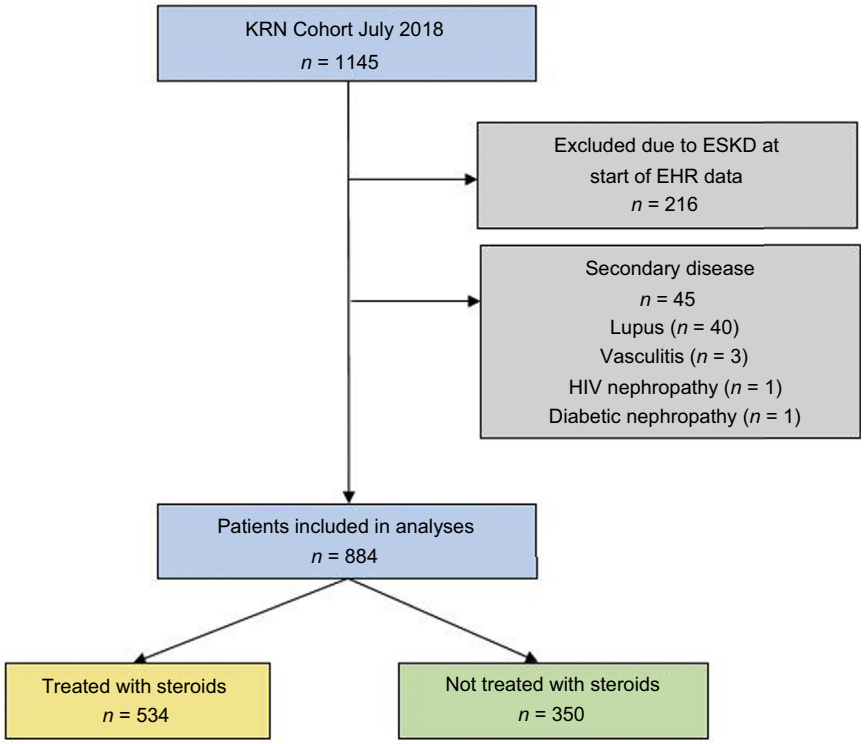

Figure 1. Flow diagram of included patients. EHR, electronic health record; ESKD, end-stage kidney disease; KRN, Kidney Research Network.

fractures, and infections (pneumonia, septicemia and bacteremia, peritonitis, and cellulitis). Each event was analyzed separately, and patients were censored at the time of event onset (single-occurrence events) in all events except for fractures and infections (multiple-occurrence events). Events were defined as steroid-associated if they occurred after steroid therapy initiation. If the date of the event was unknown, patients were removed from that specific analysis. Patients were determined to have an event using *International Classification of Diseases, Ninth Revision* and *Tenth Revision* codes (for cataracts, glaucoma, osteoporosis, osteonecrosis, pneumonia, septicemia/bacteremia, peritonitis, cellulitis, psychosis, and fractures) or in combination with medications (hypertension and diabetes), laboratory measurements (hyperglycemia and diabetes), and vital signs (hypertension, overweight, obesity, and short stature). A full list of codes used for classification is available in Supplementary Table S1. In addition to diagnosis codes, patients also were categorized as hypertensive if they had at least 2 encounters with elevated blood pressures (≥140/90 in adults age 18–65 years, ≥150/90 in adults 65+, and ≥95th percentile for age, sex, and height in children) or were treated with antihypertensive therapy, specifically beta blockers, calcium channel blockers, alpha blockers, or vasodilators (renin-angiotensin aldosterone system blockade and diuretics were not included as hypertension-defining antihypertensive therapies, as it is unclear if they were prescribed to treat hypertension or proteinuria alone). Patients with a code for "white coat" hypertension were excluded from the hypertension analysis.

Patients were categorized as hyperglycemic if they had a diagnosis code of hyperglycemia or 2 or more measurements of elevated glucose levels but did not otherwise qualify as diabetic. References for the glucose levels were per the American Diabetes Association's Standard of Medical Care in Diabetes and the University of Michigan Pathology lab values.[6,7] For fasting glucose levels, a hyperglycemic level was as follows: plasma glucose measurement of 100 to 125 mg/dl; serum glucose level was differentiated based on age: <1 year with >120 mg/dl, 1 to 4 years with >130 mg/dl, 5 to 11 years with >135 mg/dl, and 12+ years with >100 mg/dl; or blood glucose of 90 to 130 mg/dl. For nonfasting glucose levels, a hyperglycemic level was as follows: plasma glucose of 180 to 200 mg/dl; serum glucose of 140 to 200 mg/dl; or blood glucose of 160 to 180 mg/dl. Patients were censored from the hyperglycemia analysis at the time of diabetes onset.

In classifying diabetes, patients could qualify with diagnosis code of diabetes, elevated glucose levels, elevated hemoglobin A1c levels, or have a medication record indicating diabetes. Elevated glucose levels for diabetes were classified per American Diabetes Association standards as follows: for fasting glucose levels, a plasma glucose measurement of >126 mg/dl or blood glucose of >130 mg/dl. For nonfasting glucose levels, a plasma glucose of >200 mg/dl; serum glucose of >200 mg/dl; or blood glucose of >180 mg/dl. Elevated hemoglobin A1c level was defined as >6.4%.[8]

Patients were categorized as overweight if they had a diagnosis code indicating overweight or a body mass index of 25 to 30 or 85th to 95th percentile in children, and patients were censored from the overweight analysis at the time of obesity onset.[9,10] Patients were considered obese if they had a diagnosis code indicating obesity or a body mass index more than 30 or greater than the 95th percentile in children.[9,10] Patients were defined as having short stature if they had a diagnosis code of short stature or were treated with a growth hormone agent or by a height less than the third percentile.[11] Patients with adult-onset kidney disease were excluded from the short stature analysis. All other SAAEs were identified by diagnosis codes alone. Infections and fractures were eligible as multiple-occurrence events. New infection and fracture events were considered separate incidents if they occurred at least 30 days apart. eGFR was calculated using the modified Chronic Kidney Disease in Children formula for children and the Chronic Kidney Disease–Epidemiology Collaboration formula for adults.[12,13] Patients were excluded from event-specific analyses if onset dates were unknown or if onset of conditions preceded onset of kidney disease; thus, sample sizes vary by event (details in Supplementary Table S2).

Statistical Analyses

Descriptive analyses were conducted on the full analysis sample using frequencies and percentages for categorical variables and medians and interquartile ranges for continuous variables. Comparisons were made for patients who ever or never received steroid therapy during observation, using χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables. Unadjusted absolute risks of each event pre- and post-steroids were expressed using person-time incident rates. Each condition was analyzed separately using a longitudinal Poisson generalized estimating equation model with repeated measures and RRs were calculated. In addition, adjusted RRs were computed for all conditions with at least 1 event each pre- and post-steroid exposures. Analyses were adjusted for age, sex, race, ethnicity, duration of kidney disease, eGFR, proteinuria, and exposure to other immunosuppressive therapies, including calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil, and rituximab. Sensitivity analyses examined the

impact of steroid dose on risk of SAAE among patients with steroid dose available. Average daily dose was calculated for periods when a patient was on steroids based on dose and frequency (e.g., a patient on a 2 mg/kg dosage of steroids on alternating days for 8 weeks had an average daily dose of 1 mg/kg per day during that period). Dosage was analyzed on a continuous scale in units of mg/kg per day. All analyses were conducted using SAS v9.4 (Cary, NC).

RESULTS

Characteristics of the Cohort

Among the 884 patients included in these analyses (Figure 1), 534 (60%) had steroid exposure before end-stage kidney disease (Table 1). Children were more likely to be treated with steroids than adults. Most patients treated with other immunosuppressive therapies were also treated with steroids. In addition, there was a significant difference by diagnosis where minimal change disease and nephrotic syndrome–not biopsied patients were most likely to be treated with steroids ($P < 0.001$). Treated patients had higher eGFR (median 97 vs. 66 ml/min per 1.73 m^2, $P < 0.001$) and urine protein:creatinine ratio (median 3.2 vs. 1.6 g/g, $P < 0.001$) than those untreated with steroids at kidney disease onset.

Risk of SAAEs

Of the 534 patients treated with steroids, 333 (62%) had at least 1 SAAE. The risk of any SAAE after onset of steroids was 306.5 per 1000 person-years (Table 2). The most common SAAEs were hypertension (173.7 per 1000 person-years), diabetes (78.7 per 1000 person-years), obesity (66.8 per 1000 person-years), overweight (56.9 per 1000 person-years), any infection (46.1 per 1000 person-years), and short stature (29.4 per 1000

Table 1. Patient characteristics by steroid exposure

Characteristic	All patients (n = 884) n (%)	Treated with steroids (n = 534) n (%)	Not treated with steroids (n = 350) n (%)	P value
Age at kidney disease onset				<0.001
Adults (18+ yr)	473 (53.5)	237 (44.4)	236 (67.4)	
Children (<18 yr)	393 (44.5)	288 (53.9)	105 (30.0)	
Missing	18 (2.0)	9 (1.7)	9 (2.6)	
Sex				0.06
Male	367 (41.5)	208 (39.0)	159 (45.4)	
Female	517 (58.5)	326 (61.0)	191 (54.6)	
Race				0.50
White	510 (57.7)	307 (57.5)	203 (58.0)	
Black	118 (13.3)	67 (12.5)	51 (14.6)	
Asian	118 (13.3)	77 (14.4)	41 (11.7)	
Other	137 (15.5)	83 (15.5)	54 (15.4)	
Missing	1 (0.1)	0 (0.0)	1 (0.3)	
Ethnicity				0.002
Non-Hispanic	722 (81.7)	443 (83.0)	279 (79.7)	
Hispanic	126 (14.3)	62 (11.6)	64 (18.3)	
Unknown	36 (4.1)	29 (5.4)	7 (2.0)	
Diagnosis				<0.001
FSGS	231 (26.1)	119 (22.3)	112 (32.0)	
Minimal change	137 (15.5)	122 (22.8)	15 (4.3)	
Membranous nephropathy	104 (11.8)	65 (12.2)	39 (11.1)	
NS—not biopsied[a]	136 (15.4)	107 (20.0)	29 (8.3)	
Other	276 (31.2)	121 (22.7)	155 (44.3)	
Calcineurin inhibitor therapy	307 (34.7)	228 (42.7)	79 (22.6)	<0.001
Cyclophosphamide therapy	87 (9.8)	80 (15.0)	7 (2.0)	<0.001
Mycophenolate mofetil therapy	298 (33.7)	214 (40.1)	84 (24.0)	<0.001
Rituximab therapy	131 (14.8)	116 (21.7)	15 (4.3)	<0.001
	Median (IQR)	Median (IQR)	Median (IQR)	
Age at kidney disease onset (yr)	23 (5, 44)	13 (4, 40)	33 (14, 49)	<0.001
Steroid dose (mg/kg per day)	—	0.4 (0.1, 1.0)	—	—
eGFR closest to kidney disease onset	86 (46, 120)	97 (60, 127)	66 (34, 103)	<0.001
UPC closest to kidney disease onset	2.1 (0.6, 6.3)	3.2 (0.6, 7.9)	1.6 (0.5, 3.3)	<0.001
Observation period (mo)	60 (32, 112)	62 (34, 116)	54 (28, 105)	0.04

eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IQR, interquartile range; NS, nephrotic syndrome; UPC, urine protein:creatinine ratio
[a]Diagnosis of nephrotic syndrome–not biopsied was available only to pediatric participants.
Categorical variables are displayed as frequencies and percentages, and the P values represent χ^2 tests; continuous variables are displayed as medians, and IQRs and the P values represent Kruskal-Wallis tests. Other diagnoses include IgA nephropathy, C3 glomerulopathy, fibrillary glomerulonephritis, amyloidosis, and light chain nephropathy.

Table 2. Frequency, number of contributing person-years, and absolute risk of steroid-associated adverse events

	Without steroid therapy			After steroid therapy initiation		
No. patients included in analysis[a]	No. of events	Person-years	Rate per 1000 patient-years	No. of events	Person-years	Rate per 1000 patient-years
Any SAAEs ($n = 884$)	763	2806	271.9	812	2649	306.5
Single-occurrence events						
Hypertension ($n = 668$)	289	1542	187.4	182	1048	173.7
Hyperglycemia ($n = 816$)	27	2609	10.3	42	2280	18.4
Diabetes ($n = 828$)	100	2414	41.4	140	1778	78.7
Overweight ($n = 772$)	100	2461	40.6	109	1917	56.9
Obese ($n = 815$)	132	2404	54.9	124	1857	66.8
Short stature ($n = 374$)	24	975	24.6	39	1325	29.4
Cataracts ($n = 874$)	6	2785	2.2	12	2577	4.7
Glaucoma ($n = 884$)	3	2787	1.1	3	2642	1.1
Osteoporosis ($n = 880$)	4	2765	1.4	7	2626	2.7
Osteonecrosis ($n = 884$)	1	2805	0.4	3	2643	1.1
Psychosis ($n = 883$)	0	2806	0.0	3	2637	1.1
Multiple-occurrence events						
Fractures ($n = 884$)	8	2806	2.9	26	2649	9.8
Any infection ($n = 884$)	69	2806	24.6	122	2649	46.1
Pneumonia ($n = 884$)	26	2806	9.3	53	2649	20.0
Septicemia/bacteremia ($n = 884$)	9	2806	3.2	22	2649	8.3
Peritonitis ($n = 884$)	1	2806	0.4	12	2649	4.5
Cellulitis ($n = 884$)	33	2806	11.8	35	2649	13.2

SAAE, steroid-associated adverse event.
[a]See Supplementary Table S2 for patient inclusion/exclusion by event and steroid exposure.

person-years). The median number of SAAEs per patient was 1 (interquartile range: 0–2) and the mean was 1.4 (SD: 1.4).

Poisson generalized estimating equation models demonstrated that patients treated with steroids are at higher risk for any SAAE, after adjustment for age, sex, race, ethnicity, diagnosis, length of disease, other immunosuppressive therapy exposure, and eGFR and urine protein:creatinine ratio (RR: 1.4, 95% CI: 1.3–1.6; Table 3). Adjusted RR estimates varied by event. Steroid exposure was associated with increased risks of hypertension (RR: 1.4, 95% CI: 1.1–1.8), diabetes (RR: 1.8, 95% CI: 1.3–2.4), obesity (RR: 1.5, 95% CI: 1.2–1.9), fractures (RR: 3.6, 95% CI: 1.3–9.9), any infections (RR: 2.0, 95% CI: 1.1–3.5), pneumonia (RR: 2.4, 95% CI: 1.2–4.8), and septicemia and bacteremia (RR: 3.7, 95% CI: 1.3–10.3). RRs for psychosis were unable to be calculated because there were no psychosis events in the absence of steroid therapy onset. Among those treated with steroids, there was no difference in risk of SAAE between children and adults, and no difference by diagnosis with 1 exception: focal segmental glomerulosclerosis/minimal change disease less likely to develop obesity relative to membranous nephropathy (RR: 0.6; 95% CI: 0.3–1.0) (Supplementary Table S3). Calcineurin inhibitor or mycophenolate mofetil use was generally not associated with increased risk independent of steroids; however, calcineurin inhibitor use was independently associated with risk of diabetes (RR: 1.4; 95% CI: 1.1–1.8) (data not shown in Tables 3 and 4).

Corticosteroid Dose Effect

Adjusted RR of experiencing any SAAE increased 2.5-fold with every 1 mg/kg per day increase in steroid dose (Table 4). There was no difference in daily versus alternating data therapy after accounting for average dose. The risk of hypertension increased the most with higher steroid dose (RR: 4.5; 95% CI: 3.5–5.9), as did overweight (RR: 3.2; 95% CI: 2.3–4.5), obesity (RR: 2.9; 95% CI: 2.0–4.2), and pneumonia (RR: 2.9; 95% CI: 1.8–4.8). The RRs of developing diabetes (RR: 1.9; 95% CI: 1.3–2.8), short stature (RR 2.2; 95% CI: 1.4–3.6) and any infection (RR: 2.3; 95% CI: 1.5–3.8) also increased significantly with each mg/kg dose increase in daily steroid therapy. The dose analyses in Table 4 identified significant dose-dependent relationships between steroid exposure and occurrence of overweight and short stature despite these SAAEs showing no relationship with binary (ever/never) steroid exposure in the analyses and septicemia/bacteremia did not show a dose-dependent relationship. Statistically significant dose relationships are shown in Figure 2.

DISCUSSION

In this study, we provide valuable information about the frequency and type of adverse events seen in patients with proteinuric kidney disease treated with corticosteroids. This improves our understanding of the increased likelihood of adverse events that occur after initiating corticosteroid therapy while adjusting

Table 3. Person-time comparison of risk of experiencing selected adverse events on steroids compared with those not exposed to steroids

SAAE	Unadjusted relative risk[a] (95% CI)	*P* value	Adjusted relative risk[b] (95% CI)	*P* value
Any SAAEs ($n = 884$)	1.3 (1.1–1.5)	<0.001	1.4 (1.3–1.6)	<0.001
Single-occurrence events				
Hypertension ($n = 668$)	1.2 (0.9–1.5)	0.199	1.4 (1.1–1.8)	0.01
Hyperglycemia ($n = 816$)	1.1 (0.7–1.8)	0.575	1.2 (0.9–2.1)	0.19
Diabetes ($n = 828$)	1.5 (1.2–1.9)	0.002	1.8 (1.3–2.4)	<0.001
Overweight ($n = 772$)	1.2 (0.9–1.6)	0.286	1.2 (0.9–1.6)	0.21
Obese ($n = 815$)	1.1 (0.9–1.5)	0.305	1.5 (1.2–1.9)	0.002
Short stature ($n = 374$)	1.1 (0.7–1.9)	0.669	1.3 (0.7–2.4)	0.33
Cataracts ($n = 874$)	1.8 (0.7–4.7)	0.252	1.3 (0.5–3.5)	0.63
Glaucoma ($n = 884$)	0.9 (0.2–4.3)	0.868	1.1 (0.2–6.0)	0.94
Osteoporosis ($n = 880$)	1.7 (0.4–7.1)	0.432	2.4 (0.6–10.2)	0.23
Osteonecrosis ($n = 884$)	1.8 (0.2–19.4)	0.647	2.1 (0.2–23.7)	0.54
Psychosis ($n = 883$)	—	—	—	—
Multiple-occurrence events				
Fractures ($n = 884$)	3.3 (1.2–8.9)	0.022	3.6 (1.3–9.9)	0.015
Any infection ($n = 884$)	2.0 (1.1–3.6)	0.027	2.0 (1.1–3.5)	0.015
Pneumonia ($n = 884$)	2.3 (1.2–4.8)	0.018	2.4 (1.2–4.8)	0.012
Septicemia/bacteremia ($n = 884$)	3.6 (1.1–12.0)	0.035	3.7 (1.3–10.3)	0.013
Peritonitis ($n = 884$)	12.0 (1.5–94.2)	0.019	6.4 (0.7–55.5)	0.090
Cellulitis ($n = 884$)	1.1 (0.5–2.4)	0.762	1.2 (0.6–2.2)	0.596

SAAE, steroid-associated adverse event.
[a]Relative risk estimates are derived from a Poisson generalized estimating equation model that accounts for the repeated measures of subjects.
[b]Adjusted for age; sex; race; ethnicity; duration of kidney disease; treatment with other immunosuppressive therapies including calcineurin inhibitor, cyclophosphamide, mycophenolate mofetil, and rituximab; estimated glomerular filtration rate; and urine protein:creatinine ratio.

for time-varying disease characteristics. In addition, this study highlights the need for new therapies for these diseases to limit steroid exposure and burden. Even therapies that demonstrate non-inferiority to usual care in terms of proteinuria control may be useful given the excess side-effect burden associated with steroids quantified by this study.

Sixty-two percent of the patients exposed to steroids developed at least 1 SAAE, most commonly hypertension, hyperglycemia and diabetes, overweight and obesity, infections, fractures, and short stature in children. The steroid-treated patients had a 40% increased risk for any adverse event compared with those not treated, after statistical adjustment. This

Table 4. Relative risk for SAAE by corticosteroid therapy (mg/kg per day)

SAAE	Unadjusted relative risk[a] (95% CI)	*P* value	Adjusted relative risk[b] (95% CI)	*P* value
Any SAAEs ($n = 496$)	2.0 (1.8–2.3)	<0.001	2.5 (2.1–2.8)	<0.001
Single-occurrence events				
Hypertension ($n = 384$)	3.1 (2.3–4.1)	<0.001	4.5 (3.5–5.9)	<0.001
Hyperglycemia ($n = 482$)	1.0 (0.5–1.9)	0.96	1.1 (0.5–2.3)	0.76
Diabetes ($n = 466$)	1.5 (1.0–2.0)	0.03	1.9 (1.3–2.8)	<0.001
Overweight ($n = 472$)	2.9 (2.2–3.9)	<0.001	3.2 (2.3–4.5)	<0.001
Obese ($n = 464$)	2.3 (1.7–3.3)	<0.001	2.9 (2.0–4.2)	<0.001
Short stature ($n = 173$)	2.2 (1.4–3.6)	<0.001	2.2 (1.4–3.6)	<0.001
Cataracts ($n = 486$)	2.4 (0.7–8.0)	0.1417	1.7 (0.4–6.6)	0.43
Glaucoma ($n = 495$)	NA	NA	NA	NA
Osteoporosis ($n = 492$)	1.3 (0.5–3.6)	0.66	1.4 (0.9–2.2)	0.09
Osteonecrosis ($n = 513$)	1.3 (0.4–4.3)	0.72	1.1 (0.4–3.1)	0.87
Psychosis ($n = 494$)	NA	NA	NA	NA
Multiple-occurrence events				
Fractures ($n = 496$)	1.6 (0.6–4.2)	0.38	0.9 (0.4–2.3)	0.86
Any infection ($n = 496$)	2.3 (1.5–3.8)	<0.001	2.3 (1.5–3.8)	<0.001
Pneumonia ($n = 496$)	2.9 (1.8–4.8)	<0.001	2.9 (1.8–4.8)	<0.001
Septicemia/bacteremia ($n = 496$)	0.6 (0.3–1.5)	0.32	0.6 (0.3–1.5)	0.32
Peritonitis ($n = 496$)	3.3 (1.1–10.5)	0.04	1.9 (0.6–6.2)	0.27
Cellulitis ($n = 496$)	1.8 (0.7–4.6)	0.23	1.8 (0.7–4.6)	0.23

NA, not available due to insufficient event rate; SAAE, steroid-associated adverse event.
[a]Relative risk estimates are derived from a Poisson generalized estimating equation model that accounts for the repeated measures of subjects.
[b]Adjusted for age; sex; race; ethnicity; duration of kidney disease; treatment with other immunosuppressive therapies including calcineurin inhibitor, cyclophosphamide, mycophenolate mofetil, and rituximab; estimated glomerular filtration rate; and urine protein:creatinine ratio.
Risk is reported per 1 mg/kg per day increase in dose ($n = 496$).

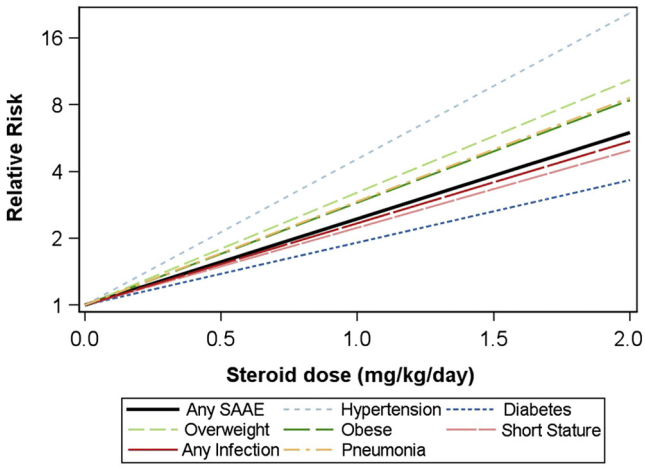

Figure 2. Adjusted relative risk for steroid-associated adverse events (SAAE) by corticosteroid therapy (mg/kg per day) ($n = 496$).

observation is similar to a meta-analysis of corticosteroid therapy compared with non-immunosuppressive therapy in adult patients with IgA nephropathy, which showed that steroid therapy was associated with 55% higher risk for adverse events.[14]

It is worth mentioning that many of the adverse events (e.g., infections, hypertension) may be a consequence of the underlying primary proteinuric kidney disease, and not necessarily a result of steroid treatment. However, a strength of this study was the ability to compare risks of events across treated and untreated patients, as well as and before and after steroid treatment and compared with other treatments. This allowed us to estimate the excess risk associated with steroid therapy, after adjusting for factors that may influence treatment and likelihood of adverse events.

The adjusted risk for hypertension after steroid exposure was 1.4 times the risk before steroid exposure. Our finding is similar to Conn and Poynard's[2] meta-analysis of randomized trials comparing steroid versus placebo for various conditions that showed that the risk of hypertension in steroid-treated patients was 2.2 times higher. Our cohort's RR of developing hypertension increased notably (adjusted RR 4.5) with each mg/kg per day steroid dose increase after adjusting for clinical factors including demographics, kidney disease duration, treatment with other immunosuppressive agents, eGFR, and proteinuria. This finding highlights the need for close blood pressure monitoring with increasing steroid therapy dose.

The risk of metabolic complications (i.e., diabetes mellitus, overweight, obesity) was also significantly higher following steroid therapy exposure. Taken together, a patient's adjusted risk of these complications following steroid exposure was 1.5 to 1.8 times that of the risk before exposure. Our findings support other studies, such as the one performed by Movahedi *et al.*,[4] analyzing UK and US national databases for nearly 22,000 patients with rheumatoid arthritis and showing that the hazard ratio of steroid-associated diabetes was 1.30 and 1.61, respectively. Another small Japanese study showed corticosteroid-induced diabetes developed in 17 of 42 (40.5%) patients undergoing steroid therapy for primary renal disease.[15] The risk of new-onset diabetes following kidney transplantation was 42% higher in patients who received steroid-based maintenance immunosuppression compared with those on steroid-free regimens.[16] Higher doses of steroid therapy increased the risks of developing these SAAEs in our cohort. For every 1 mg/kg per day increase in steroid therapy, the adjusted RRs of diabetes, obesity, and overweight were 1.9, 2.9, and 3.2, respectively. Interestingly, the RR of hyperglycemia did not increase with each mg/kg per day increase in steroid dose, whereas the risk of diabetes did. This finding may be due to incomplete capture of hyperglycemic laboratory values (2 or more elevated glucose values for age), particularly for those patients who complete clinical laboratory studies at local laboratory centers rather than at the nephrologist's center. In addition, clinicians are more likely to identify and add diabetes as diagnosis code in the EHR and less likely to add hyperglycemia as a diagnosis code.

The morbidity and mortality risk associated with serious infection in this patient population is well described.[17,18] The patient's immunity may be impaired by advanced chronic kidney disease, urinary loss of immunologic factors due to nephrotic range proteinuria, decreased immunologic response to vaccinations, or inability to receive live vaccines in the setting of chronic immunosuppressive therapy. Patients on immunosuppression developed serious infectious adverse events at 2.5 times the rate as the non-immunosuppression group in the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial.[17] Similarly, our study shows a 2.0-fold higher risk of infections in the steroid-treated group compared with those without steroid treatment. Importantly, steroid exposure increased the risk of infections even after adjusting for treatment with other immunosuppressive therapies, disease duration, and severity. The adjusted RR of infection also increased 2.3-fold with each mg/kg per day steroid dose increase in our cohort. We observed a notably higher risk for peritonitis following steroid exposure than before steroid therapy. This may in part represent residual confounding, as the study may have been unable to fully capture active nephrotic phases despite adjusting for urine protein-to-creatinine ratio.[19,20] Clinicians may not routinely measure the

degree of proteinuria in patients with known nephrotic syndrome presenting in relapses that are based on home urine protein monitoring and recurrent edema. The gravity of infectious complications is highlighted by the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study, which showed that serious infections occurred in 8% of patients on steroid therapy for proteinuric IgA nephropathy, including 2 deaths due to infection, compared with no serious infections in the non-immunosuppression group.[18] This trial was terminated early because of increased risk of adverse events, mainly infections, in the steroid group.

Bone disorders were infrequently observed in this sample. Steroid-treated patients were 3.6 times as likely to have fractures compared with those not treated with steroids. Large population-based studies have shown higher risk of fractures, especially vertebral fractures, in those exposed to oral corticosteroid therapy even after adjusting for confounding factors such as age, sex, coexisting disease, and concomitant medications.[21,22] Vertebral fractures have been reported in children with nephrotic syndrome on episodic corticosteroid therapy as well.[23,24] Albuminuria and progression of chronic kidney disease are also independent risk factors for fractures, which may have an additive effect in patients with proteinuric kidney disease.[25–27]

This study was unable to assess psychiatric side effects of corticosteroids because of infrequent event rates. Literature review strongly supports a higher incidence of psychosis with the use of steroids. Aggressive behavior, altered mood, and impaired attention have been described in children with new-onset nephrotic syndrome after starting steroid therapy compared with before steroid exposure.[28,29] Our study did not examine other possible psychiatric adverse events, such as anxiety or depression. Further research will be needed to expand assessment for behavioral and mood disorders.[29,30]

The risk of cataracts was 4.7 per 1000 patient-years after initiation of steroid compared with 2.2 per 1000 patient-years when untreated with steroids. Steroid-associated cataracts have been reported in 10% to 27% of children with nephrotic syndrome who had routine prospective ophthalmologic evaluations.[31,32] Our cohort's cumulative cataract frequency likely represents an underdocumentation in the EHR as well as an underdiagnosis.

This is the largest cohort study to date that examines 16 well-known steroid-associated complications in patients with proteinuric kidney disease. This represents a diverse patient population in age, sex, race, and diagnosis observed for a median of 5 years. Our study used various data elements, such as laboratory values, vital signs, and medication history, in addition to the diagnostic codes within the EHR to characterize the occurrence of SAAEs of interest.

Some of the limitations of this study include lack of data with regard to steroid exposure before the time of study data availability and expected lack of steroid dose taper detail contained in the EHR medical sources. The data were limited to extracted discrete EHR data, so it is not totally reflective of the patient care that may have occurred outside the participating centers. We were limited in our ability to assess the impact of steroid duration. Duration data were right skewed with long durations of steroids, but these longer durations were more often low-dose and more often from patients who tolerated steroids and did not experience adverse events within the first year (e.g., patients experiencing SAAEs would be more likely to stop steroid treatment and have shorter durations of steroid use).

Despite these limitations, this study provides valuable information about the commonly seen SAAEs in patients with proteinuric kidney disease, that may be used to inform patient education, medical monitoring, and intervention.

DISCLOSURE

JPT and DSG have research funding through the University of Michigan with Complexa Inc., Retrophin Inc., and Goldfinch Bio (DSG additionally has funding through the University of Michigan with Bristol-Meyers Squibb; JPT additionally has funding through the University of Michigan with Vertex Pharmaceuticals and Pfizer Inc.). ESK is a site principal investigator for 2 industry-sponsored studies (Pfizer and Complexa Inc.), has served as a 1-time consultant for Mallinckrodt, and serves on the Board of NephCure Kidney International. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Computable phenotypes for each event using diagnosis codes, medications, labs, and vitals in electronic health records.

Table S2. Event frequencies among those exposed or not exposed to steroids.

Table S3. Person-time comparison of risk of experiencing selected adverse events: comparisons by age and diagnosis limited to those treated with steroids.

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