UNIVERSITY OF CALGARY

Immunoglobulin A nephropathy in children: clinical characteristics, outcomes, and response

to therapy

By

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A THESIS PROPOSAL

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

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Summary

IgA nephropathy is the most common primary glomerular disease worldwide.[1–3] Damage to glomeruli, the filtering units of the kidney, can lead to the leakage of protein and blood into the urine (proteinuria and hematuria, respectively) and approximately 40% of individuals with this disease will progress to kidney failure despite treatment.

There are no trials in children comparing steroids with supportive care or other immunosuppressive drugs and there are no pediatric, evidence-based guidelines for the treatment of IgA nephropathy, resulting in high practice variation. Currently, children are treated with prolonged courses of corticosteroids, also referred to as steroids, for 4-6 months based on adult studies (Pozzi 1999).[4] Children are sometimes treated with multiple courses of steroids and additional steroid-sparing immunosuppressive drugs despite the lack of evidence to support this practice. Exposure to steroids can lead to harmful effects such as severe infections, poor growth and bone health, hypertension, diabetes, behavioral disturbances, and poor sleep.[5] A clearer understanding of the risks and benefits of steroid therapy is required to better inform decision-making.

To address knowledge gaps, we will first conduct a systematic review of the literature on the effectiveness of treatments for IgA nephropathy in children to summarize the evidence. We will then conduct a local retrospective cohort study of children with biopsy-proven IgA nephropathy to assess the association between steroids and the progression of kidney disease. Finally, we will develop a local clinical pathway, based on the findings of the first two studies.

Chapter 1: Overview of the literature

1.1 Pathophysiology

Immunoglobulin A (IgA) nephropathy is an autoimmune disease that is the most common cause of primary glomerulonephritis worldwide.[1,2,6] It is caused by the deposition of IgA immune complexes in the glomeruli of the kidneys which triggers a cascade of inflammatory events by activating immune pathways that lead to kidney damage. This process is best explained by the multi-hit hypothesis.[7–9] The first hit is the abnormal production of an IgA molecule that is deficient in galactose, this molecule called galactose-deficient IgA is found in susceptible individuals. In the second hit, naturally occurring antibodies (anti-IgG or anti-IgA antibodies) recognize the galactose-deficient IgA and bind to it. These form immune complexes that deposit in the glomeruli of the kidney during the third hit. The deposition of immune complexes in the glomeruli activate local inflammatory pathways and the complement system, ultimately leading to kidney damage, which is the fourth hit. Galactose-deficient IgA may be deposited directly in glomeruli. The multi-hit pathway may be triggered by an infection or an immune process causing the overproduction of galactose-deficient IgA and augmenting the inflammatory cascade. The process of self-antibody binding to self-antigen qualifies IgA nephropathy as an autoimmune disease.[1,7–9] Diagnosis of IgA nephropathy is made through a kidney biopsy which is characterized by a predominance of IgA deposits in the glomeruli of the kidney, the hallmark of IgA nephropathy.[2]

1.2 Epidemiology

The incidence of IgA nephropathy varies according to geography, population, urine screening, and kidney biopsy practices.[10] The variation in incidence among countries and regions (Eastern versus the Western Hemisphere) is thought to be due to differences in screening practices.[1,10] It is difficult to determine the incidence of pediatric IgA nephropathy

in children since mass urine screening is not routinely done in most countries and kidney biopsies are not performed for all suspected cases.[1,11] Countries that do not have mass urine screening programs have an incidence rate for IgA nephropathy ranging from 0.1 to 2 cases/year per 100,000 population while countries with mass urine screening have much higher incidence rates ranging from 4.5-9.9 cases/year per 100,000 children under 15 years of age.[10,12–14]

There is variation in the incidence of IgA nephropathy by ethnicity that may be partially explained by genetic differences.[15] Variations in kidney biopsy availability and thresholds for proceeding to a biopsy do not explain the variation in incidence by region. Genetic factors in some populations may account for higher incidences and more severe disease. Genome-wide association studies (GWAS) have identified risk alleles affecting the immune and complement pathways in Chinese, but not European populations which may explain the higher incidence and more severe disease among the Chinese.[15] In Japan and Korea, IgA nephropathy represents 32% and 40% of kidney biopsies in children respectively, while in Europe, it is detected in 20–26%. In the US, the incidence was highest in Native Americans and lowest in Whites.[1] In India and South America, IgA nephropathy represented 14.5% while in Africa, it represented 2.8% of kidney biopsies performed in children.[16,17] The distribution of IgA nephropathy by sex differs by country with a male-to-female ratio for children and adults of 2:1 in North America and 1:1 in Asia which may be attributable to differences in risk allele profiles in the Asian population.[1,15]

IgA nephropathy can present at any age, but most commonly presents in the second and third decades of life.[1] The age at diagnosis of IgA nephropathy in children varies by screening practices and is not well described. In a report of 1,203 cases from the Pediatric Nephrology Group in China the **median age at diagnosis was 9 years** and all cases presented after 6 years of age.[18]

1.3 Presentation and outcomes

IgA nephropathy commonly presents with blood in the urine (hematuria), with or without protein in the urine (proteinuria), and variable degrees of kidney function. The degree of proteinuria and kidney function vary at presentation and during the disease course.[3] Kidney function is determined by serum creatinine (sCr), a biomarker of kidney filtration, used to calculate an estimated glomerular filtration rate (eGFR). As kidney function declines, the nephron (filter) function decreases, and less blood is cleared of creatinine, resulting in elevated sCr. This effect is not usually noticeable until 50% of the nephron mass is lost.[19] Normal GFR is 90-120 ml/minute/1.73m^2. A reduced GFR for at least 3 months is known as chronic kidney disease (CKD).[20] The five stages of CKD are based on eGFR and proteinuria. Stage 5 CKD is end-stage kidney disease (ESKD) and is characterized by an eGFR of <15 ml/minute/1.73m.[20] CKD can also regress with increasing age.[21]

Clinical presentation of IgA nephropathy varies by several factors such as age and screening practices.[22,23] In places where screening is established, asymptomatic children are discovered through urine tests.[22] Hematuria, either gross or microscopic, is the most common presentation of IgA nephropathy, isolated microscopic hematuria is the presenting feature in 30-40% of cases and can be discovered through urine screening.[6,11,24–26] Another 40-50% of IgA nephropathy cases present with visible blood in the urine (gross hematuria) which may occur concurrently with respiratory tract infections.[11,27] Less common presentations include acute kidney injury and nephrotic syndrome, representing about 5% of cases.[1,24,28,29] IgA nephropathy can also mimic urinary tract infections with symptoms of pain or discomfort with urination, hematuria, and fever.[30] Rarely, IgA nephropathy presents as rapidly progressive glomerulonephritis that is more common in adolescents and adults compared with younger children.[31]

IgA nephropathy is a leading cause of CKD and ESKD.[2,24] Thirty to forty percent of persons with IgA nephropathy will develop progressive kidney failure requiring kidney replacement therapy (dialysis or transplant).[1,6,10,32] Pooled cohorts from the Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA) and the North American validation study comparing the prediction of kidney outcomes in IgA nephropathy found 5-year and 10-year risks of ESKD of 11.2% and 26.8% respectively.[33]

IgA nephropathy is associated with reduced life expectancy and quality of life. Hastings *et al.* reviewed 251 adults with IgA nephropathy diagnosed between 1976 and 2005 in the US with a mean follow-up of 19 years. Fifty-three percent progressed to ESKD and 39% died during follow-up (83% of the deaths occurred in ESKD patients and life expectancy was reduced by 10 years).[34] Children with ESKD from any cause have a reduction in life expectancy of approximately 20-40 years and both adults and children with IgA nephropathy have reduced health-related quality of life.[35]

1.4 Clinical and pathological predictors of outcomes

There are clinical and pathological markers that can inform clinical outcomes in IgA nephropathy. Clinical prognostic markers include proteinuria, hypertension, and kidney function at the time of biopsy.[1,20,24]

Proteinuria is regarded as the most important clinical predictor of progression to kidney failure.[27,36] Damage to the glomeruli allows proteins to enter the urine. The duration and quantity of urine protein excretion is an important predictor of kidney outcomes and can reflect disease control.[1,20,27,36] Kamei *et al*. followed 100 children with IgA nephropathy for 10-12 years and kidney survival rates for those with urine protein excretion > 1g/day was

61% at 5 years and 41% at 10 years.[27] In contrast, patients with mild proteinuria did not

develop CKD, and 63% experienced resolution of proteinuria.

Hypertension, defined as blood pressure >140/90 mmHg or >95th percentile +12 mmHg for

age and sex in children, is a poor prognostic factor in IgA nephropathy. The severity,

duration, and type of hypertension (systolic or diastolic) are important considerations.[37,38]

The relationship between hypertension and kidney disease is bidirectional in that

hypertension causes CKD and patients with CKD are prone to hypertension.[39] Sustained

increases in blood pressure that are transmitted to the kidney microvasculature result in

compensatory enlargement of the glomeruli and subsequent scarring.[20,39] At the same time,

kidney disease can activate pathways to maintain normal filtration in the kidneys, including

the renin-angiotensin-aldosterone system (RAAS). As a consequence of RAAS activation,

there is constriction of blood vessels leading to elevated blood pressure. Persistent RAAS

activation exacerbates pre-existing hypertension and can lead to worse kidney outcomes.[20,39]

Inflammation, chronic changes, and scarring on kidney biopsies can predict the progression

of kidney disease. **A definitive diagnosis of IgA nephropathy requires a kidney biopsy**.

The current system for classifying and scoring kidney biopsy findings, first published in

2009, is the Oxford classification system.[40] This classification is based on the degree of

inflammation, mesangial proliferation, and scarring in the kidney. Pathologists examine the

kidney for signs of reversible changes such as mesangial (M) and endocapillary proliferation

(E), marked by an increase in the number of inflammatory cells. They also score chronic

changes including sclerosis (S) or scarring of glomeruli, and atrophy of the kidney tubules

(T). The presence of cellular crescents (C), which are crescent-shaped collections of

inflammatory cells that are typical of more aggressive disease, were captured in the revised

Oxford criteria. Collectively, these findings are known as the MEST-C criteria (Mesangial proliferation, Endocapillary hypercellularity, Segmental sclerosis, Tubular atrophy, and Crescents).[41,42] The MEST-C classification has been used to inform treatment and predict outcomes.[43] A high ME score indicates acute changes that may be reversible with management, whereas a high ST score indicates chronic, irreversible changes.[43,44] In the VALIGA study, high M, S, and T scores were independently associated with reduced kidney survival [M1 (HR 2.3, CI 1.7-3, reference to M0), S1(HR 4.1, CI 2.6-6.5, reference to S0), T1-2 (HR 5.6, CI 4.2-7.5, reference to T0)].[44]

1.5 Differences between children and adults

Children were once thought to have a more benign form of IgA nephropathy, compared to adults. However, this difference is believed to be attributed to lead time bias where adults have more advanced disease at the time of presentation or biopsy, due to a delay in diagnosis.[45,46] At the time of diagnosis, children are more likely to have hematuria, proteinuria, and normal kidney function while adults are more likely to have reduced kidney function with variable degrees of hematuria and proteinuria.[45] Cambier et al.[45] reviewed 89 children and 129 adults in France. Children had higher eGFRs at diagnosis compared with adults [89.5 vs. 64 ml/min/1.73 m2; p = 0.0001). After steroid treatment (41 children and 28 adults), proteinuria decreased in both children and adults [p < 0.001], while eGFR significantly increased in children (91 to 110 ml/min/1.73m2, p=0.01) and was relatively stable in adults (41 to 37 ml/min/1.73m2). Proteinuria in children is thought to be a marker of acute (inflammatory) lesions (M and E lesions) and is more amenable to treatment, whereas proteinuria in adults often reflects chronic, irreversible lesions (S and T lesions).[45,47,48]

1.6 Treatment

1.6.1 Supportive care

The optimal treatment for IgA nephropathy in children is unknown. We currently offer supportive therapy which is evidence-based and shown to be of benefit but there is some data to support the use of immunosuppressive medications as targeted therapy in children.[20,49] Supportive therapy (standard of care) includes angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) which block the RAAS pathway and reduce proteinuria; optimal supportive care for 6 months improves kidney outcomes in IgA nephropathy.[50,51] There is no targeted therapy approved for children.[47,49,52]

1.6.2 Steroids

The benefits of immunosuppressive therapy, when added to optimal supportive care, are not clear and are associated with significant side effects when used for prolonged periods.[50,51,53] Several trials investigated corticosteroids, hereafter referred to as steroids, for the treatment of IgA nephropathy. **Pozzi** *et al.* conducted the **first landmark**, randomized controlled trial (**RCT**) on steroids in IgA nephropathy in adults.[54] Eighty-six patients with biopsy-proven IgA nephropathy were randomly assigned to either supportive therapy alone, or steroid treatment for 6 months (intravenous methylprednisolone 1 g/d for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg on alternate days for 6 months). At year 5 of follow-up, 9/43 (21%) in the steroid group and 14/43 (33%) in the control group had a 50% increase in creatinine and 1/43 (2%) in the steroid group, and 9/43 (21%) in the support group had a 100% increase. Renal survival was better in the steroid group versus the control group [log rank p=0.048 for 50% increase in creatinine and log rank p=0.005 for 100% increase]. No significant side effects were reported by the study investigators, but it was not clear if participants were systematically screened for adverse events. The trial led to the widespread use of steroids for IgA nephropathy in children and

adults (a 6-month steroid course known as the "Pozzi protocol"), in spite of the fact that no children were included in the trial.

Welch *et al*. conducted the **first pediatric RCT** (1992) evaluating steroids in 20 children (mean age of 13 years) with biopsy-proven IgA nephropathy who served as their own controls. There were 3 phases, each lasting 3 months. In phase 1, children were randomized to either a 3-month course of prednisolone (2mg/kg daily x 2 weeks then every 2 days x 10 weeks) or placebo. Phase 2 was a 3-month washout phase, followed by phase 3 where they received whatever intervention was not given in Phase 1. There were no significant changes in urine protein excretion in either phase and kidney function remained relatively stable. This small pediatric trial did not find any benefit of steroid therapy with respect to its short-term impact on proteinuria or kidney function.[55] These findings had little impact on clinical practice and the Pozzi protocol continued to be used in children.

Steroids compared with supportive care

Contemporary, well-designed trials have failed to confirm the findings of the Pozzi study. **The STOP IgAN trial** investigators randomized 162 adults with IgA nephropathy and persistent proteinuria ($\geq$0.75g/d) after a 6-month run-in phase (optimization with supportive therapy) to either supportive therapy alone or supportive therapy plus steroids (Pozzi protocol). After 3 years, 4/80 (5%) in the supportive group and 14/82 (17%) in the steroid group had full clinical remission [p=0.01]. 22/80 in the supportive group and 21/82 in the steroid group had a decrease in the mean eGFR of $\geq$ 15 ml/min/1.73m^2 [OR, 89; 95% CI: 0.44–1.81].

More patients receiving steroids had severe infections, impaired glucose tolerance, weight

gain, and one died of sepsis.[50] This trial called into question the risk-benefit trade-off with the

use of steroids for IgA nephropathy, reporting serious side effects and a lack of clear benefit.

Two years later, the first phase of the **TESTING RCT** examining the benefit of steroids in

preserving kidney function in adults (n=503) was terminated early due to safety concerns in

the steroid group. The trial was continued as phase 2, but with a reduced dose of steroids [0.4

mg/kg/d, maximum 32 mg/d, weaning by 4 mg/d/mo]. The primary outcome of a 40%

decline in eGFR occurred in 28.8% of the steroid group versus 43.1% in the placebo group

[HR, 0.53; 95% CI: 0.39-0.72] after a mean follow-up of 4.2 years. Twenty-eight (10.9%)

participants experienced serious adverse events in the steroid group (20 from the full dose

protocol) versus 7 (2.8%) in the placebo group. There were 4 deaths in this study, all

infection-related, and in the steroid group, 3 of these deaths were in the full-dose protocol

(which prompted the study pause) and 1 in the low-dose protocol.

These trials highlighted the potentially harmful effects of steroids and the need to revisit how

children with IgA nephropathy were treated.

Targeted steroid therapy

Budesonide, a steroid that targets the gut mucosa, is the first targeted drug for adults with

IgA nephropathy based on results from the **NEFIGAN** trial.[52] This RCT randomized 150

adults with persistent proteinuria on supportive (ACEi/ARB) care to budesonide or placebo,

while continuing ACEi/ARB. There was a reduction in proteinuria by 27.3% in the 48

patients who received budesonide 16 mg/day and an increase of 2.7% in those who received

placebo after 9 months [mean change in proteinuria from baseline p=0·009].

Steroid toxicity

Prolonged, and sometimes multiple courses of steroids are often used to treat primary glomerular diseases in children and adults. The serious adverse effects of steroids (steroid toxicity) are well documented. Analysis from the Kidney Research Network found that 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: 1.21.9], fractures [RR: 3.6; 95% CI: 1.3–9.9], all-cause 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]. There were no differences in risk between children and adults and adverse events increased with higher doses of steroids. There was a dose-dependent relationship between steroids and the development of obesity and short stature.[5] This analysis highlighted the need to minimize steroid doses and to search for alternative, safer treatments.

1.6.3 Steroid-sparing immunosuppressive drugs

Several second-line immunosuppressive drugs are used for IgA nephropathy to minimize steroid exposure and toxicity.[49,56] The main second-line immunosuppressive drugs include cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate, mizoribine, leflunomide, and rituximab. However, currently used second-line drugs also have significant side effects.[57]

Cyclophosphamide is an alkylating agent that prevents cell division by decreasing DNA synthesis.[58] Cyclosporine and tacrolimus are calcineurin inhibitors that impair the transcription of interleukin-2 and several other cytokines in T lymphocytes.[57] Mycophenolate mofetil (MMF), azathioprine, and leflunomide inhibit lymphocyte proliferation and antibody production. Mizoribine inhibits DNA synthesis and lymphocyte proliferation and is commonly used in Japan for IgA nephropathy.[59,60] Rituximab depletes CD 20 B lymphocytes, inhibiting the production of antibodies.[49,57]

An RCT on MMF in IgA nephropathy was terminated due to a lack of benefit after 6 months of therapy.[61] Rituximab has not been shown to be superior to ACEi in adults with IgA nephropathy.[62] A systematic review (Natale *et al*. 2020) on immunosuppressive therapy for IgA nephropathy (58 studies, 3933 randomized participants) was inconclusive on the effects of steroid-sparing immunosuppressive drugs due to insufficient data.[63]

1.6.4 Fish oil

Fish oil contains omega -3- polyunsaturated fatty acids which have anti-inflammatory properties that are hypothesized to disrupt the immune process in IgA nephropathy.[64] The evidence and recommendations for fish oil have been inconsistent. A systematic review and meta-analysis of RCTs by Uwaezuoke et al (3702 adults and children) found a reduction of proteinuria with no improvement in eGFR. Fish oil is not recommended for IgA nephropathy by the Kidney Disease Improving Global Outcomes (KDIGO) 2021 Glomerulonephritis Guideline.[20]

1.6.5 Tonsillectomy

Tonsillectomy is a therapeutic option for IgA nephropathy that is utilized frequently in East Asian countries.[49,65] Repeated tonsillitis can trigger the production of galactose-deficient IgA in susceptible persons which can amplify antibody and immune complexes production that can cause kidney damage.[49,65,66] Therefore, removal of the tonsils is seen by some experts as a way of reducing immune complex production, especially in individuals with recurrent tonsillitis that is associated with flares in IgA nephropathy.[65] Japanese studies have reported improvement in proteinuria and kidney survival, the majority of these studies are observational.[67] Tonsillectomy is not recommended for Caucasian patients by KDIGO, the Japanese IgA nephropathy Guideline recommended tonsillectomy as an option for patients with recurrent tonsillitis.[20,65]

1.7 Current recommendations

There are no pediatric-specific guidelines for the management of IgA nephropathy and this has led to a lack of consensus regarding optimal treatment of children and high practice variation.[32] KDIGO 2021 Glomerulonephritis Guideline suggests that children with persistent proteinuria >1 g/d or 100 mg/mmol, after optimized supportive care (ACEi or ARBs and blood pressure control) and an eGFR >50 ml/min/1.73m^2 receive a 4-6-month course of steroid treatment.[2] KDIGO does not recommend other immunosuppressive therapy.[2,63] The Japanese IgA Nephropathy guideline (2014) recommended a combination "cocktail" therapy for 2 years with 4 drugs, consisting of a steroid, a non-steroidal immunosuppressive agent, an anticoagulant, and an antiplatelet agent for children with severe IgA nephropathy and poor prognosis.[65]

1.8 Rationale

There are significant knowledge gaps in the treatment of pediatric patients with IgA nephropathy. It is unclear as to why some persons have progressive CKD while others have a more benign course, independent of treatment, or why clinical progression does not always correlate with kidney biopsy findings.[6,36,47,49] There is no cure for IgA nephropathy and there is a recurrence rate of up to 60% after kidney transplant, even though patients are on long-term immunosuppressive therapy. As a consequence, it is unclear if immunosuppressive therapy alters the disease course or if the course is determined by other factors. Importantly, steroids have not been convincingly shown to improve outcomes when added to optimal supportive therapy.[50] There are no pediatric trials that investigated the long-term impact of prolonged steroid therapy compared with placebo or supportive therapy. It is clear that treatment with steroids is not benign and recent trials in adults highlighted the importance of side effects such as infections, and death. In children, steroids can lead to poor growth,

necrosis of bones, and behavioural disturbances, among other side effects seen in adults.[56] Immunosuppressive drugs in general, are associated with an increased risk for infections and malignancies. It may be that treatment needs to be individualized to delay the progression of CKD and minimize the side effects of therapy and further research is needed in children with IgA nephropathy to determine optimal treatment pathways.[47] Patients are advocating for better treatments through the IgA Nephropathy Foundation (IGAN.org) which is a patient-led foundation.[68]

1.9 Need for a Local clinical pathway

There is a lack of consensus on the ideal treatment due to inconsistent data linking immunosuppressive medications to the preservation of kidney function. Children are currently treated with prolonged courses of steroids (Pozzi protocol) and other second-line immunosuppressive medications which increase the risk of adverse drug events.[5,69] The International Pediatric Nephrology Association (IPNA) guidelines committee has recently established a working group to develop a global guideline for the management of IgA nephropathy in children, and this will be the first pediatric-specific guideline. International guidelines, however, once available for use by publication in journals, will not ensure full uptake of evidence into practice.[70] A systematic review by Correa *et al*. summarized several barriers to the implementation of clinical practice guidelines.[71] Important barriers included lack of awareness of the guidelines, beliefs that the guideline is too rigid and not practical or applicable, reduction in clinical judgment and professional autonomy, and limiting treatment options. Evidence suggests that adapting a guideline to the local context can overcome these barriers and promote facilitators which can increase guideline uptake and utilization.[70]

In objective 3, we will develop a local clinical pathway by adapting the international

guideline for IgA nephropathy that is now being developed.

1.10 Significance

There are many challenges one must overcome to improve care for those with IgA

nephropathy.

Our study will address knowledge and practice gaps with three broad objectives. First, we

will conduct a systematic review and meta-analysis of treatments for IgA nephropathy in

children. This review will include both RCTs and observational studies since RCTs are scarce

due to nuances in conducting clinical trials in children with rare diseases, and the majority of

published literature on pediatric IgA nephropathy is observational. Important longitudinal

data on treatment and outcomes in routine practice is captured in observational studies,

providing real-world evidence to assess the efficacy and safety of treatments. Therefore

observational studies provide a unique opportunity to examine findings from RCTs in daily

practice in children and serve as a rich source of information.[72,73] Observational studies also

provide real-world evidence to assess the efficacy and safety of treatments. This is the first

systematic review that will include both RCTs and observational studies and will provide a

first-time summary of the management and outcomes of IgA nephropathy in children

globally. This review will inform clinical practice by providing evidence for the international

guideline and the local clinical pathway for the management of IgA nephropathy in children.

The second study is a local cohort study on the management and outcomes of biopsy-proven

IgA nephropathy in children in Alberta. We will use a biopsy registry to identify this cohort

which will be linked to electronic medical records providing a rich source of longitudinal

data. This study will provide first-time Canadian pediatric data, highlighting treatment

practices, outcomes, and the impact of steroids on the progression of kidney failure. Findings

from this study will inform the local clinical pathway in objective three, and designs for future trials.

The third objective will focus on knowledge translation through the development of a local clinical pathway for the management of IgA nephropathy in children. We will adapt the international guideline being developed by the International Pediatric Nephrology Association (IPNA) and modify it based on the findings from phases one and two. This knowledge translation component is integral for changing clinical practice, optimizing patient care, and improving patient outcomes.

Overall, this thesis will inform clinical practice and provide preliminary data to design future trials interactively examining traditional and novel therapies for IgA nephropathy in children. Future research will follow the local cohort created in objective two longitudinally to understand the impact of the local clinical pathway on patient outcomes, and develop a multi-center, international registry for children with IgA nephropathy providing cohorts for various research projects.

2: Thesis overview

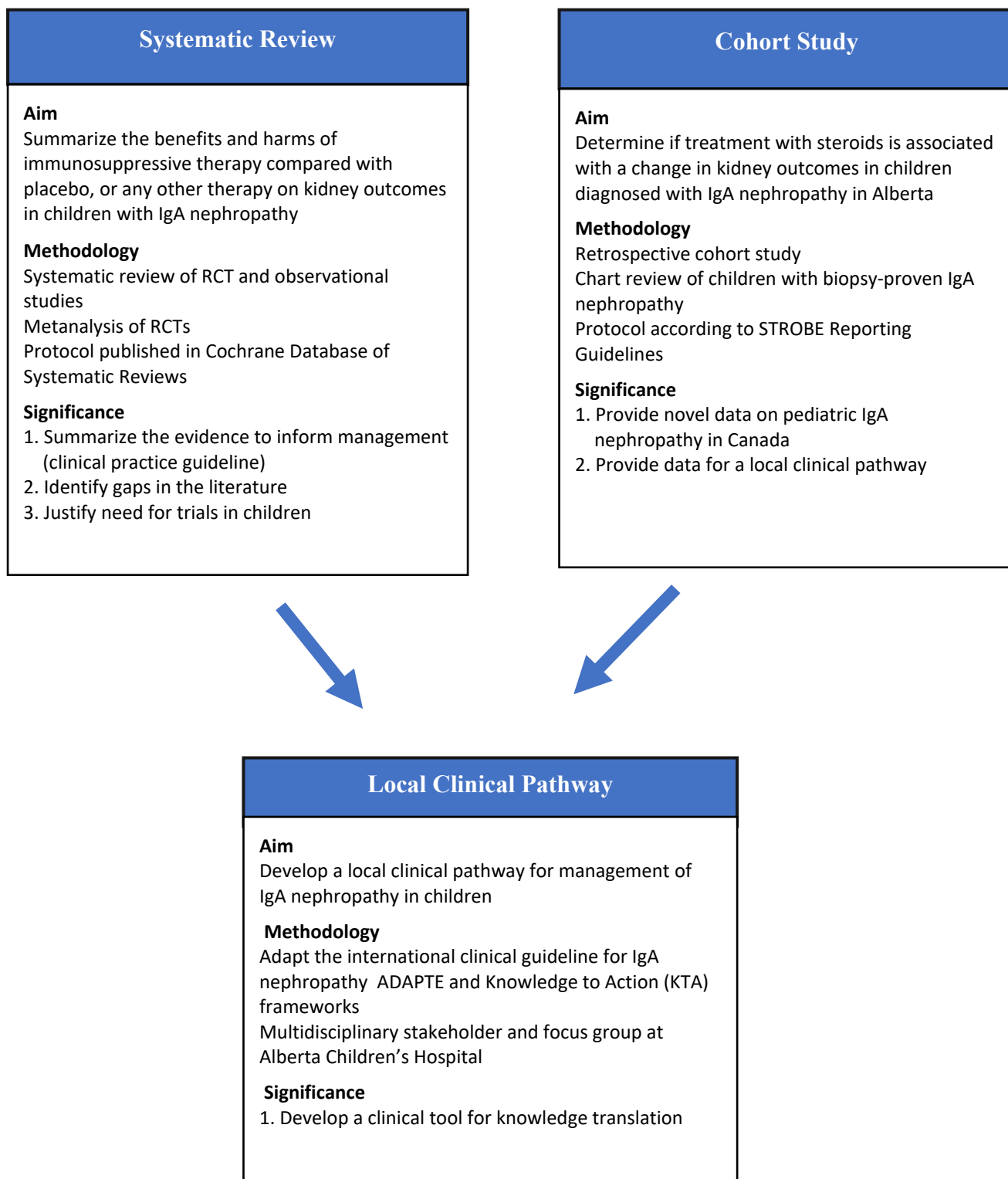The three objectives for this thesis are summarized in Figure 1

Systematic Review

Aim
Summarize the benefits and harms of immunosuppressive therapy compared with placebo, or any other therapy on kidney outcomes in children with IgA nephropathy

Methodology
Systematic review of RCT and observational studies
Metanalysis of RCTs
Protocol published in Cochrane Database of Systematic Reviews

Significance
1. Summarize the evidence to inform management (clinical practice guideline)
2. Identify gaps in the literature
3. Justify need for trials in children

Cohort Study

Aim
Determine if treatment with steroids is associated with a change in kidney outcomes in children diagnosed with IgA nephropathy in Alberta

Methodology
Retrospective cohort study
Chart review of children with biopsy-proven IgA nephropathy
Protocol according to STROBE Reporting Guidelines

Significance
1. Provide novel data on pediatric IgA nephropathy in Canada
2. Provide data for a local clinical pathway

Local Clinical Pathway

Aim
Develop a local clinical pathway for management of IgA nephropathy in children

Methodology
Adapt the international clinical guideline for IgA nephropathy ADAPTE and Knowledge to Action (KTA) frameworks
Multidisciplinary stakeholder and focus group at Alberta Children's Hospital

Significance
1. Develop a clinical tool for knowledge translation

Figure 1: The three objectives and their methodologies for the thesis project

Chapter 2: The Systematic Review

2.1: Introduction

Although IgA nephropathy is the most common primary glomerular disease worldwide, it is a rare disease that poses several issues for the pediatric population. Children will have chronic kidney disease (CKD) and nearly 40% will go on to develop end-stage kidney disease (ESKD).[1,24,74] Deterioration in kidney function is measured by the estimated glomerular filtration rate (eGFR) which is calculated from serum creatinine, and urine protein excretion (proteinuria).

The literature on IgA nephropathy in children is sparse with few clinical trials. since it is difficult to justify clinical trials in children using prolonged courses of immunosuppressive medications. The majority of published studies are observational and heterogenous therefore the inclusion of observational studies for IgA nephropathy in the pediatric population is important. There has been no systematic review of the literature looking at both randomized controlled trials (RCTs) and observational studies and no evidence-based pediatric-specific guideline for IgA nephropathy. We will review the literature to evaluate the benefits and harms of immunosuppressive therapy for the management of IgA nephropathy in children.

Our **primary objective** is to summarize the benefits and harms of immunosuppressive therapy compared with placebo, or any other therapy on kidney outcomes (change in proteinuria, change in eGFR, or development of ESKD), in children with IgA nephropathy through a systematic review and meta-analysis.

Our **secondary objective** is to determine the adverse events associated with therapies (immunosuppressive drugs, supportive therapy, tonsillectomy) for IgA nephropathy in children. These outcomes include infections, malignancies, poor growth or bone health, diabetes, hypertension, obesity, mortality, and patient-oriented outcomes.

2.2 Methods

Study overview, design, and setting

This systematic review and meta-analysis protocol will be reported in accordance with the

Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)

guidelines.[75] This study will be done in collaboration with the Cochrane Library

(Cochrane Kidney and Transplant Group). The finalized protocol which follows the

Cochrane Library guidelines for systematic review and meta-analyses was published

[*Cochrane Database of Systematic Reviews* 2022:6]. Any amendments to the protocol will be

recorded in the Cochrane Database of Systematic Reviews records. This review will include

RCTs and observational studies [also known as Non-Randomized Studies of Intervention or

NRSI]. NRSI is any quantitative study estimating the effectiveness of an intervention that

does not use randomization to allocate units to intervention groups.[76]

Table 1: Population, intervention, comparison, and outcomes (PICO). Abbreviations: ACEi,
angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SGLT2,
sodium-glucose cotransporter; eGFR, estimated glomerular filtration rate; ESKD, end-stage
kidney disease.

Population, intervention, comparison and outcomes	
Population	Children ≤18 years with biopsy-proven IgA nephropathy
Intervention	Immunosuppressive agents (steroids, rituximab, cyclophosphamide, cyclosporine, tacrolimus, azathioprine, mycophenolate, mizoribine, leflunomide, budesonide) Any other immunosuppressive agent
Comparison	Supportive therapy (ACEi, ARB, SGLT2 inhibitors) Immune-modulating agents (Fish oil, Vitamin E) Surgery (Tonsillectomy) Antiplatelet or anticoagulant agents Placebo or any other treatment
Primary outcomes	Change in proteinuria, change in eGFR, or development of ESKD (dialysis, transplant, of eGFR<15 ml/min/1,73m^2)
Secondary Outcomes	Infection, malignancies, diabetes, hypertension, growth failure, hospitalization, death, obesity, patient-oriented outcomes

Population

We will include all children with biopsy-proven IgA nephropathy diagnosed ≤ 18 years of age. We included children who are 18 years old because some European databases that will be searched, classify children inclusive of 18 years. Biopsy-proven means that the primary diagnosis of IgA nephropathy was made by a pathologist after a review of kidney biopsy findings that are consistent with IgA nephropathy, defined as IgA deposition within the mesangium of the kidney.[77] We will exclude children with IgA vasculitis, secondary IgA nephropathy (associated with liver failure, celiac disease), and IgA nephropathy in a kidney transplant recipient.

Types of interventions

Interventions include any form of immunosuppression, given via oral or intravenous route, over any duration, and in any combination. Immunosuppressive medications include corticosteroids (hereafter referred to as steroids), alkylating agents (cyclophosphamide, chlorambucil), calcineurin inhibitors (cyclosporine, tacrolimus), azathioprine, mycophenolate mofetil, rituximab, mizoribine, leflunomide, budesonide and potentially, other agents.

Types of Comparisons

We will make the following comparisons.

1. Immunosuppression versus placebo

2. Immunosuppression versus supportive care for kidney protection. These include

ACEi or ARB, SGLT2 inhibitors

3. Immunosuppression versus antithrombotic therapy (warfarin, heparin, dipyridamole, acetylsalicylic acid (aspirin) and enoxaparin)

4. Immunosuppression versus any recently developed agents

Primary outcomes

Our primary outcomes will be kidney outcomes and will reflect disease severity and kidney function. These include 1. Change in eGFR (reflecting disease progression or regression). 2. Change in proteinuria. 3. Development of ESKD.

Estimated GFR is a measure of kidney filtration and function and is used to stage CKD. It is calculated from serum creatinine which is a marker of kidney function. There are various equations for eGFR calculation, we will report eGFR as per the study as we will not have individual patient data and creatinine to calculate eGFR. We will describe kidney function as a change in eGFR in mL/min/1.73m^2 determined by any method reported (creatinine clearance (CrCl) in mL/min or any appropriate equation).[78,79] ESKD will be defined as the initiation of dialysis or receipt of a kidney transplant or a sustained decline in eGFR of <15 mL/min/1.73 m^2 for more than 3 months duration.[2] (See appendix A for CKD staging)

We will report a change in proteinuria using any of the measurements for urine protein excretion that was reported. Some measures of proteinuria include urine protein excretion rate or PER (g/24 hours), urine albumin excretion rate (AER), protein to creatinine ratio (PCR mg/mmol or g/g), or albumin to creatinine ratio (ACR mg/mmol or g/g). Remission of proteinuria will be reported as per the study definition. The most common definition of remission is absolute urine protein < 0.5 to 1g/day, a relative decline in proteinuria of 30% from the time of renal biopsy, or a change from nephrotic to non-nephrotic range proteinuria defined as PCR <50 mg/mmol or ACR <300mg/mmol on spot urine.[2]

Secondary outcomes

Secondary outcomes will be adverse events. These outcomes will most likely be described

due to anticipated heterogeneity in reporting adverse events in children. Secondary outcomes

of interest include 1. Treatment-related adverse events (infections, diabetes, impaired blood

glucose levels, obesity, hypertension, malignancy, and poor bone health (documented

reduced growth, avascular necrosis, fractures/osteoporosis)). 2. Death 3. Number of days in

hospital 4. Patient-oriented outcomes (life participation, missed school days, and any other

reported outcomes that may affect quality of life). 5. Dropout rate due to treatment-related

adverse events. Outcomes and outcome measures are reported in Appendix B.

Search methods

Electronic searches

Literature search strategies will be developed in consultation with a medical librarian from

the University of Calgary and an information specialist from Cochrane Library using medical

subject headings (MeSH) and text words related to IgA nephropathy. We will search the

Cochrane Kidney and Transplant Register of Studies through contact with the Information

Specialist using search terms relevant to this review (search strategy in Appendix C). The

Register contains studies identified from the following sources which will be searched as per

below.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)

2. Weekly searches of MEDLINE OVID SP

3. Searches of kidney and transplant journals, and the proceedings and abstracts from

major kidney and transplant conferences

4. A search of the current year of EMBASE OVID SP

5. Weekly current awareness alerts for selected kidney and transplant journals

6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

7. Reference lists of review articles, relevant studies, and clinical practice guidelines.

Details of search strategies and a list of hand-searched journals, conference proceedings, and current awareness alerts, will be published on the CKT website under the CKT Register of Studies. The search will be updated toward the end of the review to capture new studies.

Study inclusion criteria

We will include all RCTs, quasi-experimental, crossover trials, and NRSIs (observational studies) that compare any immunosuppressive therapy with, placebo, supportive care, or another intervention for IgA nephropathy management with a minimum follow-up of 6 months.

Study exclusion criteria

We will exclude studies that we are unable to obtain source data from primary investigators, including data regarding children participating in a trial, and studies that can't be translated into English. We will exclude pre-post-study design, descriptive studies, and studies with no interventions or comparators. Studies comparing immunosuppressive treatment to non-conventional treatments, including traditional and herbal therapies will be excluded.

Selection of studies, data extraction, and management

The search will be done according to Cochrane protocol for electronic searches. Search results will be imported into www.covidence.org for screening and full-text review, duplicates will be removed. A pilot was done to refine the screening questions and the final search. Two authors will independently screen titles and abstracts yielded by the search. We will obtain the full-text article for all titles that meet the inclusion criteria or where there is any uncertainty. Two authors will independently screen full texts for data extraction

eligibility. Disagreements at each stage of screening will be resolved in consultation with a third author. Where more than one publication of one study exists, reports will be grouped and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions, these data will be used. Any discrepancy between published versions will be highlighted. Neither of the review authors will be blinded to the journal titles, study authors, or institutions. Agreement between reviewers will be assessed by the kappa statistic. A score of 1 indicates perfect agreement and 0 equates agreement totally due to chance, we will aim for a kappa of 0.8.[80]

Risk of Bias

Risk of bias (ROB) within studies will be assessed independently by two authors. For RCTs, the Cochrane Risk-Of-Bias tool for randomized trials (RoB-2) will be used.[76] The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool will be used for NRSI.[76] Disagreements will be resolved first by discussion and then by consulting a third author for arbitration. We will compute graphic representations of potential bias within and across studies using RevMan[TM] 5.4 (Review Manager 5.4).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of publication bias if 10 or more studies are included in the meta-analysis.[76]

Statistical methods

Measures of treatment effect

For categorical outcomes (mortality, infection, ESKD**)** results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Continuous outcomes (sCr, GFR, PCR**)** will be analyzed using a weighted mean difference (MD) or standardized MD with 95% CI if

different measurement scales are used. Skewed data and non-quantitative data will be presented descriptively.

Meta-analysis of change scores

Studies may include a mixture of change-from-baseline and final value scores. A meta-analysis of mean differences is an acceptable method for reporting a mixing of outcomes.[76] The appropriate means and standard deviations (of either final measurement or change from baseline) will be used for each study, and since mean values and standard deviations for the two types of outcomes may differ substantially, we will place them in separate subgroups for analysis to avoid confusion for the reader.[76]

Imputing Standard Deviations

If the majority of studies have missing standard deviations, these values will not be imputed. If, however, a small proportion of studies with missing standard deviations can be combined with studies for which full data are available, imputation will be considered. If several candidate standard deviations are available, we will decide whether to use the average, highest, or 'reasonably high' value. Before imputing missing standard deviations, we will look for statistics (e.g. confidence intervals, p-values, standard errors) that allow calculation or estimation of the standard deviation.[76]

Time-to-event data

Time-to-event data will be summarized using survival analysis and expressed as hazard ratios.

Rates

Hospitalisation duration will be reported as rates of hospitalisation or number of days as a continuous measure.

Unit of analysis issues

Unit of analysis in almost all scenarios will be individuals. We will not include studies where the unit of analysis is a clinic or a group. When a study has more than two treatment groups, we will present the additional treatment arms. Where the additional treatment arms are not relevant, they will not be taken into account. We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis.

Cluster-randomized studies

We suspect that we will not encounter any cluster-randomized studies, but in the event that we do, we will consider the following approaches.

We anticipate that studies using clustered randomization will have controlled for clustering effects. In case of doubt, we will contact the authors to ask for individual participant data to calculate an estimate of the intra-cluster correlation coefficient (ICC). If this is not possible, we will obtain external estimates of the ICC from a similar study or from a study of a similar population as described in the Cochrane Handbook for Systematic Reviews of Interventions. If ICCs from other sources are to be used, we will report this and will conduct sensitivity analyses to investigate the effect of variation in the ICC.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (emailing to the corresponding author/s) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomized patients, intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up, and withdrawals will be detailed. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised.[76]

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the I² statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error.[81] A guide to the interpretation of I² values will be as follows: 0% to 40%: might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity, 75% to 100%: may represent considerable heterogeneity. The importance of the observed value of I² will depend on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. p-value from the Chi-squared test, or a confidence interval for I²).[76] Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

Data synthesis

Data will be pooled using the random-effects model if studies are sufficiently homogeneous in terms of design, comparator, and outcomes. Data will be pooled if at least 2 studies contribute to the required data.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity. Heterogeneity among participants could be related to age, ethnicity, and renal pathology. Heterogeneity in treatments could be related to prior agent(s) used and the dose, and duration of therapy. Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the

risk difference with 95% CI will be calculated for each adverse effect, either compared

to no treatment or to another agent. Subgroup analysis will be done for ethnicity (East-Asian

versus other population), biopsy class, and for different age categories in children. East-

Asians are known to have a higher prevalence of IgA nephropathy and worse kidney

outcomes (progression to ESKD) compared with Europeans.[82] With regard to biopsies for

IgA nephropathy, the MEST score has been shown to be an independent predictor of

outcome. For age subgroup analysis, we would explore the impact of earlier age of diagnosis

with kidney outcomes. Wyatt *et al.* found that earlier age of diagnosis of IgA nephropathy in

childhood was not associated with progression to kidney failure.[83] Studies will be grouped

according to follow-up time for subgroup analysis.

Sensitivity analysis

We will perform sensitivity analyses to explore the influence of the following factors on

effect size: We will repeat the analysis as follows. 1. Excluding unpublished studies. 2.

Taking account of the risk of bias, as specified. 3. Excluding any prolonged or large studies

to establish how much they dominate the results. 4. Excluding studies using the following

filters: diagnostic criteria, language of publication, source of funding (industry versus other),

and country.

Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in the 'Summary of findings' tables. These

tables will present key information concerning the certainty of the evidence, the magnitude of

the effects of the interventions examined, and the sum of the available data for the main

outcomes.[84] The 'Summary of findings' tables will also include an overall grading of the

evidence related to each of the main outcomes using the GRADE (Grades of

Recommendation, Assessment, Development and Evaluation) approach which will be assessed by two authors.[85] The GRADE approach defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The certainty of a body of evidence involves consideration of the within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates, and risk of publication bias.[84] Data will not be pooled for RCTs and observational studies. However, if there are matched controls in observational studies, we will consider pooling.

2.3 Potential Limitations

There are several limitations for studies in children. We anticipate that we will identify few small pediatric RCTs and the majority of the studies will be observational. Long-term follow-up data for children might be captured in adult studies since progression to ESKD may occur in adulthood. We will look at studies that include adults and children to capture ESKD and any reported outcomes of interest. Another limitation associated with systematic reviews of observational studies includes frequent lack of a comprehensive study protocol in advance of the study, leading to variation in treatment and follow-up data that can lead to errors in the analysis.[76] To avoid error, some findings will be described and not pooled. Studies with small sample sizes may not be powered to detect outcomes.

2.4 Significance

This systematic review will summarize the evidence to inform development of the first international clinical guideline for IgA nephropathy in children. It will also identify gaps in the management of IgA nephropathy for future research.

Chapter 3: Local Cohort Study

3.1 Introduction

IgA is the most common primary glomerular disease and leads to chronic kidney disease (CKD) which progresses to kidney failure in 30-40% of patients.[1,86] It causes a decline in the glomerular filtration rate (GFR) which can be estimated (eGFR) from serum creatinine (a biomarker of kidney function). Damage to the glomeruli results in protein leaking into the urine (proteinuria). Historically, children and adults with IgA nephropathy have been treated with the Pozzi Protocol (steroids for 6 months), as recommended by Kidney Disease Improving Global Outcomes (KDIGO) Glomerulonephritis (GN) Guideline for IgA nephropathy management.[20] It remains unclear if a decline in kidney function and kidney failure are associated with baseline characteristics of the patients, medications taken, or both. We do not know if there are certain factors associated with the response to steroids in children or if the timing of introduction of steroids is important for preservation of kidney function. We aim to describe the clinical characteristics, examine the response to steroids, and outcomes in a cohort of children diagnosed with IgA Nephropathy by a kidney biopsy in Alberta.

This project will be done through an observational study utilizing available data within Alberta. Increasingly, observational studies with longitudinal data are being used to understand disease course and the effects of various interventions on outcomes in real-world settings, especially when randomized controlled trials (RCTs) are not feasible or available as is the case in this rare disease.[72,73]

Objectives

Primary objective: Determine if treatment with steroids in children (<18 years) diagnosed with IgA nephropathy on a kidney biopsy is associated with a change in kidney function (as measured by eGFR).

Secondary objectives:

1. To determine if treatment with steroids in children (<18 years) diagnosed with IgA nephropathy on a kidney biopsy is associated with changes in proteinuria or the development of ESKD.

2. To determine if the timing of initiation of steroids therapy following a biopsy diagnosis of IgA nephropathy is associated with kidney outcomes (change in eGFR, change in proteinuria, development of ESKD).

We hypothesize that there is no difference in eGFR in children with IgA nephropathy who are managed with supportive therapy versus those who initiated steroid therapy.

Conceptual Map

In this study, we will examine the relationship between treatment with steroids versus no treatment on change in eGFR as shown in Figure 2. Baseline variables such as kidney biopsy report, proteinuria, eGFR, and previous medications can influence a clinician's decision to start steroids in a patient with IgA nephropathy. Further, measures of eGFR and proteinuria will be repeated over time, and changes in values will also provide more information and inform the decision to initiate treatment with steroids. Therefore, eGFR, proteinuria, and timing of initiation of steroids are all important in the relationship between treatment with steroids and the outcome (which are also measures of eGFR and proteinuria).
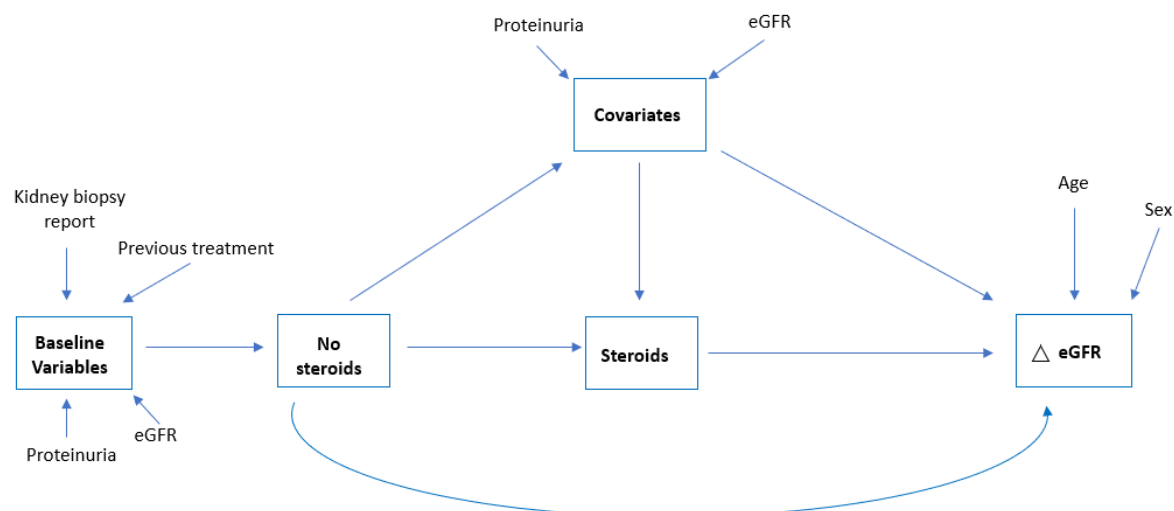
Figure 2: Conceptual map showing the relationship between treatment with steroids (exposure), or no treatment, and change in eGFR (outcome) and how this relationship is influenced by baseline variables and covariates during follow-up. Abbreviations: eGFR, estimated glomerular filtration rate.

3.2. Methods

Study design

This is a retrospective longitudinal, population-based, cohort study. The study protocol is written according to STROBE reporting standards to ensure transparency (The Strengthening the Reporting of Observational Studies in Epidemiology).[87]

Setting

The region of Southern Alberta had an estimated population of 1,530,332 in the year 2016.[88,89] Inpatient and outpatient management of children (< 18 years) with kidney diseases occur almost exclusively at the Alberta Children's Hospital (ACH). The nephrology division at ACH also provides care remotely to patients residing in rural areas. Alberta has a single-payer healthcare system administered by Alberta Health Services (AHS). Nephrology services are available free of cost, including dialysis and transplant.

Data sources and data linkage

We will use multiple sources of data to conduct this study.

The Biobank for Molecular Classification of Kidney Disease (BMCKD) is a population-based clinical registry of patients (of any age) who have had kidney biopsies performed in Southern Alberta. It was established at the University of Calgary in 2015 in collaboration with AHS and the Department of Pathology and Laboratory Medicine (DPLM). This registry was facilitated by the centralized renal pathology (biopsy) services of the Calgary Laboratory Services (CLS) for Southern Alberta, including Calgary. BMCKD contains banked biopsy materials, detailed pathology reports, digitalized light and electron microscopy images.[90] This repository of kidney biopsies although established in 2015, has biopsy data from January 2000 that will be used to identify the cohort of children (<18 years) with IgA nephropathy. Kidney biopsy reports for IgA nephropathy staged using the Oxford Classification (Mesangial hypercellularity, Endocapillary proliferation, Segmental sclerosis, Tubular atrophy, and Crescents [MEST-C scores]) will be obtained from the BMCKD.

Sunrise Clinical Manager™ (SCM™) and Connect Care™ are electronic medical records (EMRs) or patient charts in Alberta. SCM™ is a Calgary-specific EMR, owned by AHS, that has been operational since 2010. Connect Care™ is a province-wide EMR that is now being adopted in Calgary (2022). These databases store routinely collected clinical data which will be used to obtain longitudinal patient data. Hude Quan *et al.* published the advantages of using SCM™ for health research in Calgary.[91] EMRs such as SCM™ are useful in improving case definitions, and identification of key exposure and outcome variables which can reduce error and bias in research using databases.[91] SCM™ is currently being validated for health research by Hude Quan *et al.* and SCM™ has been used in studies in Alberta, to validate findings from administrative health databases and clinical registries.[91,92] Demographics,

comorbidities, history of IgA vasculitis, laboratory data, and procedures will be obtained

from SCM[TM] (chart review) as shown in Figure 3. Death and death date will be identified

from SCM[TM] and supplemented with Alberta Vital Statistics[TM]. SCM[TM] will also be used to

supplement medication data obtained from Pharmaceutical Information Network[TM] (PIN[TM])

as explained below.

The PIN[TM] is a Drug Information System (DIS) electronic network unique to Alberta that was

implemented in January 2008 with records for active and historical prescription dispensing

data from community and outpatient pharmacies. It contains drug dosage, duration,

prescribing physician specialty, known allergies, and medication intolerance.[93] Drugs are

classified according to the organ system being targeted and according to the pharmacological

groups (structure and mechanism of action), this classification is known as the anatomic

therapeutic codes (ATC).[94] PIN[TM] has been validated for drug prescriptions for senior

patients in the Alberta's Tomorrow Project.[95] All medication data will be obtained from PIN

and supplemented with SCM[TM]. We will collect steroid dispensing information (date of

dispensation, duration, dose, and repeat prescriptions) as shown in Figure 3.

Alberta Vital Statistics[TM] is the Alberta provincial registry that contains all deaths and is

linked to AHS through unique personal identifiers (Personal Health Numbers [PHNs]). This

database will supplement death information obtained from SCM[TM]. All data will be extracted

into REDCap[TM] which is an online application for managing survey and research data.[96]

Data linkage

We will identify this cohort from a clinical registry (BMCKD) and use personal identifiers

(PHNs) to link the cohort to EMRs, PIN[TM], and Alberta Vital Statistics[TM] data as shown in
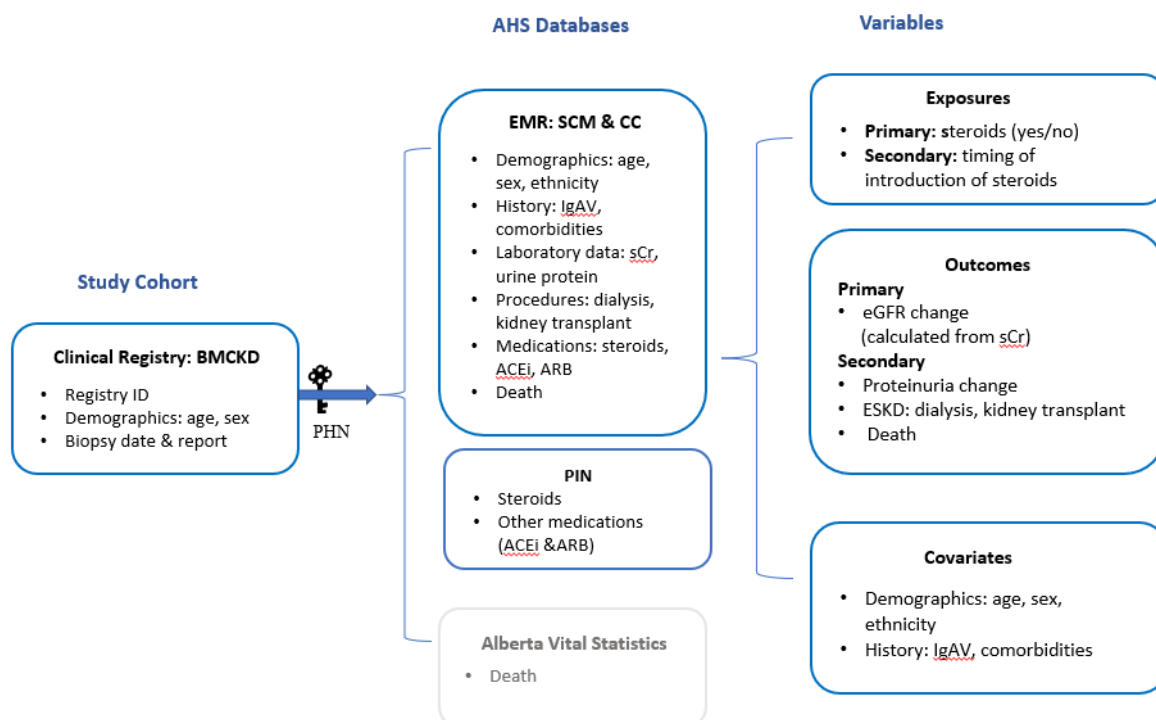
Figure 3.

Figure 3: Cohort study design showing data linkage from the clinical registry (BMCKD) with AHS databases (EMR, PIN, and Vital Statistics). Abbreviations: BMCKD, Biobank for Molecular Classification for Kidney Diseases; PHN, Personal Health Number; AHS, Alberta Health Services; EMR, Electronic Medical Records; SCM, Sunrise Clinical Manager; CC, Connect Care; IgAV, IgA vasculitis; sCr, serum creatinine; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.

Study Timeline

The index event will be a kidney biopsy which is the start of the observation period. We will have a look-back window for a maximum of 2 years before the index date. Baseline characteristics will be assigned at the time of kidney biopsy and if unavailable, from the look-back window. Patients will be followed from the date of biopsy until the occurrence of ESKD, death, or the end of study follow-up (December 31, 2022). All patients will have a minimum of 1year and a maximum of 13 years of potential follow-up. Patients will be censored if they migrate from Southern Alberta or if they are lost to follow-up. The study design time flow is depicted in Figure 4
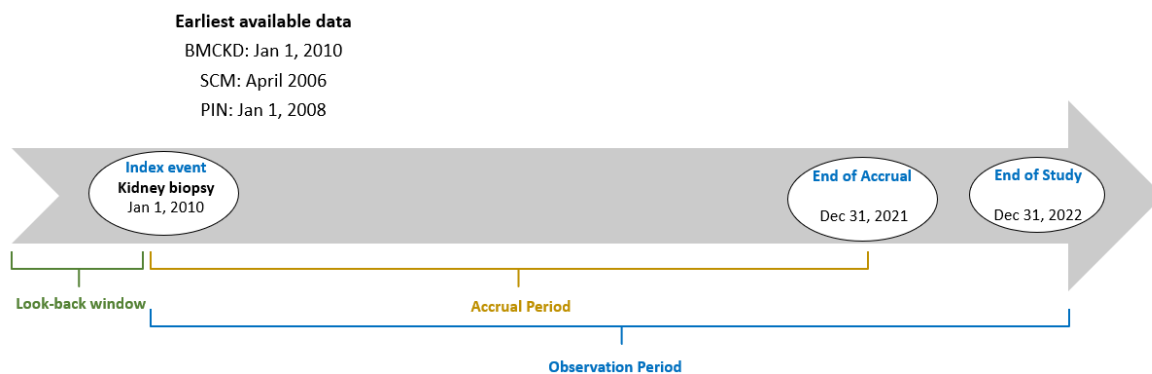
Figure 4: Study timelines**.** Abbreviations: CC, Connect Care; IgAV, IgA vasculitis.

Study population

We will identify a cohort of children in Southern Alberta who meet the following criteria:

Inclusion criteria

1. Age <18 years at the time of a kidney biopsy

2. Had a kidney biopsy between January 2010 and December 2021 with a diagnosis of IgA nephropathy in the pathology report

Exclusion criteria

1. Diagnosis of a disease known to cause a secondary form of IgA nephropathy (liver failure, celiac disease, Human Immunodeficiency Virus [HIV] infection, and others as documented)

2. Prior kidney transplant

3. ESKD

4. Steroid exposure during the look-back window

5. Persons without unique identifiers to link to provincial and regional datasets as required

Primary Exposure

The primary exposure will be the use of steroids, defined as the dispensing of oral or intravenous steroids during the study period (from the date of biopsy to June 30, 2022) for the

purpose of treating their IgA nephropathy (which is likely documented in the chart [SCM[TM]] and PIN).

The exposure date will be defined as the date of dispensing the first steroid prescription as shown in Figure 5. Once a patient is exposed, they will remain exposed throughout the study period. Steroid treatment for IgA nephropathy is not a dynamic treatment strategy, dose adjustments are not usually based on laboratory values but on patient tolerance, since a patient is usually committed to a course of treatment.[97] We don't expect significant variability in steroid dose or regimen in children treated at Alberta Children's Hospital.

Timing of steroid therapy

We will also record the timing of initiation of treatment with steroids from the date of kidney biopsy (index event), defined as the number of days from a biopsy diagnosis to the date that the first steroid prescription was dispensed (exposure date).

Primary Outcomes

Our primary outcome will be a 30% reduction in eGFR from baseline, this will be a dichotomous outcome (yes/no). Thirty percent change in eGFR was chosen based on data from Barbour *et al*.[98] Trends in eGFR in children with IgA nephropathy are different from adults, eGFR increases until late teenage years and is followed by a linear decline resulting in a 30% change in eGFR being used in the pediatric risk prediction tool as opposed a 50% change in eGFR in the adult risk prediction tool.[98]

eGFR will be calculated from standardized serum creatinine measures as per the Schwartz equation (regardless of age).[99,100] We will record all creatinine measurements (umol/L) from the beginning of the look-back window until the end of the follow-up, which will be used to calculate the eGFR at each time point. Baseline eGFR will be the eGFR immediately

preceding the kidney biopsy within 2 months in the look-window. If there are multiple eGFR

on the same day, the mean eGFR value will be recorded as the baseline value.

We will calculate 3-monthly eGFR means as depicted in Figure 5 to observe the first

sustained 30% eGFR change (for more than 3 months) from study entry which will be

considered as experiencing the outcome.

Secondary Outcomes

The secondary outcomes are (1) change in proteinuria category, (2) development of ESKD

(3) death (4) eGFR as a continuous measure.

Proteinuria measures commonly used in this population are albumin-to-creatinine ratio

(ACR) or protein-to-creatinine ratio (PCR), or urine dipstick based on random spot urine

measurements.

Proteinuria measures will be categorized as per KDIGO CKD staging (Appendix A).[2] We

will categorize proteinuria as none/mild (A1: dipstick negative/trace, or PCR <15 mg/mmol,

or ACR <3 mg/mmol), moderate (A2: dipstick 1+, or PCR 15-50 mg/mmol, or ACR 3-30

mg/mmol), or severe/nephrotic (A3/A4: dipstick 2+ to 4+, or PCR >50mg/mmol, or ACR

>30 mg/mmol).[2]

We will collect PCR or ACR in mg/mmol every 3 months as a continuous measure from the

beginning of the look-back window to the end of the observation period as depicted in Figure

5. PCR will be the primary measure of proteinuria as this most common measure of

proteinuria in our practice, and if unavailable, it will be supplemented with ACR. When both

ACR and PCR are unavailable, urine dipstick measures will be used.[101] We will categorize

proteinuria as none/mild, moderate, or severe for each time point as defined above.

ESKD will be defined as the earlier of initiation of kidney replacement therapy (chronic

dialysis or kidney transplant) or a sustained eGFR of < 15 mL/min/1.73 m^2 for more than 90

days (values are separated by >90 days). eGFR will be calculated from serum creatinine

collected as described above. When ESKD and kidney replacement therapy are documented

on the same day, we will define the outcome as kidney replacement therapy.[21] ESKD will be

a dichotomous outcome (yes/no).

Death will be defined as all-cause mortality at any location, which will be a dichotomous

outcome (yes/no).

We will also examine the in the absolute value of eGFR over the observation period for each

participant and between the exposed and unexposed groups.

Patients' timeline

Each patient will enter the study at time zero (t=0) based on a kidney biopsy diagnosis of IgA

nephropathy and will have variable lengths of follow-up. Patients will have serial serum

creatinine (eGFR) and urine protein measurements which will be plotted 3-monthly. These

results may trigger a treatment course with steroids. Once steroids are dispensed, a patient

will be considered exposed and will remain exposed. Some patients may have repeat courses

of steroid treatment based on changes in eGFR and urine protein measurements, repeated

courses will not alter the exposure status. The timing of initiation of a steroid treatment will

vary among patients. Figure 5 is an example of a course in the study for one patient.
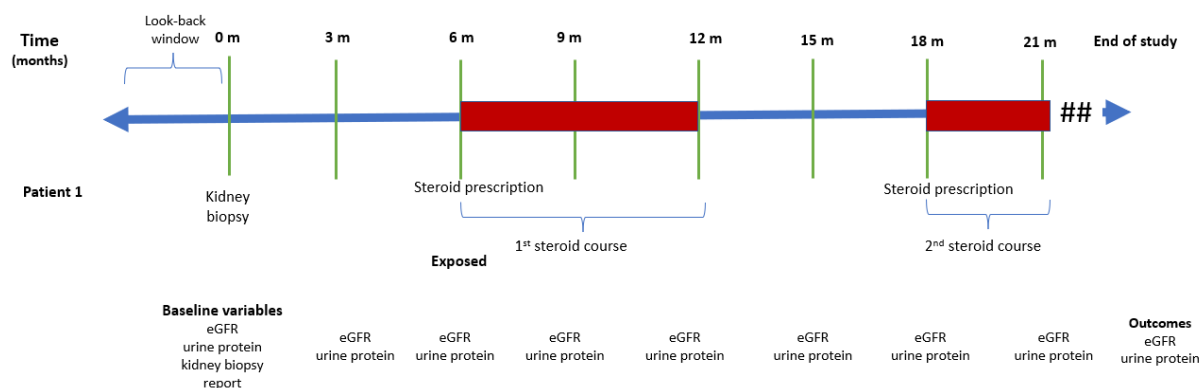

Figure 5: A patient's timeline in the study. Abbreviations: m, months; eGFR, estimated glomerular filtration rate.

Covariates

For objective 2, we will collect the following variables which are potential effect modifiers or

confounders in the relationship between the outcomes and exposure.

1. Baseline characteristics

a. Demographics and history: age, sex, ethnicity, comorbidity, and history of IgA vasculitis.

Age will be defined in calendar years calculated from the date of birth. Sex will be defined

as sex assigned at birth as per chart documentation of male, female or unknown. Ethnicity

will be documented as reported in the chart (this is self-reported), and unavailable ethnicity

will be coded as missing. Comorbidities will be collected as any documented chronic

medical condition with an International Classification of Diseases (ICD-10) coding. History

suggestive of IgA vasculitis will be defined as any documentation of palpable purpura or

rash along with hematuria or chart documentation of IgA vasculitis (previously known as

Henoch Schonlein Purpura) at first nephrology clinic visit to a maximum look-back window

in SCM™.

b. Baseline medications: We will document all relevant prescribed medications (for CKD,

IgA nephropathy, and IgA vasculitis). For each medication, we will collect the date of

dispensing, dose, and duration (based on the number of days and refills). We will look back

to a maximum of 2 years for all relevant medication exposure as children may have been

exposed to steroids, angiotensin-converting enzyme inhibitors (ACEi), or angiotensin

receptor blockers (ARB) before or at the time of kidney biopsy, these will be documented as

baseline medications.

c. Histological classification of kidney biopsy: MEST scores M and T, when combined with

clinical data such as eGFR or proteinuria, have been shown to predict outcomes.[33] We will

collect MEST scores for each diagnostic kidney biopsy and include M and T scores into the

model to assess if these scores are independent predictors of kidney survival.

3.2.1 Statistical analysis

The baseline characteristics for the IgA cohort, both exposed and unexposed to steroids will

be described using means (± standard deviation) or medians (interquartile range), and

proportions as appropriate.

Primary outcome

The primary outcome is eGFR, and a 30% change in eGFR over the observation period will

be the primary outcome measure. We will examine the data visually, time to 30% eGFR

change will be plotted using a Kaplan Meier graph for the steroid-exposed group and the

unexposed group. A time dependent cox proportional hazards model will be created to

examine the difference in experiencing the event between the exposed and the unexposed

while adjusting for baseline eGFR, proteinuria, and other covariates (age, sex, ethnicity, with

or without a history of IgA vasculitis, comorbidities, ACEi / ARB, MEST scores).

Proportional hazards assumption will be checked.

Secondary outcomes

ESKD and death will be analyzed as binary outcomes expressed as absolute frequencies and

percentages. We will compare these outcomes (ESKD and death) between the exposed group

and the unexposed group using the Pearson chi-square test or the Fisher-Exact test as

appropriate. The results will be expressed as risk ratios (RR) with 95% confidence intervals

(CI).

Proteinuria will be analyzed as an ordinal outcome (mild/moderate/severe) using the ordinal

mixed effects model as per the secondary analysis of eGFR.

As a secondary analysis, we will examine a continuous measure for eGFR over time. Each

patient will have a baseline measurement and a final measurement for eGFR. We will

visually examine eGFR for each participant during the study period by plotting the calculated

eGFRs for each patient in the study at each timepoint to detect any effect of steroids on

eGFR. We will then compare eGFR (ml/min/1.73m^2/year) over time in the exposed and

unexposed group using a linear mixed effects model (multilevel model [MLM]) with time-

varying covariates for steroid exposure and adjusting for important baseline covariates.

Mixed effects model assumptions will be checked

We will examine effect modification between the exposure and various predictors including

age, sex, MEST score, ethnicity (if adequately reported), baseline eGFR, and proteinuria

through interaction terms for the Cox proportional hazard model and the linear mixed effects

model. We will assess for confounding if there is no effect modification by looking at clinically meaningful differences in the adjusted and unadjusted estimates.

Analysis will be done using the STATA^{TM} statistical software package, version 17. A 2-sided hypothesis test with $\alpha < 0.05$ as the cut-off will indicate statistical significance.

3.3 Missing data

Missing predictor variables will be addressed through imputation. If <5% missing data for predictors and will use single imputation of means and medians to address missingness in predictors' data. However, if ≥5% of the data is missing for predictors, we will consider multiple imputation.

In multilevel modelling, missing data are assumed to be missing at random (MAR). We do not expect that there will be missing baseline serum creatinine as this is usually the indication for a kidney biopsy. However, if there is no baseline serum creatinine or GFR, this will be back-calculated by reversing the MDRD equation using age and sex (assuming that all patients are non-black) and an assumed normal GFR is 75 ml/min/1.73m2 as described by Zappitelli *et al*.[102]

MDRD equation: baseline creatinine = $0.74 - 0.2$ (if female) + $0.003 \times$ age (in years)

3.4 Potential Limitations

There are several potential limitations to this study. This cohort will be selected through kidney biopsies. Biopsies are not done for all cases of IgA nephropathy, biopsies are usually done if there is significant proteinuria, deterioration of kidney function, and immunosuppressive drugs are being considered or before the transition to adult care. This cohort will not capture mild cases of IgA nephropathy who did not undergo a kidney biopsy or were not followed by nephrology services. Our results may overestimate adverse kidney

outcomes as our population may have a more severe presentation or decline in kidney function, as we are selecting a cohort based on biopsy status. We cannot mitigate this bias as there is no other way to confirm IgA nephropathy other than by a kidney biopsy.

Relying on chart data can lead to information bias. We can have measurement errors in serum creatinine, urine protein, height, and weight. Self-reporting of ethnicity cannot be confirmed. We expect that this bias will be common across both groups and will be minor.

ESKD may not be captured in the pediatric data, and progression to kidney failure may occur during adulthood which may underestimate adverse kidney outcomes, but we will supplement the data with observation in chart data during adult nephrology follow-up, this is possible using Connect Care^{TM} EMR.

This retrospective study is vulnerable to measured and unmeasured confounders. We will do stratification and logistic regression modeling to assess for confounding and modification. Confounding by indication will be the main unmeasured confounding that we will encounter. Physicians are likely to systematically treat children with severe disease with steroids and those with severe disease at baseline are more likely to experience the outcome. Therefore, severe disease will be related to the exposure and the outcome.

A retrospective observational study will be subjected to attrition in the cohort due to missing data from charts. We will use imputation to deal with missing lab values.

3.5 Significance

This study will provide first-time data about IgA nephropathy in children in Canada, and more so in Alberta. We will be able to understand how this disease presents, who are susceptible, identify clinical and laboratory predictors for kidney failure and assess the efficacy of steroids. Findings from this phase will inform the development of a local pathway

for IgA nephropathy management and the design of future trials to examine current and novel

treatments for IgA nephropathy.

3.6 Knowledge translation

Results from this study will be published in a key Nephrology Journal and presented at the

International Pediatric Nephrology (IPNA) conference. It will also be used to design a local

clinical pathway for the management of IgA nephropathy in children.

Chapter 4: Local clinical pathway

4.1 Introduction

Practice variation in the management of IgA nephropathy in children is common, there is no

pediatric-specific guideline. There is a lack of consensus on the ideal treatment due to

inconsistent data linking immunosuppressive medications to the preservation of kidney

function. Children are currently treated with prolonged courses of steroids (Pozzi protocol)

and other second-line immunosuppressive medications which increase the risk of adverse

drug events.[5,69]

The International Pediatric Nephrology Association (IPNA) guidelines committee has

recently established a working group to develop a global guideline for the management of

IgA nephropathy in children, and this will be the first pediatric-specific guideline.

International guidelines, however, once available for use by publication in journals, will not

ensure full uptake of evidence into practice.[70] A systematic review by Correa *et al*.

summarized the barriers and facilitators for the implementation of clinical practice guidelines

by examining 25 articles across various specialties.[71] Important barriers identified from the

guideline context included a lack of awareness of the existence of guidelines, clarity, and

beliefs that the evidence is incorrect or that the guideline is too rigid and not practical or

applicable on a daily basis. Guidelines were also thought to reduce clinical judgment and

challenge professional autonomy, limiting treatment options. Health professionals had more

confidence in their clinical experience than in guideline recommendations. Other barriers were deficiency in staff continuous education, additional workload, and lack of skills and specialist knowledge within services. Some facilitators included a structured management plan for patients, good communication, behaviour change skills of healthcare professionals, technology (electronic records, reminders, audiovisual aids), and adequate time to promote and implement the new practice. From the context of a guideline, interventions that demonstrated clear and consistent clinical evidence of benefit and solid and clear recommendations, and leader or champion facilitated implementation.[71] Evidence suggests that adapting a guideline to the local context can address these barriers and promote facilitators which increases guideline uptake and utilization.[70]

A **clinical pathway** is defined as a knowledge translation tool often used to implement guidelines in a local context. The pathway will meet all 4 criteria: (1) the intervention was a structured multidisciplinary plan of care; (2) the intervention was used to translate guidelines or evidence into local structures; (3) the intervention detailed the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention had time-frames or criteria-based progression); and (4) the intervention aimed to standardize care for a specific population.[103] Clinical pathways are important knowledge translation tools commonly used for quality improvement by organizing and standardizing patient care which improves patient outcomes and the overall efficiency of the healthcare system.[103]

Our **objective** is to develop a local clinical pathway for pediatric IgA nephropathy in Alberta.

The **goal** of this clinical pathway is to change clinical practice and reduce practice variation.

4.2 Methods

For objective 3, we will adapt the international guideline for pediatric IgA nephropathy that is now in development by IPNA grounded in the Knowledge to Action (KTA) Framework (Figure 6) and the ADPATE Collaboration methodology for guideline adaptation.[70,104] Flores *et al*. from the Center for Evidence-based Practice, University of Pennsylvania designed a 10-step process for a clinical pathway development, adaptation, and implementation based on KTA and ADAPTE frameworks.[105] This 10-step process has been successfully used for the development, adaptation, and implementation of clinical pathways.[105] We will modify this 10-step process for our local pathway development.[105] We will integrate the Capability, Motivation, Opportunity, and Behaviour framework (COM-B) and the Theoretical Domain Framework (TDF) to map barriers and facilitators to guideline implementation as shown in Figure 6.[106–108]

Frameworks

The KTA Framework

The KTA framework was developed in 2006 by Graham *et al*. to aid in the understanding of knowledge creation, knowledge transfer, knowledge implementation, dissemination, and sustainability.[104] This framework is highly recommended by the Canadian Institutes of Health Research (CIHR) and KT (Knowledge Translation) Canada. We selected this framework because it contains all of the components of this thesis, and it is an iterative process that includes knowledge synthesis, adaption, and implementation. This framework also allows for the inclusion of other frameworks at various stages.[105]
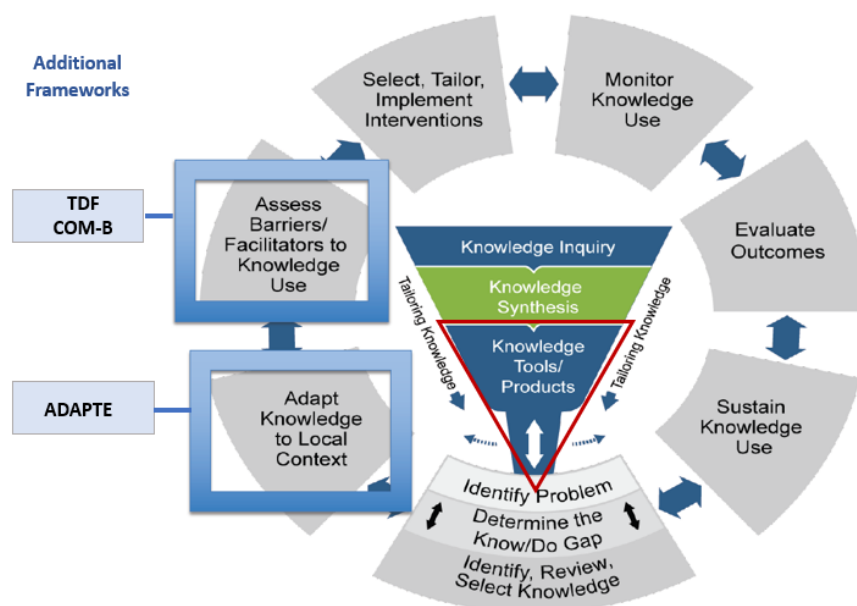
Figure 6: Frameworks integrated into the Knowledge to Action Cycle (KTA) for development and adaptation of a local clinical pathway. Abbreviations: COM-B, Capability, Opportunity, Motivation, and Behaviour framework; TDF, Theoretical Domain Framework. Adapted from Graham *et al.* 2006[104]

The ADAPTE Framework

The ADAPTE framework is designed for adapting national and international guidelines into a local context. This framework was selected because it provides a pragmatic and stepwise approach to guideline adaptation that is modifiable.[70,105] This framework consists of 3 main phases: 1. Planning and set-up 2. Adaptation 3. Development of the final product.

Phases and steps for the adaptation of the local clinical pathway
Phase 1: Project Set-Up
Step 1
1.1 Site and knowledge users
This clinical pathway will be developed locally at the Alberta Children's Hospital. This Southern Alberta pediatric nephrology service has 6 pediatric nephrologists, 2 pharmacists, 1 dietician, 1 social worker, and 1 psychologist. There are several specialized nephrology

nurses who care for patients with kidney diseases. A multidisciplinary team, like ours in Calgary, is integral for optimal patient care for complex kidney diseases.[109] Alberta Children's Hospital has managed approximately 80 children with biopsy-proven IgA nephropathy from 2010 to 2020, reflecting the rarity of this condition among the population of Alberta.

1.2 Target

This clinical pathway is intended for physicians (family physicians, pediatricians, nephrologists, rheumatologists) and allied health professionals involved in the care of children, <18 years, with biopsy-proven IgA nephropathy in Alberta.

1.3 Clinical owner

The owner of this pathway will be someone with clinical experience who is also a decision maker who will be involved throughout the project life cycle and act as a champion for dissemination, implementation, and sustainability. Dr. Susan Samuel and I will share clinical ownership of this pathway for the adaptation phase while Dr. Silviu Grisaru will take ownership of the implementation phase to ensure continuity as he is the Nephrology Section Chief.

1.4 Define the clinical pathway scope

The PICOTS Framework will define the Population, Intervention, Comparison, Outcomes, Timing, and Setting of the clinical pathway as shown in Table 2.[105]

Table 2: PICOTS Framework defining the scope of the clinical pathway. Abbreviation: PICOTS, Population, Intervention, Comparison, Outcomes, Timing, Setting

PICOTS Framework	
Population	Children 1-<18 years with biopsy-proven IgA nephropathy
Intervention	Clinical pathway for the management of IgA nephropathy in children
Comparison	No clinical pathway

Outcomes	Clinical outcome: reduce exposure to steroids and second-line immunosuppressive drugs which may reduce adverse drug events Process outcome: utilization of the pathway, and reduction of practice variation
Timing	The adaptation phase will take 1 year; implementation and assessment of guideline utilization will occur in the second year which is not a part of this project
Setting	Alberta Children's Hospital

Step 2: Key stakeholder group and terms of reference

A multidisciplinary working group will be established which will include and clinical owner, 2 pediatric nephrologists, 1 adult nephrologist, 1 pediatrician, 1 renal pathologist, 1 family physician, 1 pediatric emergency medicine physician, 1 nephrology nurse, 1 nephrology pharmacist, 1 social worker, 1 knowledge translation and implementation expert, 1 patient and 1 parent partner. The group will be responsible for reviewing the evidence and pathway prototypes and deciding how the evidence can be adapted to the local context.

Terms of reference will be drafted for this stakeholder group. The group will have 3 mandatory meetings, the first meeting will be in-person and subsequent meetings will be in-person or hybrid if necessary. Additional meetings may be held at the request of the clinical owners. Meetings will be audio recorded and transcribed with permission from all attendees. Minutes of the meetings will be circulated within 1 week of the last meeting. All documents under review shall be circulated at least 2 weeks before the next meeting.

Phase 2: Evidence review, and pathway development

Step 3: Assessment of the international guidelines and pathways

The international guideline for pediatric IgA nephropathy is in development by IPNA. Our team from Calgary is providing the evidence for this guideline development, the systematic review from objective 1 will contribute to the evidence. The working group for this guideline includes global experts in guideline development, and pediatric and adult IgA nephropathy

specialists. A parent partner and chair of the IgA Nephropathy Foundation is also on this

working group. The guideline is expected to have a first draft by August 2023.

The content, quality, acceptability, and applicability of the recommendations from the

international guideline for pediatric IgA nephropathy will be assessed by the stakeholder

group through meetings. This guideline will be circulated electronically at the establishment

of the stakeholder group for review and feedback.

Step 4: Develop a prototype clinical pathway

A prototype clinical pathway will be created informed by the evidence review and the local

cohort study in objective 2 and uploaded into a cloud-based platform. This document will

also include questions about discordant recommendations.

Step 5: Share the evidence review and prototype pathway

This prototype will be shared via the online platform with the stakeholder group before the

first meeting. The first in-person meeting with the stakeholder group will aim for a 2-hour

duration to review the evidence, any discordant recommendations, and the proposed protocol

pathway. During this process, additional clinical questions may arise which may require

further evidence review.

Step 6: Perform additional targeted rapid evidence reviews as clinical questions arise

During any phase of this process, additional clinical questions may arise which will require

rapid evidence reviews. The clinical owners will perform these rapid reviews according to the

Rapid Review Guidebook by the National Collaborating Centre for Methods and Tools.[110]

 The updated evidence will be circulated to the stakeholder group electronically.

Step 7: Update and refine the pathway prototype

The pathway will be refined after the first in-person meeting and any evidence review as per

steps 5 and 6. The refined pathway will be circulated through an online platform to the

stakeholder group for further comments and recommendations. The final draft must be

approved by all stakeholders before dissemination.

Step 8: Assess barriers and facilitators to the implementation of clinical pathways

Assessing barriers and facilitators to knowledge use is the best predictor of uptake and

sustainability of clinical guidelines and pathways. These determinants should be actively

addressed in the design and pre-implementation phases. Barriers and facilitators to guideline

implementation are well described in the literature, Correa *et al*. published a comprehensive

review of these determinants.[71] We will map these barriers and facilitators identified in the

literature with the COM-B and TDF frameworks to identify key target areas to increase

uptake and sustainability. The COM-B and TDF are chosen because they address barriers and

facilitators to the implementation of tools, guidelines, and educational interventions that

require behavioural change.[106–108,111] We will then have a focus group meeting to discuss

these barriers and facilitators and identify interventions to address the barriers and optimize

facilitators. This focus group with include the key stakeholder group.

Table 3 combines the COM-B and TDF to map barriers and facilitators to the implementation

of clinical guidelines.

Table 3: Mapping COM-B and TDF to barriers, facilitators, and possible interventions.
Abbreviations: COM-B, Capability, Motivation, Opportunity, and Behavior; TDF,
Theoretical Domain Framework.

COM-B	**TDF**	**Determinants**	**Interventions**
Capability	Knowledge Cognitive and interpersonal skills Memory, attention, and decision processes Behaviour regulation Environmental context and resources	Barriers: 1. Limits judgment, treatment, and autonomy 2. Evidence is not based on RCTs Facilitator: 1. Structured management plan for patients	Education: group and one-on-one sessions Posters for each desk and clinic Printed pathway
Opportunity	Social influences: uptake by colleagues will promote behaviour change	Barriers: 1. Existing culture/climate in the work unit 2. Lack of communication between health professionals regarding patient's care plan	Pathway champion Reminders Leadership Reinforcement at rounds

| | | 3. Time constraints, workload

Facilitator:
1. Positive working relationship among health professionals | |
| Motivation | Beliefs about capabilities
Beliefs about consequences
Intentions
Goals of the pathway: it will address risk and benefits of treatments
Reinforcement and emotion | Barriers:
1. Beliefs that the guideline evidence is incorrect or not credible
2. Belief in experiences

Facilitators:
1. Structured management plan for patients can improve patient outcomes
2. Patients can follow treatment course which may improve patient satisfaction | Follow-up education
Audits
Documentation
Champion |

Step 9: Finalize the pathway content and design, and conduct quality assurance

Once all questions are addressed and resolved and there is an agreement, the final clinical

pathway will be designed, this will include the list of clinical owners, stakeholders,

references, goals, and outcomes.

Phase 3: Finalization

Step 10: External review and dissemination

We will circulate the drafted guideline for review by the target audience. Two weeks will be

given for review by the target audience after which comments will be addressed by the

stakeholders as per steps 6-9.

Dissemination of the clinical pathway

We will use a multicomponent dissemination strategy. The local clinical pathway will be

presented at Rounds (Grand rounds, City-Wide Rounds, and Education rounds). This

pathway will be added to the shared computer drive for easy access. Email copies will be

circulated to end users and the pathway will be printed and posted in nephrology clinics and in physicians' workspaces.

Monitoring, evaluation, scale up, and spread

This phase will be done as a future project post-PhD. The SHIELDGN registry is a local registry at Alberta Children's Hospital for children with glomerular diseases such as IgA nephropathy. This registry, along with the cohort study set up in objective 2, will be used to monitor longitudinal treatment and outcomes for children with IgA nephropathy and will provide data on guideline uptake and sustainability.

4.3 Significance

Developing a clinical pathway for the management of IgA nephropathy in children can improve clinical outcomes by reducing ineffective therapy and adverse events while promoting safer options.[112,113] It can encourage physicians to standardize treatment and follow-up, which can improve patient satisfaction as patients can be informed about their treatment course and follow their course. Clinical pathways can be monitored for impact and can contribute to research.[112,114] Adapting the international guideline to the local context will consider local expertise, resources, and fit.[70] The adaption process will involve the end-users in development which can increase awareness and utilization, it will also avoid duplication of efforts to create a guideline.[70]

Chapter 5: Ethics and timeline

5.1 Ethics

Ethics approval is not needed for the systematic review. Ethical approval with be sought from the Conjoint Health Research Ethics Board (CHREB) for the local cohort study and for the development of a local clinical pathway for the management of IgA nephropathy in children. A waiver of consent will be requested from CHREB as per requirement under the Alberta Health Information Act (HIA). PHN will be used to access the charts; data will be stored using a unique identifier that will be linked to the PHN. This link will be in possession by the researcher only and stored safely. No names or other personal identification will be documented. Once analysis is completed, the link will be destroyed, and de-identified data will be stored on AHS drive.
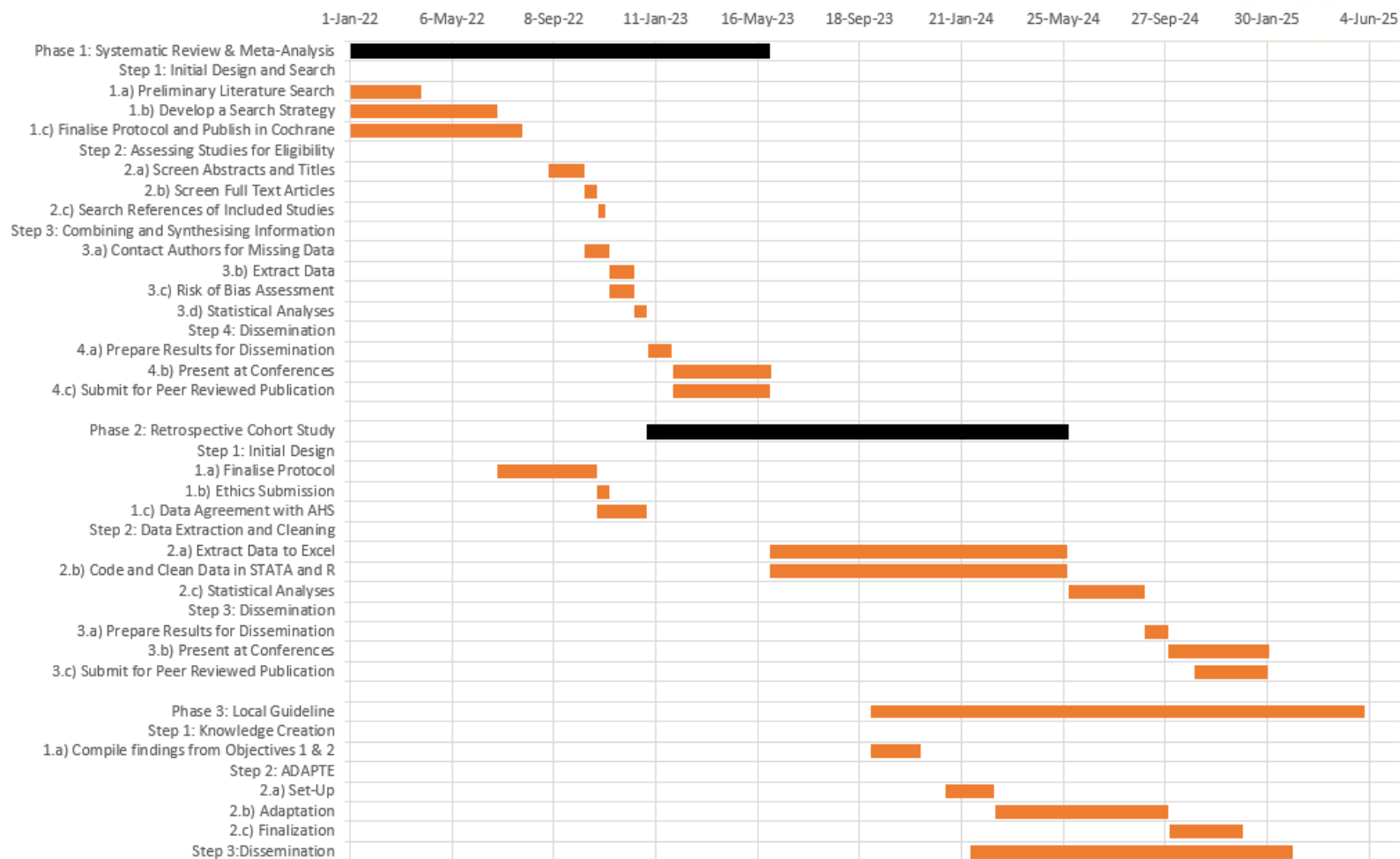
5.2: Timeline

Figure 7: Gantt chart of thesis timeline

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Appendices

Appendix A: Chronic kidney disease (CKD) Staging, Kidney Disease Improving Global Outcome (KDIGO)

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk. GFR, glomerular filtration rate

Foot notes: Heal Map of Chronic kidney disease (CKD) based on glomerular filtration rate (GFR) and proteinuria (albuminuria). CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

Appendix B: Outcomes measures for the systematic review

Outcomes	Outcome measure	Synthesis
Proteinuria	Remission – dichotomous or yes/no as defined by the study	RR or OR, CI, I^2
	Mild/Moderate/Severe or similar qualitative descriptive scale	Summarise
	Absolute proteinuria measurements: • % change • Difference pre and post, time point A versus time point B • Continuous data – measurement (g/L or UPCR)	MD
Haematuria	Gross or microscopic	Summarise
	Change: • Difference pre and post, time point A versus time point B	MD
Kidney function	SCr (µmol/L) • Pre, post absolute change • Rate of change over time • Relative change: doubling of SCr - yes/no eGFR • GFR loss ≥ 50% during follow-up - dichotomous or yes/no • Absolute change (pre, post) • Rate of change Kidney failure • Dialysis, kidney transplant – yes/no • Kidney survival	RR or OR, CI, I^2 Time to event
Infection	Dichotomous or yes/no	RR or OR, CI, I^2 Descriptive
Malignancy	Dichotomous or yes/no	RR or OR, CI, I^2 Descriptive
Diabetes or impaired blood glucose	Dichotomous or yes/no	RR or OR, CI, I^2 Descriptive
Hypertension	Dichotomous or yes/no	RR or OR, CI, I^2 Descriptive
Hospitalisation	Number of hospitalised days	RR or OR, CI, I^2
Death	Death (any cause) - dichotomous or yes/no	RR or OR, CI, I^2
Patient-oriented outcomes	Missed school days – number of days	MD
	Reduced quality of life - scale	RR, CI, I^2 Descriptive
Adverse events	Dropout rate due to treatment related adverse events	Descriptive
	Bone density, fracture or short stature	

Footnotes: CI - confidence interval; eGFR - estimated glomerular filtration rate; MD - mean diLerence; OR - odds ratio RR - risk ratio; SCr - serum creatinine; UPCR - urinary protein:creatinine ratio

Appendix C: Search Strategy for systematic review
DATABASE Search terms

MEDLINE
1. Glomerulonephritis, IGA/
2. iga glomeruloneph$.tw
3. berger$ disease.tw
4. iga nephropath$.tw
5. IgAN$.tw.
6. IgAGN.tw
7. igA-N.tw.
8. immunoglobulin a nephropathy.tw
9. or/1-8
10. adrenal cortex hormones/
11. glucocorticoids/
12. Prednisone/
13. exp Prednisolone/
14. Dexamethasone/
15. (prednisone or prednisolone or dexamethasone or methylprednisolone).tw.
16. Cyclosporine/
17. cyclosporin$.tw.
18. Cyclophosphamide/
19. cyclophosphamide.tw.
20. Azathioprine/
21. azathioprine.tw
22. Mycophenolic Acid/
23. (mycophenolate mofetil or mycophenolic acid).tw
24. Rituximab/
25. rituximab.tw.
26. mizoribine.tw.
27. Leflunomide/
28. leflunomide.tw
29. exp Immunosuppressive Agents/
30. immunosuppressive agent$.tw.
31. or/10-30
32. exp Child/
33. exp Infant/
34. Adolescent/
35. exp Puberty/
36. Pediatrics/
37. exp Schools/
38. (infant* or infancy or newborn* or baby or babies or neonat* or preterm or prematur* or postmatur*
or child* or schoolchild* or school age* or preschool* or kid or kids or toddler* or adolesc*
or teen* or boy* or girl* or minor or minors or pubert* or pubescen* or prepubescen* or paediatric*
or pediatric* or nursery school* or kindergar* or primary school* or secondary school* or
elementary school* or high school* or highschool*).tw.
39. or/32-38
40. and/9,31,39

EMBASE
1. Immunoglobulin a Nephropathy/
2. iga nephropath$.tw.
3. iga glomeruloneph$.tw.
4. berger$ disease.tw
5. IgAGN.tw.
6. igAN.tw.
7. immunoglobulin a nephropathy.tw
8. or/1-7
9. exp corticosteroid/
10. prednisone/
11. prednisolone/
12. dexamethasone/
13. methylprednisolone/

14.cyclosporine/
15.cyclosporin$.tw.
16.cyclophosphamide/
17.cyclophosphamide.tw.
18.azathioprine/
19.azathioprine.tw.
20.mycophenolate mofetil/
21.mycophenolic acid/
22.(mycophenolate mofetil or mycophenolic acid).tw.
23.rituximab/
24.rituximab.tw.
25.mizoribine/
26.mizoribine.tw.
27.leflunomide/
28.leflunomide.tw.
29.exp immunosuppressive agent/
30.or/9-29
31.exp child/
32.exp Infant/
33.adolescent/
34.exp adolescence/
35.school/
36.Pediatrics/
37.(infant* or infancy or newborn* or baby or babies or neonat* or preterm or prematur* or postmatur*
or child* or schoolchild* or school age* or preschool* or kid or kids or toddler* or adolesc*
or teen* or boy* or girl* or minor or minors or pubert* or pubescen* or prepubescen* or paediatric*
or pediatric* or nursery school* or kindergar* or primary school* or secondary school* or
elementary school* or high school* or highschool*).tw.
38.or/9-15
39.and/8,30,38

Appendix D: Outcome definitions and measurements for the Cohort Study

Exposure Variables	Definition	Outcome Measurement	Analysis
Non modifiable variables: At time of kidney biopsy or within 3 months as patients may not be admitted or have labs done at the time of biopsy.			
Age	Age at time of kidney biopsy	Years Calendar year	Descriptive
Sex	Sex at birth	Male Female Unknown	Descriptive
Weight		Kilograms (kg) or converted to kg	
Height		Centimetres (cm) or converted to cm	
Proteinuria	None/mild (A1: dipstick negative/trace, PCR <15 mg/mmol, ACR <30 mg/g),	Dichotomous – Yes/ No	RR or OR, CI, I2
	Moderate (A2: dipstick 1+, PCR 15-50 mg/mmol, ACR 30-300 mg/g), or Severe/nephrotic (A3/A4: dipstick 2+ to 4+, PCR >51mg/mmol, ACR >301 mg/g).	Absolute proteinuria measurements: - % change - Difference pre and post, time point A vs time point B	Mean difference

		Continuous data – measurement (g/l or protein to creatinine ratio)	
		Mild/Moderate/Severe or similar qualitative descriptive scale	Summarize
Remission of proteinuria	Disappearance of proteinuria Trace protein on urine dipstick PCR <30 mg/mmol	Dichotomous – Yes/ No	RR or OR, CI, I² Descriptive
Relapse of proteinuria	Defined as reappearance of proteinuria after remission and meets standard definition for relapse [urine dipstick protein ≥2+ or PCR ≥200 mg/mmol	Dichotomous – Yes/ No	RR or OR, CI, I² Descriptive
Outcomes			
Kidney function	KDIGO definition and staging for CKD (5 stages)	Serum creatinine (μmol/L) - Pre, post absolute change - Rate of change over time - Relative change: doubling of serum creatinine yes/ no Estimated glomerular filtration rate (eGFR) - GFR loss ≥ 25% during follow up - dichotomous (yes/ no) - Absolute change (pre, post) - Rate of change ESKD - Dialysis, renal transplant – (yes/no)	RR or OR, CI, I2, time to event Survival analysis

Footnotes: CI - confidence interval; eGFR - estimated glomerular filtration rate; ESKD – end stage kidney disease; MD - mean diLerence; OR - odds ratio RR - risk ratio; SCr - serum creatinine; UPCR - urinary protein:creatinine ratio

Appendix E: Mapping of the COM-B and TDF with barriers and facilitators

COM-B	TDF	Determinants
Psychological Capability	Knowledge Decision processes Behaviour regulation	Barrier: 1. limits judgment, treatment and autonomy 2. evidence is not based on RCTs Facilitator: Structured management plan for patients
Social Opportunity	Social influences: uptake by colleagues will promote behaviour change	Facilitator: Positive working relationship among HCP
Reflective Motivation	Beliefs about capabilities Beliefs about consequences Intentions Goals: CPG will address risk and benefits of treatments	Barrier: Beliefs that the guideline evidence is incorrect or not credible
Automatic Motivation	Reinforcement and emotion	Facilitator: Structured management plan for patients can improve patient outcomes

Footnote: COM-B: Capability, Motivation, Opportunity and Behavio;. TDF: Theoretical Domain Framework; BCW: Behaviour Change Wheel