INSIGHT NEWSLETTER

VOLUME 8. WINTER 2023

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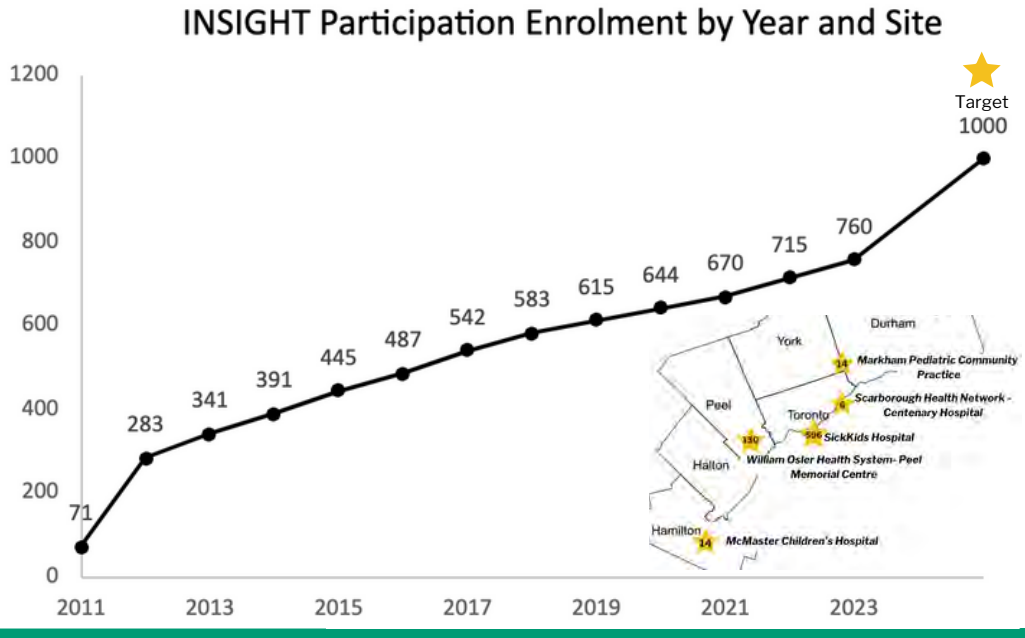
As another year comes to an end, we have officially recruited **760** individuals into the INSIGHT study!

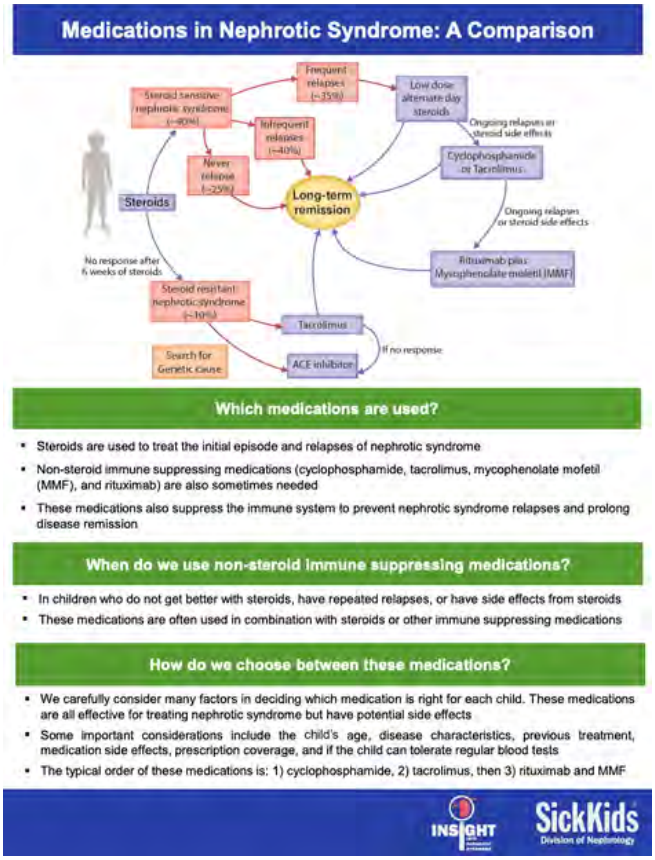


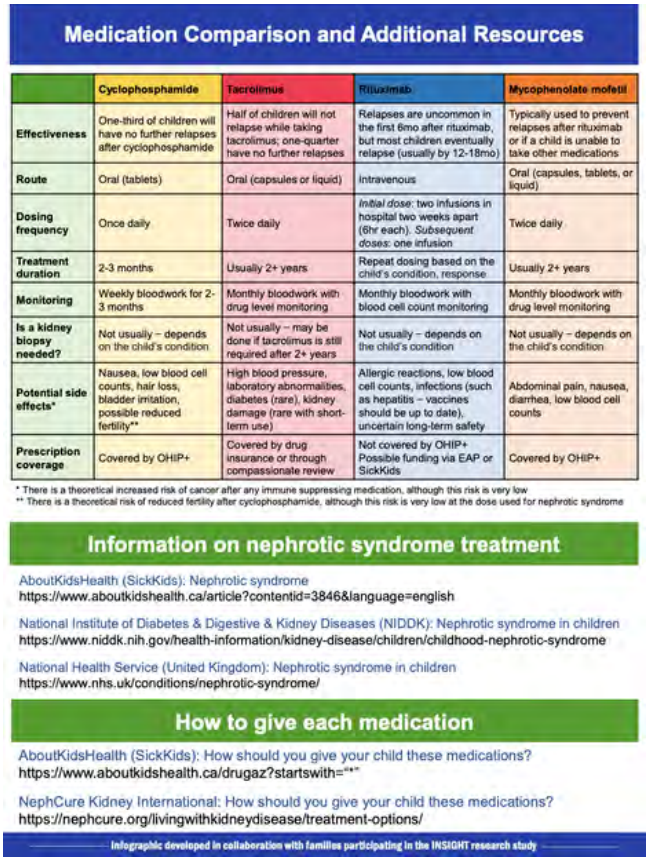
IT'S FINALLY HERE! - INTRODUCING OUR NEW WEBSITE!

Thanks to our Administrative Coordinator, Andrea Verdugo, our newly designed website is now available! This new look features our latest projects, infographics, publications, and educational videos to guide patients and patient families.

★ Click here : https://study.research.sickkids.ca/insight/

NEW INFOGRAPHICS





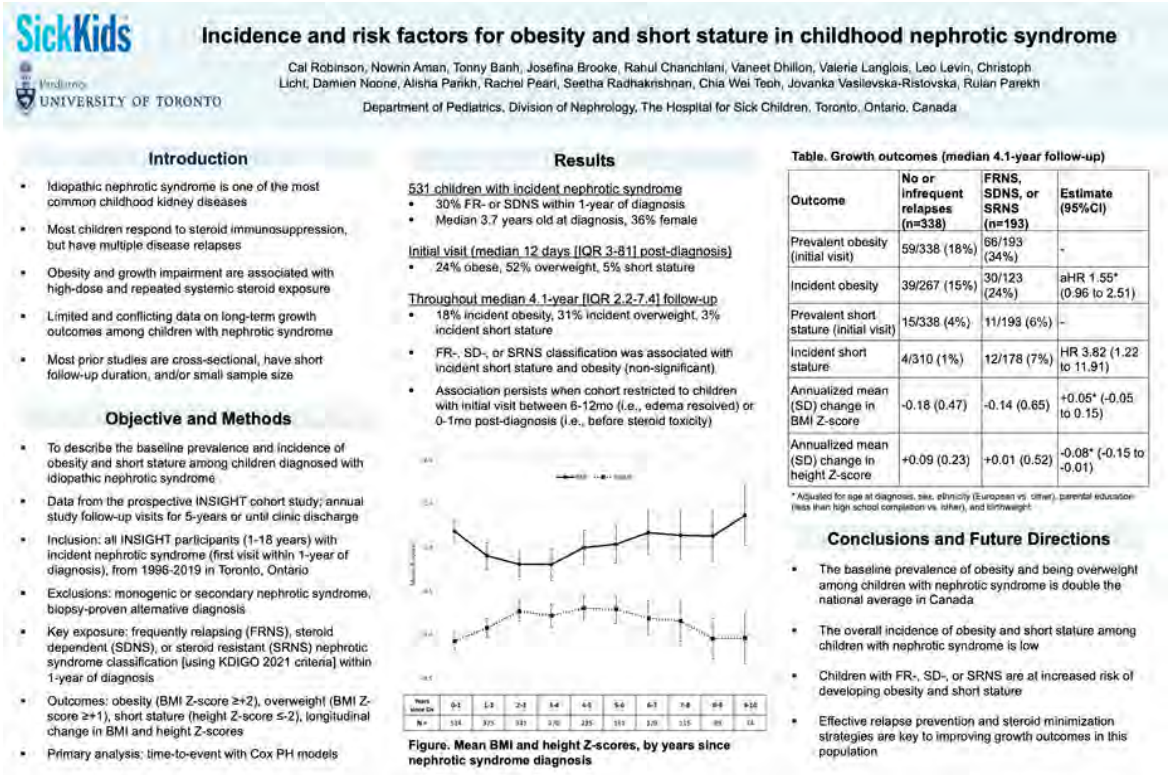
	Cyclophosphamide	Tacrolimus	Rituximab	Mycophenolate mofetil
Effectiveness	One-third of children will have no further relapses after cyclophosphamide	Half of children will not relapse while taking tacrolimus; one-quarter have no further relapses	Relapses are uncommon in the first 6mo after rituximab, but most children eventually relapse (usually by 12-18mo)	Typically used to prevent relapses after rituximab or if a child is unable to take other medications
Route	Oral (tablets)	Oral (capsules or liquid)	Intravenous	Oral (capsules, tablets, or liquid)
Dosing frequency	Once daily	Twice daily	*Initial dose*: two infusions in hospital two weeks apart (6hr each). *Subsequent doses*: one infusion	Twice daily
Treatment duration	2-3 months	Usually 2+ years	Repeat dosing based on the child's condition, response	Usually 2+ years
Monitoring	Weekly bloodwork for 2-3 months	Monthly bloodwork with drug level monitoring	Monthly bloodwork with blood cell count monitoring	Monthly bloodwork with drug level monitoring
Is a kidney biopsy needed?	Not usually – depends on the child's condition	Not usually – may be done if tacrolimus is still required after 2+ years	Not usually – depends on the child's condition	Not usually – depends on the child's condition
Potential side effects*	Nausea, low blood cell counts, hair loss, bladder irritation, possible reduced fertility**	High blood pressure, laboratory abnormalities, diabetes (rare), kidney damage (rare with short-term use)	Allergic reactions, low blood cell counts, infections (such as hepatitis – vaccines should be up to date), uncertain long-term safety	Abdominal pain, nausea, diarrhea, low blood cell counts
Prescription coverage	Covered by OHIP+	Covered by drug insurance or through compassionate review	Not covered by OHIP+ Possible funding via EAP or SickKids	Covered by OHIP+

* There is a theoretical increased risk of cancer after any immune suppressing medication, although this risk is very low
** There is a theoretical risk of reduced fertility after cyclophosphamide, although this risk is very low at the dose used for nephrotic syndrome

If you or a family member is interested in translating the infographics, or want to pitch in ideas, please contact us at **insight.study@sickkids.ca.**

Contact us to receive an electronic copy of our Infographic or on your next visit, ask for a paper copy from the clinic!

RESEARCH UPDATES



SickKids

UNIVERSITY OF TORONTO

Incidence and risk factors for obesity and short stature in childhood nephrotic syndrome

Cal Robinson, Nowrin Aman, Tonny Banh, Josefina Brooke, Rahul Chanchlani, Vaneet Dhillon, Valerie Langlois, Leo Levin, Christoph Licht, Damien Noone, Alisha Parikh, Rachel Pearl, Seetha Radhakrishnan, Chia Wei Teoh, Jovanka Vasilevska-Ristovska, Rulan Parekh

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Introduction

- Idiopathic nephrotic syndrome is one of the most common childhood kidney diseases
- Most children respond to steroid immunosuppression, but have multiple disease relapses
- Obesity and growth impairment are associated with high-dose and repeated systemic steroid exposure
- Limited and conflicting data on long-term growth outcomes among children with nephrotic syndrome
- Most prior studies are cross-sectional, have short follow-up duration, and/or small sample size

Objective and Methods

- To describe the baseline prevalence and incidence of obesity and short stature among children diagnosed with idiopathic nephrotic syndrome
- Data from the prospective INSIGHT cohort study; annual study follow-up visits for 5-years or until clinic discharge
- Inclusion: all INSIGHT participants (1-18 years) with incident nephrotic syndrome (first visit within 1-year of diagnosis), from 1996-2019 in Toronto, Ontario
- Exclusions: monogenic or secondary nephrotic syndrome, biopsy-proven alternative diagnosis
- Key exposure: frequently relapsing (FRNS), steroid dependent (SDNS), or steroid resistant (SRNS) nephrotic syndrome classification [using KDIGO 2021 criteria] within 1-year of diagnosis
- Outcomes: obesity (BMI Z-score ≥+2), overweight (BMI Z-score ≥+1), short stature (height Z-score ≤-2), longitudinal change in BMI and height Z-scores
- Primary analysis: time-to-event with Cox PH models

Results

531 children with incident nephrotic syndrome
- 30% FR- or SDNS within 1-year of diagnosis
- Median 3.7 years old at diagnosis, 36% female

Initial visit (median 12 days [IQR 3-81] post-diagnosis)
- 24% obese, 52% overweight, 5% short stature

Throughout median 4.1-year [IQR 2.2-7.4] follow-up
- 18% incident obesity, 31% incident overweight, 3% incident short stature
- FR-, SD-, or SRNS classification was associated with incident short stature and obesity (non-significant)
- Association persists when cohort restricted to children with initial visit between 6-12mo (i.e., edema resolved) or 0-1mo post-diagnosis (i.e., before steroid toxicity)

Figure. Mean BMI and height Z-scores, by years since nephrotic syndrome diagnosis

Table. Growth outcomes (median 4.1-year follow-up)

Outcome	No or infrequent relapses (n=338)	FRNS, SDNS, or SRNS (n=193)	Estimate (95%CI)
Prevalent obesity (initial visit)	59/338 (18%)	66/193 (34%)	-
Incident obesity	39/267 (15%)	30/123 (24%)	aHR 1.55* (0.96 to 2.51)
Prevalent short stature (initial visit)	15/338 (4%)	11/193 (6%)	-
Incident short stature	4/310 (1%)	12/178 (7%)	HR 3.82 (1.22 to 11.91)
Annualized mean (SD) change in BMI Z-score	-0.18 (0.47)	-0.14 (0.65)	+0.05* (-0.05 to 0.15)
Annualized mean (SD) change in height Z-score	+0.09 (0.23)	+0.01 (0.52)	-0.08* (-0.15 to -0.01)

* Adjusted for age at diagnosis, sex, ethnicity (European vs. other), parental education (less than high school completion vs. other), and birthweight

Conclusions and Future Directions

- The baseline prevalence of obesity and being overweight among children with nephrotic syndrome is double the national average in Canada
- The overall incidence of obesity and short stature among children with nephrotic syndrome is low
- Children with FR-, SD-, or SRNS are at increased risk of developing obesity and short stature
- Effective relapse prevention and steroid minimization strategies are key to improving growth outcomes in this population

Dr. Cal Robinson, presented his poster at the American Society of Nephrology (ASN)

It was found that children with nephrotic syndrome had high rates of obesity at the time of diagnosis, but the risks of developing obesity or short stature later on were low. Children with frequent relapses or resistance to steroids were at higher risk of developing short stature.

INSIGHT Simulation Clinical Trial

We are currently using existing INSIGHT data to simulate a clinical trial comparing the use of tacrolimus and cyclophosphamide to prevent relapses among children with frequently-relapsing or steroid-dependent nephrotic syndrome. Preparations are also underway to launch a new clinical trial next year to determine if low-dose steroids are effective for treating nephrotic syndrome relapses. As a start, we will be reaching out to INSIGHT patients and caregivers in Spring 2024 to ask that you participate in a survey. We want to hear your perspectives on which treatment outcomes are most important to study and how to measure a meaningful difference in those outcomes. Thank you in advance for your participation and help to make our future clinical trial a success!

AWARDS

Dr. Rulan Parekh

2023 American Society of Nephrology , Barbara T Murphy Lifetime Achievement Award

Dr. Cal Robinson

2022 – 2023 Canada Graduate Scholarships Master's Program Award
2022 – 2023 University of Toronto Postgraduate Medical Education Research Award
2022 – present University of Toronto Clinician-Investigator Program Award
2022 – present The Hospital for Sick Children Clinician-Scientist Training Program Award
2023 – 2024 Cure Glomerulonephropathy Consortium Career Development Fellowship Award

STUDY TEAM

Principal Investigator:
Dr. Rulan Parekh

Co-investigators:
Dr. Rachel Pearl
Dr. Valerie Langlois
Dr. Seetha Radhakrishnan
Dr. Christoph Licht
Dr. Damien Noone
Dr. Leo Levin
Dr. Lisa Strug
Dr. Chia Wei Teoh
Dr. Priya Saini
Dr. Mathieu Lemaire
Dr. Ashlene McKay

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Hamilton McMaster Children's Hospital:
Dr. Rahul Chanchlani

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Laura Uribe

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Tonny Banh
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Andrea Verdugo
Mackenzie Garner
Alisha Parikh
Ranie Ahmed
Cal Robinson
Ana Catalina Alvarez Elias
Veronique Rowley

Contact Us:
insight.study@sickkids.ca

Research Award - Grant

2024 - 2028: Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics
Granting agency: Canadian Institutes of Health Research (CIHR)

PI: Rulan Parekh
Co-I's: Dr. A. Dart, Dr. M. Dow nie, Dr. A. Heath, Dr. L. Hiraki, Dr. A. Paterson, Dr. L. Strug, Dr. T. Takano, Dr. A Weins

Dr. Parekh has recently recieved a CIHR project grant to help support the INSIGHT project.

Upcoming Family Appreciation Event 2024!

Following the success and turnout of our last event, we are thrilled to announce the date for our 2024 annual Family Appreciation Event! This year, we will have International speakers joining us to provide study updates.

We get one opportunity to host all our INSIGHT patient and families each year, please come out and allow us to show our gratitude for your ongoing contribution!

Thank You!

Thanking you all for your continued support! We greatly appreciate the time you have taken to be a part of the INSIGHT study. All publications, future work, infographic and study information can be found on our NEW lab website.