Ethnic Disparities in Incidence and Outcomes of Childhood Nephrotic Syndrome

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Supplementary Methods

Nephrotic syndrome treatment protocol

In 1993, a common treatment protocol was implemented and a nurse-managed program was instituted to educate families on home-management of nephrotic syndrome, monitoring, and treatment of relapses. Clinic nurses communicate frequently with the families to ensure adherence to the protocol, especially at disease onset and during relapses. There have been a total of nine nurses managing this program since 1993. The standardized protocol was followed by physicians for children presenting with nephrotic syndrome. Our consensus protocol is similar to the currently reported KDIGO guidelines, with an initial 6 week course of daily prednisone and then tapering to every other day.[1] Prior to October 2002, the taper was over 6 weeks (12 weeks total) and since October 2002, the prednisone is continued for 6 weeks every other day and then tapered over a month (16 weeks total). The specific tapering protocol for prednisone is listed below:

Treatment Protocol (Pre-October 2002)

Initial Treatment only:
60 mg/m^2/day as a single morning dose x 6 weeks (max dose 60 mg/day)
40 mg/m^2/every other day as a single morning dose x 2 weeks (max dose 60 mg/day)
30 mg/m^2/every other day as a single morning dose x 8 days (max dose 30 mg/day)
20 mg/m^2/every other day as a single morning dose x 8 days (max dose 20 mg/day)
10 mg/m^2/every other day as a single morning dose x 12 days (max dose 10 mg/day)

Treatment Protocol (Post-October 2002)

Initial Treatment only:
60 mg/m^2/day as a single morning dose x 6 weeks (max dose 60 mg/day)
40 mg/m^2/every other day as a single morning dose x 6 weeks (max dose 60 mg/day)
30 mg/m^2/every other day as a single morning dose x 8 days (max dose 30 mg/day)
20 mg/m^2/every other day as a single morning dose x 8 days (max dose 20 mg/day)
10 mg/m^2/every other day as a single morning dose x 12 days (max dose 10 mg/day)

Relapse Dosing:
60 mg/m^2/day as a single morning dose until urinary protein is trace/negative for 5 consecutive days then taper:
60 mg/m^2/every other day as a single morning dose x 8 days (max dose 60 mg/day)
50 mg/m^2/every other day as a single morning dose x 8 days (max dose 50 mg/day)
40 mg/m^2/every other day as a single morning dose x 8 days (max dose 40 mg/day)
30 mg/m^2/every other day as a single morning dose x 8 days (max dose 30 mg/day)
20 mg/m^2/every other day as a single morning dose x 8 days (max dose 20 mg/day)
10 mg/m^2/every other day as a single morning dose x 8 days (max dose 10 mg/day)

Cyclophosphamide was the primary second-line medication prescribed to children with frequently-relapsing or steroid-dependent disease. As an alternative to cyclophosphamide, physicians also prescribed calcineurin inhibitors, primarily cyclosporine or tacrolimus, since 1996 and 2003, respectively. Newer biological agents were not used standardly during this period. Renal biopsies were also not part of the routine clinical protocol and indications for biopsy typically included frequently relapsing disease, steroid resistance and/or possible calcineurin toxicity.

Details of ethnic classification

Ethnic origin was classified using the 2011 Statistics Canada National Household Survey (http://www12.statcan.gc.ca/nhs-enm/2011/ref/dict/a1-2-eng.cfm). We classified ethnicity in 591 (83%) of the 711 children. Subject ethnicity was identified using self-report of all 4 grandparents' ethnic origins where available

(n=324), clinical staff involved in their disease management (n=136), medical chart review (n=25) and electronic naming programs (n=106). Statistics Canada classifies ethnicity based on categories such as European, Asian, African, and Latin/Central/South American. Under the category of 'Asians', it is further subdivided into 'West Central Asians/Middle Eastern', 'South Asians', and 'East/Southeast Asians'. West Central Asians/Middle Eastern are from countries such as Afghanistan, Iran, Lebanon and Syria. Children of South Asian ethnicity include those from India, Bangladesh, and Pakistan while East/Southeast Asian children are from countries such as China, Philippines, Tibet and Vietnam. Others include West Central Asians/Middle Eastern, West Indian/Caribbean & African, Latin/Central/South and Aboriginal, multiethnic and unknown.

Ethnicity was determined for 106 children using two electronic naming programs by way of surname analysis, (Nam Pehchan and Quan's Chinese Name List).[2,3] Quan's Chinese Name List categorized patients as Chinese if from China, Taiwan, or Hong Kong, and Nam Pehchan as South Asian if from India, Pakistan or Bangladesh. Kappa demonstrated 100% agreement among East/Southeast Asians and 79.5 % agreement among South Asians.

Supplementary Results

Table S1: **Baseline characteristics of 711 children with nephrotic syndrome from 1993-2014**

	European (n=173)	South Asian (n=237)	East/Southeast Asian (n=69)	West Central Asian/Middle Eastern (n=20)	West Indian/ Caribbean & African (n=33)	Latin/Central/South American & Aboriginal (n=9)	Multi-ethnic (n=50)	Unknown (n=120)
	Mean ± SD/median [Interquartile Range]/n (%)							
Baseline Characteristics								
Male	106 (61.3)	153 (64.6)	43 (62.3)	14 (70.0)	19 (57.6)	4 (44.4)	31 (62.0)	72 (60)
Age of diagnosis (years)	3.7 [2.4-6.8]	3.4 [2.5-5.4]	4.2[2.7-10.8]	3.5 [2.8-6.0]	3.8 [2.7-6.1]	3.8 [2.4-5.2]	3.4 [2.6-5.4]	4.2 [2.7-7.2]
Annual household income [a] (CAD$)	45,987 ± 35,016	29,859 ± 8,596***	31,612 ± 13,220***	31,474 ± 10,156**	33,239 ± 23,866***	26,765 ± 4,739***	35,386 ± 13,306**	34,138 ± 12,350***
Percent of immigrants in neighborhood [a]	21 [10-38]	57 [48-65]***	56 [45-71]***	48 [37-63]***	54 [48-64]***	44 [20-58]	38 [22-50]***	52 [27-63]***
Laboratory Factors [b]								
Serum albumin (g/L)	20 ± 5	18 ± 5***	20 ± 5	18 ± 3*	20 ± 5	20 ± 5	19 ± 4	19 ± 5
Serum creatinine (µmol/L)	34 [28-50]	32 [27-39]*	47 [33-63]*	37 [27-51]	38 [32-50]	31 [16-46]	34 [27-44]	38 [30-48]
Serum cholesterol (mmol/L)	9.92 ± 2.95	11.64 ± 3.25***	10.92 ± 2.59	9.97 ± 2.20	10.62 ± 2.98	10.50 ± 5.02	10.64 ± 3.16	10.65 ± 2.90
Clinical Outcomes[c]								
Complete remission (CR) [d]	26 (15.0)	52 (21.9)	19 (27.5)*	0	5 (15.6)	<5	8 (16.0)	44 (36.7)***
Initial steroid resistance	13 (7.51)	6 (2.53)*	5 (7.24)	0	<5	<5*	<5	<5)*
Steroid dependent at 6 months [e]	17 (10.63)	20 (8.66)	<5	<5	<5	<5*	8 (16.33)	9 (7.63)*
Total relapses over entire follow-up (n) [e]	5 [2-13]	4 [1-8]*	2 [0-6]***	7 [5-16]	4 [2-8]	5 [3-6]	5 [1-9]	1 [0-4]***
Time followed (years)	4.68 [2.66-8.67]	3.63 [1.84-5.97]***	3.53 [1.76-5.95]**	5.55 [2.11-8.67]	4.35 [2.08-5.47]	8.93 [5.72-11.08]	3.98 [2.00-7.98]	2.27 [1.22-4.31]***
Relapses per year [e]	1.12 [0.42-1.72]	1.15 [0.24-1.81]	0.67 [0-1.53]*	1.75 [1.12-2.42]***	1.31 [0.48-1.89]	0.61 [0.45-0.74]*	1.22 [0.62-1.94]	0.52 [0-1.31]***
Biopsy diagnosis	59 (34.1)	50 (21.1)**	24 (34.8)	5 (25.0)	9 (27.3)	5 (55.6)	14 (28.0)	15 (12.5)***
Minimal change disease	32 (54.2)	35 (70.0)	16 (66.7)	<5	6 (66.7)	<5	11 (78.6)	10 (66.7)
Focal segmental glomerulosclerosis	23 (39.0)	14 (28.0)	5 (20.8)	<5	<5	<5	<5	<5
Other	<5	<5	<5	0	<5	0	<5	<5
Use of second-line medication	95 (54.9)	109 (46.0)	31 (44.9)	10 (50.0)	20 (60.6)	6 (66.7)	29 (58.0)	35 (29.2)
Cyclophosphamide	86 (90.5)	99 (90.8)	23 (74.2)*	9 (90.0)	18 (90.0)	6 (100)	24 (82.8)	33 (94.3)
Calcineurin inhibitors [f]	9 (9.48)	7 (6.42)	8 (25.81)*	0	<5	0	<5	<5
CR after cyclophosphamide	29 (33.7)	33 (33.3)	9 (39.1)	<5	9 (50.0)	<5	8 (33.3)	15 (45.4)

Statistical tests conducted with Europeans as the reference group. * p-value ≤ 0.05 using χ^2 or t-test; ** p-value ≤ 0.01 using χ^2 or t-test; *** p-value ≤ 0.001 using χ^2 or t-test; [a] Determined using data from Statistics Canada (2006) based on Dissemination Area; [b] At onset of nephrotic syndrome, albumin (n=332) , creatinine (n=322), and cholesterol (n=291); [c] 6 individuals that never went into remission were excluded from the analysis (n=705) for initial steroid resistance, steroid dependent nephrotic syndrome, total relapses and relapse rate; [d] Complete remission defined as no further episodes of proteinuria requiring medical intervention after the initial course of therapy; [e] 31 individuals with initial steroid resistance were excluded from the analysis (n=680); [f] Includes tacrolimus and cyclosporine. All cells less than 5 were not reported to maintain confidentiality.

Association of ethnicity adjusting for laboratory values with nephrotic syndrome outcomes

High levels of creatinine and cholesterol at disease onset were previously shown to confer a more rapid progression to end-stage renal disease.[4] To account for possible confounding, models were adjusted by laboratory values at disease onset available in only 181 children (n=181).

Nephrotic syndrome outcomes after adjustment for laboratory values by ethnicity are shown in Table S2. Laboratory values measured at onset did not change the outcomes of nephrotic syndrome, while South Asians and East/Southeast Asians remain significantly less likely to develop first relapse.

Table S2. Adjusting for laboratory values at onset (albumin, creatinine, cholesterol)

	European (n=63)	South Asian (n=90)	East/Southeast Asian (n=28)
Frequently relapsing nephrotic syndrome at 12 months			
OR	ref.	0.64	0.15
95% CI	–	[0.18, 2.23]	[0.02, 1.14]
p-value	–	0.48	0.07
Relapse rate			
RR	ref.	0.86	0.58
95% CI	–	[0.52, 1.41]	[0.17, 2.00]
p-value	–	0.54	0.39
Developing first relapse			
HR	ref.	0.78	0.65
95% CI	–	[0.70, 0.87]	[0.43, 0.97]
p-value	–	0.001	0.04
Use of cyclophosphamide as second-line			
HR	ref.	1.16	0.54
95% CI	–	[0.60, 2.36]	[0.22, 1.33]
p-value	–	0.68	0.18

Period effect in outcomes

We conducted stratified analysis before and after 2002 to ensure that there was no period effect with the change in steroid regimen on outcomes (Table S3).

The point estimates were in a similar direction with larger confidence intervals due to limited power in each group.

Table S3. Change in length of initial steroid treatment

	Pre-2002 (12 weeks of steroid treatment)			Post-2002 (16 weeks of steroid treatment)		
	European (n=78)	**South Asian (n=78)**	**East/Southeast Asian (n=27)**	**European (n=82)**	**South Asian (n=153)**	**East/Southeast Asian (n=37)**
Frequently relapsing nephrotic syndrome at 12 months						
OR	ref.	0.46	0.39	ref.	0.71	0.39
95% CI	–	[0.20, 1.06]	[0.10, 1.43]	–	[0.34, 1.47]	[0.11, 1.46]
p-value	–	0.07	0.16	–	0.36	0.16
Relapse rate						
RR	ref.	0.72	0.44	ref.	1.07	0.87
95% CI	–	[0.51, 0.99]	[0.28, 0.71]	–	[0.79, 1.43]	[0.57, 1.34]
p-value	–	0.05	0.001	–	0.66	0.54
Developing first relapse						
HR	ref.	0.83	0.70	ref.	0.73	0.59
95% CI	–	[0.59, 1.17]	[0.42, 1.15]	–	[0.54, 1.00]	[0.37, 0.95]
p-value	–	0.29	0.15	–	0.05	0.03
Use of cyclophosphamide as second-line						
HR	ref.	0.56	0.52	ref.	0.97	0.56
95% CI	–	[0.31, 0.99]	[0.20, 1.35]	–	[0.63, 1.53]	[0.26, 1.23]
p-value	–	0.05	0.18	–	0.92	0.15

Association of ethnicity with outcomes in nephrotic syndrome stratified by average income

We demonstrate statistically significant differences in the average income of Europeans compared to South Asians and East/Southeast Asians (both $p \leq 0.001$). To account for effect modification, an analysis of outcomes was stratified by average income which was grouped into above and below the median ($31,521) of the entire cohort, to determine whether income attenuated the ethnic differences. We consistently demonstrate lower risk in the outcomes of nephrotic syndrome by South Asian and East/Southeast Asian ethnicity regardless of income (Table S4).

Table S4. Average income based on 2006 Statistics Canada dissemination area data

	Average Income ≤ $31,521			Average Income > $31,521		
	European (n=35)	**South Asian (n=137)**	**East/Southeast Asian (n=38)**	**European (n=125)**	**South Asian (n=93)**	**East/Southeast Asian (n=26)**
Frequently relapsing nephrotic syndrome at 12 months						
OR	ref.	0.41	0.29	ref.	0.78	0.50
95% CI	–	[0.20, 0.87]	[0.15, 0.55]	–	[0.70, 0.87]	[0.24, 1.01]
p-value	–	0.02	0.001	–	0.001	0.05
Relapse rate						
RR	ref.	0.68	0.32	ref.	0.70	0.87
95% CI	–	[0.61, 0.76]	[0.12, 0.91]	–	[0.43, 1.15]	[0.69, 1.09]
p-value	–	0.001	0.03	–	0.16	0.22
Developing first relapse						
HR	ref.	0.60	0.54	ref.	0.91	0.64
95% CI	–	[0.43, 0.83]	[0.50, 0.59]	–	[0.80, 1.05]	[0.29, 1.40]
p-value	–	0.002	0.001	–	0.21	0.26
Use of cyclophosphamide as second-line						
HR	ref.	0.80	0.63	ref.	0.84	0.42
95% CI	–	[0.64, 1.00]	[0.61, 0.66]	–	[0.59, 1.20]	[0.32, 0.56]
p-value	–	0.05	0.001	–	0.34	0.001

Outcomes in nephrotic syndrome among all reported ethnic origins

We determined variation in outcomes by other reported ethnic origins. Table S5 outlines the differences in outcomes across all reported ethnic groups that did not have initial steroid resistance or received levamisole. West Central Asian/Middle Eastern and multi-ethnic children show similar outcomes compared to South Asian and East/Southeast Asian children. In contrast, West Indian/Caribbean & African and Latin/Central/South American & Aboriginal children show increased risk compared to Europeans, however, the groups are very small to draw conclusions.

Table S5. Association of childhood nephrotic syndrome with all reported ethnicities

	European (n=160)	South Asian (n=231)	East/Southeast Asian (n=64)	West Central Asian/Middle Eastern (n=20)	West Indian/ Caribbean & African (n=32)	Latin/Central/South American & Aboriginal (n=6)	Multi-ethnic (n=49)	Unknown (n=118)
Frequently relapsing nephrotic syndrome at 12 months								
OR	ref.	0.57	0.38	0.93	0.86	1.85	0.95	0.34
95% CI	–	[0.34, 0.88]	[0.38, 0.39]	[0.39, 2.21]	[0.66, 1.10]	[0.14, 24.57]	[0.59, 1.53]	[0.28, 0.42]
p-value	–	0.01	0.001	0.86	0.23	0.64	0.83	0.001
Relapse rate								
RR	ref.	0.76	0.57	1.41	0.77	0.95	0.85	0.35
95% CI	–	[0.53, 1.11]	[0.30, -1.06]	[1.32, 1.50]	[0.30, 2.02]	[0.67, 1.36]	[0.45, 1.59]	[0.25, 0.51]
p-value	–	0.16	0.08	0.001	0.60	0.78	0.62	0.001
Developing first relapse								
HR	ref.	0.76	0.63	1.40	1.05	1.37	0.75	0.58
95% CI	–	[0.67, 0.87]	[0.53, 0.74]	[0.82, 2.40]	[0.82, 1.35]	[0.73, 2.58]	[0.72, 0.79]	[0.53, 0.63]
p-value	–	0.001	0.001	0.22	0.70	0.33	0.001	0.001
Use of cyclophosphamide as second-line								
HR	ref.	0.82	0.55	0.69	1.37	1.59	1.18	0.39
95% CI	–	[0.51, 1.33]	[0.52, 0.59]	[0.51, 0.95]	[0.48, 3.92]	[1.19, 2.13]	[0.70, 1.99]	[0.34, 0.46]
p-value	–	0.43	0.001	0.02	0.56	0.002	0.54	0.001

Baseline characteristics and outcomes in childhood nephrotic syndrome stratified by neighbourhood immigration status

We conducted an analysis among children with postal code information (n=658) by quartiles based on their neighborhood's percentage of immigrants to determine whether there were any differences

When studying ethnic differences and adjusting for immigration quartiles, it did not attenuate the association with frequently relapsing nephrotic syndrome at 12 months (South Asians-adj OR: 0.35, 95% CI: 0.27,0.44; East/Southeast Asians-adj OR: 0.25, 95% CI: 0.12,0.52), relapse rate per person year (South Asians-adj RR: 0.77, 95% CI: 0.67,0.89; East/Southeast Asians-adj RR: 0.56, 95% CI: 0.51,0.62), developing first relapse (South Asians-adj HR: 0.84, 95% CI: 0.50,1.41; East/Southeast Asians-adj HR: 0.69, 95% CI: 0.45,1.05) and use of cyclophosphamide agent (South Asians-adj HR: 0.74, 95% CI: 0.64, 0.87; East/Southeast Asians-adj HR: 0.48, 95% CI: 0.35, 0.66).

Table S6. Neighbourhood Immigration Status by Quartiles [a]

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	n (%)/median (interquartile range[IQR])			
Baseline Characteristics				
Male	102 (61.8)	101 (61.6)	113 (68.5)	97 (59.2)
Age of diagnosis (years)	3.1 [2.3, 5.1]	4.6 [3.2, 8.4]	4.1 [2.6, 8.2]	3.2 [2.3, 4.7]
Clinical Course				
Complete remission	35 (21.2)	27 (16.5)	38 (23.0)	36 (22.0)
Initial steroid resistance	8 (4.9)	4 (2.5)	11 (6.7)	2 (1.2)
Steroid dependent at 6 months	14 (9.1)	18 (11.5)	11 (7.1)	18 (11.1)
Relapses per year	0.99 [0.23, 1.64]	1.08 [0.38, 1.67]	1.00 [0.08, 1.82]	1.09 [0.28, 1.82]
Clinical Outcomes				
Frequently relapsing nephrotic syndrome				
Odds Ratio [95%CI]	ref.	1.16 [0.60, 2.27]	0.73 [0.36, 1.48]	0.90 [0.61, 1.32]
Adjusted Odds Ratio [95%CI] [b]	ref.	2.36 [1.08, 5.13]*	1.61 [0.53, 4.85]	2.57 [0.76, 8.75]
Relapse rate per person year				
Relative Risk [95%CI]	ref.	0.86 [0.48, 1.52]	0.84 [0.60, 1.18]	0.99 [0.61, 1.62]
Adjusted Relative Risk [95%CI] [b]	ref.	0.98 [0.45, 2.15]	0.98 [0.47, 2.03]	1.23 [0.51, 2.96]
Developing first relapse				
Hazard Ratio [95%CI]	ref.	1.03 [1.02, 1.04]***	0.83 [0.66,1.04]	0.82 [0.81, 0.83]***
Adjusted Hazard Ratio [95%CI] [b]	ref.	1.18 [0.92, 1.52]	0.84 [0.36, 2.01]	0.89 [0.56, 1.44]
Use of cyclophosphamide as second-line				
Hazard Ratio [95%CI]	ref.	1.20 [1.09, 1.33]	1.23 [0.72, 2.10]	0.87 [0.45, 1.68]
Adjusted Hazard Ratio [95%CI] [b]	ref.	1.66 [1.25, 2.18]	1.66 [0.78, 3.53]	1.27 [0.57, 2.80]

Statistical tests conducted with Quartile 1 as the reference group. * p-value $\leq$ 0.05; ** p-value $\leq$ 0.01; *** p-value $\leq$ 0.001;

[a] Quartile 1: 0-27.22%, Quartile 2: 27.22-49.64%, Quartile 3: 49.64-62.62%, Quartile 4: 62.62-100%;

[b] Adjusted for European, South Asian or East/Southeast Asian ethnicity

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