Management of idiopathic childhood nephrotic syndrome in sub-Saharan Africa: Ibadan consensus statement

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Christopher Esezobor[1], Adebowale D. Ademola[2], Adewale E. Adetunji[3], Emmanuel A. Anigilaje[4], Anthony Batte[5], Fatima N. Jiya-Bello[6], Francis F. Furia[7], Uzoamaka Muoneke[8], Mignon McCulloch[9], Peter Nourse[10], Patience Obiagwu[11], Odutola Odetunde[12], Perditer Okyere[13], Adaobi Solarin[14], Elliot K. Tannor[15], Damien Noone[16], Rasheed Gbadegesin[17], Rulan S. Parekh[16] and the Human Hereditary and Health in Africa Kidney Disease Research Network[18]

[1]Department of Paediatrics, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Idi-Araba, Lagos, Nigeria; [2]Department of Paediatrics, Faculty of Clinical Sciences, College of Medicine, University of Ibadan, Ibadan, Oyo State, Nigeria; [3]Department of Paediatrics, Irrua Specialist Teaching Hospital, Irrua, Edo State, Nigeria; [4]Nephrology Unit, Department of Pediatrics, University of Abuja Teaching Hospital, Abuja, Nigeria; [5]Child Health and Development Centre, College of Health Sciences, Makerere University, Kampala, Uganda; [6]Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria; [7]Department of Paediatrics and Child Health, School of Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; [8]Department of Pediatrics, College of Medicine, University of Nigeria, Ituku-Ozalla, Enugu, Nigeria; [9]Red Cross Children's Hospital, Cape Town, South Africa; [10]Red Cross War Memorial Children's Hospital, Cape Town, South Africa; [11]Aminu Kano Teaching Hospital, Nigeria; [12]University of Nigeria Teaching Hospital, Enugu, Nigeria; [13]Department of Internal Medicine, Komfo Anokye Teaching Hospital, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [14]Lagos State University Teaching Hospital, Ikeja, Lagos State, Nigeria; [15]Komfo Anokye Teaching Hospital, Kumasi, Ghana; [16]Division of Nephrology, The Hospital for Sick Children, Toronto, Ontario, Canada; and [17]Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina, USA

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Correspondence: *Rulan S. Parekh, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. E-mail: rulan.parekh@sickkids.ca*

[18]The members of the Human Hereditary and Health in Africa Kidney Disease Research Network are listed in the Appendix.

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In sub-Saharan Africa, glomerular disease, specifically nephrotic syndrome (NS), is the leading cause of chronic kidney disease and end-stage kidney disease in children.[1–3] The prevalence of NS is estimated at 2 to 7 per 100,000 children worldwide,[1] and it is one of the more common causes of pediatric kidney disorders in Africa. Despite limited reports from Nigeria and Sudan,[2–4] the overall incidence of NS in Africa is unknown. Among the 54 African countries, only 17 have information on the burden of childhood NS, indicating substantial under-reporting.[5] The absence of large-scale studies of NS in Africa addressing key questions of incidence and outcomes reflects the limited resources available including medical records, diagnostics, medications, and clinical and research staff. Based on historical data, black children with NS have relatively higher steroid resistance rates than children of other ethnicities throughout Africa,[6–8] and focal segmental glomerulosclerosis is the most common histopathologic diagnosis.[9] Recent studies from several regions in Nigeria recently documented high and increasing rates of steroid responsiveness.[5,10,11]

Treatment guidelines for NS developed in Western countries are not always applicable to low-resource settings,[4] often failing to consider economic issues impacting clinical care, such as access to medications, drug level monitoring, and kidney biopsy.[5]

The Human Hereditary and Health in Africa–Kidney Disease Research Network (H3A-KDRN), was established to conduct genomic studies of kidney disease in sub-Saharan Africa.[12]

Table 1 | Variability in clinical practice among 30 practicing nephrologists across sub-Saharan Africa

Clinical guideline	KDIGO guidelines	IPNA guidelines	Responses from physicians		
			n (%)	Mode (minimum–maximum)	Consensus
Age of child, y	18		30 (100)	18 (12–18)	18
Steroid (prednisone)[a] treatment					
Treatment at initial presentation					
Total duration of prednisone, wk	12	12	30 (100)	12 (8–44)	12–16[b]
Duration of daily prednisone, wk	4–6	4–6	30 (100)	6 (4–30)	6
Duration of alternate-day prednisone, wk	8–20	4–6	30 (100)	6 (0–20)	6
Maximum daily dose of prednisone, mg	60	60	30 (100)	60 (40–100)	60
Maximum alternate-day dose of prednisone, mg	40	40	30 (100)	40 (20–100)	40
Treatment of relapses					
Maximum daily dose of prednisone, mg	60	—	30 (100)	60 (10.0–100)	60
Maximum alternate-day dose of prednisone, mg	40	—	30 (100)	40 (40.0–40)	40
Steroid-sparing treatment[c]					
Levamisole (n = 12)[d]					
Prescribed dose on alternate days, mg/kg	2.5	—	12 (40)[d]	2.5 (1.5–4)	2.5
Minimum duration of treatment, mo	12	—		12 (2–24)	6
Maximum duration of treatment, mo	—	—		24 (6–36)	24
Cyclophosphamide (n = 17)[d,e]					
Prescribed dose, mg/kg per day	2	N/A	17 (57)[d]	2 (2–20)	2
Minimum duration of treatment, wk	8			8 (8–32)	12
Maximum duration of treatment, wk	12			12 (4–72)	12
Calcineurin inhibitors					
Cyclosporine (n = 14)[d]					
Prescribed dose in mg/kg per day (divided into 2 doses)	4–5	3–5	14 (47)[d]	3 (0.5–15)	3–5
Minimum duration of treatment, mo	12	6[f]		6 (3–24)	6
Maximum duration of treatment, mo	—	24		24 (6–48)	24
Monitoring of drug levels during therapy	—	Weekly, then 1–3 mo			
Minimum target trough level, ng/ml	—	80	10 (33)	100 (20–100)	50
Maximum target trough level, ng/ml	—	120		100 (100–200)	100
Tacrolimus (n = 8)[d]					
Prescribed dose in mg/kg per day (divided into 2 doses)	0.1	0.1–0.2	8 (27)[d]	0.1 (0.05–0.5)	0.1 – 0.2
Minimum duration of treatment, mo	12	6[f]		12 (3–24)	6
Maximum duration of treatment, mo	—	24		24 (12–48)	24
Monitoring of drug levels during therapy	—	Weekly, then 1–3 mo			
Minimum target trough level, ng/ml	—	4	7 (24)	5 (3–5)	5
Maximum target trough level, ng/ml	—	8		8 (8–10)	8
Mycophenolate (n = 11)[d]					
Prescribed dose in mg/m^2 per day (divided into 2 doses)	1200	1200	11 (37)[d]	1200 (800–1500)	600
Minimum duration of treatment, mo	12	12		6 (3–24)	6
Maximum duration of treatment, mo	—			24 (6–60)	24
Monitoring of white blood cell during treatment	—		10 (33)		
Frequency of monitoring white blood cells, wk	—			4 (1–12)	4

IPNA, International Pediatric Nephrology Association; KDIGO, Kidney Disease: Improving Global Outcomes; N/A, not available; —, not available in the KDIGO guidelines.
[a]Also may be referred to as prednisolone in some countries.
[b]This accounts for a 6-week daily duration, a 6-week alternate-day duration, and an additional 4 weeks of tapering.
[c]Only 22 physicians responded to this portion of the survey. However, all percentages listed are based on a denominator of 30.
[d]Responses were available only from clinical sites that had access to corresponding steroid-sparing medication.
[e]One clinical center prescribes cyclophosphamide intravenously. The consensus was to prescribe intravenous cyclophosphamide at 500 mg/m^2 per dose, given monthly for 4 months.
[f]Calcineurin inhibitors should be stopped if partial remission is not achieved at 6 months (grade B, moderate recommendation, IPNA guideline).

The network also provides a platform for capacity building and development of consensus clinical guidelines that address variability in care of those with chronic kidney disease. Our aim was to use the network to assess practice variation in management of NS among centers participating in H3A-KDRN, and generate a consensus statement on the management of childhood NS in sub-Saharan Africa using the modified Delphi approach.

RESULTS

The working group included 30 pediatric and/or adult nephrologists from 18 clinical sites across 6 countries who completed a survey on NS management in children/adolescents and participated in the consensus meeting (Supplementary Figure S1).

There was significant variation in clinical practice, specifically the hospital policy on age of a child, dose and duration of prednisone, and choice of steroid-sparing agents (Table 1).

Table 2 | Summary of the consensus agreement compared with the KDIGO glomerulonephritis and IPNA guidelines

KDIGO	IPNA	Consensus agreement
Definitions of nephrotic syndrome in children		
Relapse: uPCR ≥2000 mg/g (≥200 mg/mmol) or ≥3+ protein on urine dipstick for 3 consecutive days	Relapse: urine dipstick ≥3+ protein for 3 consecutive days or uPCR ≥2000 mg/g (≥200 mg/mmol)	Relapse: ≥2+ proteinuria for 3 consecutive days on an early morning urine or ≥2+ proteinuria with edema
Remission: uPCR <200 mg/g (<20 mg/mmol) or <1+ of protein on urine dipstick for 3 consecutive days	Remission: uPCR <200 mg/g (<20 mg/mmol) or <1+ of protein on urine dipstick for 3 consecutive days	Remission: trace/negative for at least 3 consecutive days on urine dipstick only

KDIGO guideline number	KDIGO recommendation statement	IPNA guidelines	Summary of the consensus agreement
3.1.1	We recommend that corticosteroid therapy (prednisone or prednisolone) be given for at least 12 wk (1B)	Prednisone therapy for 10–12 wk	We agreed on the total duration of prednisone therapy for up to 16 wk to account for tapering of steroids, similar to KDIGO guidelines
3.1.1.1	We recommend that oral prednisone be administered as a single daily dose (1B) starting at 60 mg/m^2 per day or 2 mg/kg per day to a maximum of 60 mg/d (1D)	The initial treatment of children with idiopathic NS usually comprises oral prednisone 60 mg/m^2 per day or 2 mg/kg per day (maximum, 60 mg/d)	We agreed that oral prednisone be administered for the initial episode of NS as a single daily dose at 60 mg/m^2 per day, up to a maximum of 60 mg
3.1.1.2	We recommend that daily oral prednisone be given for 4–6 wk (1C) followed by alternate-day medication as a single daily dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum, 40 mg on alternate days) (1D) and continued for 2–5 mo with tapering of the dose (1B)	Oral prednisone is given for 4–6 wk followed by 40 mg/m^2 or 1.5 mg/kg per dose on alternate days for another 4–6 wk	We agreed on daily oral prednisone at 60 mg/m^2 per day up to a maximum of 60 mg as a single daily dose for 6 wk followed by 40 mg/m^2 prednisone as a single morning dose on alternate days for another 6 wk and thereafter tapered at the rate of 10 mg/m^2 per week to 5 mg on alternate days The dose of the prednisone should be discontinued once tapered down to 5 mg on alternate days Total duration of therapy will be 16 wk
3.2.1.1	We suggest that infrequent relapses of SSNS in children be treated with a single-daily dose of prednisone 60 mg/m^2 or 2 mg/kg (maximum, 60 mg/d) until the child has been in complete remission for at least 3 days (2D)	N/A	We agreed, consistent to KDIGO guidelines, 60 mg/m^2 (maximum, 60 mg/d) oral prednisone for relapse daily until remission (urine dipstick trace/negative for at least 3 consecutive days)
3.2.2.1	We suggest that relapses in children with FR or SD SSNS be treated with daily prednisone until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 mo (2C)	N/A	We agreed for relapse to be treated with oral prednisone 60 mg/m^2 (maximum, 60 mg/d) daily until remission (urine dipstick trace/negative for at least 3 consecutive days) Once in remission, decrease prednisone to 40 mg/m^2 per day (maximum, 40 mg/d) on alternate days for 1 wk, then taper by 10 mg/m^2 per day per week to complete a total of 4 wk Similar to the initial course, all doses to be rounded up to account for 5-mg tablets
3.3.2	We recommend that alkylating agents, cyclophosphamide, or chlorambucil be given as corticosteroid-sparing agents for FR SSNS (1B) We suggest alkylating agents, cyclophosphamide, or chlorambucil be given as corticosteroid-sparing agents for SD SSNS (2C)	N/A	We agreed to use levamisole as the first-line steroid-sparing agent if available and then cyclophosphamide
3.4.1	Indications for kidney biopsy in children with SSNS are as follows (not graded): late failure to respond after initial response to corticosteroids; a high index of suspicion	Quantification of proteinuria by urine protein/creatinine ratio in either first morning urine or 24-hour urine sample at least once before defining SRNS and/or	Indications for kidney biopsy in children with SSNS: late-onset steroid resistance; suspicion of a secondary cause of disease; assessment of CNI nephrotoxicity; NS

(*Continued on following page*)

Table 2 | (Continued) **Summary of the consensus agreement compared with the KDIGO glomerulonephritis and IPNA guidelines**

KDIGO guideline number	KDIGO recommendation statement	IPNA guidelines	Summary of the consensus agreement
	for a different underlying pathology; decreasing kidney function in children receiving CNIs	starting alternate immunosuppression Use this baseline value for assessing subsequent response (Grade A, strong recommendation)	diagnosis before the age of 1 year or older than the age of 12 yr
4.1.1	We suggest a minimum of 8 wk of treatment with corticosteroids to define steroid resistance (2D)	Lack of complete remission within 4 wk of treatment with prednisone at standard dose If no remission is achieved by 6 wk, the diagnosis of SRNS is confirmed	We agreed to define steroid resistance as lack of response to daily prednisone after 8 wk of therapy consistent with definition in KDIGO guidelines
4.1.2	The following are required to evaluate the child with SRNS (not graded): a diagnostic kidney biopsy; evaluation of kidney function by GFR or eGFR; quantitation of urine protein	A renal biopsy in all children diagnosed with SRNS, except in known infection or malignancy-associated secondary disease or potentially in patients with familial and/or syndromic cases or genetic causes of SRNS (grade A, strong recommendation) Genetic testing results (grade B, moderate recommendation) as soon as possible, ideally within the 2-wk confirmation period In low-resource countries where genetic and/or histopathology assessment is not available, immediate immunosuppressive treatment with CNI may be started If CNIs are not available, intravenous or oral cyclophosphamide may be started	We agreed to evaluate the child with SRNS with the following: percutaneous kidney biopsy to ascertain histopathology and guide treatment (the light microscopy with special immunohistochemistry stains if immunofluorescence and electron microscopy are not available); evaluation of kidney function with serum creatinine measurement to estimate GFR; quantification of uPCR instead of the 24-hour urine collection Prescribe CNI if biopsy not readily available in the country
4.2.1.1	We suggest that CNI therapy be continued for a minimum of 6 mo and then stopped if a partial or complete remission of proteinuria is not achieved (2C)	We suggest a minimum treatment period of 6 mo to determine the response to CNIs (grade B, weak recommendation) We recommend that CNIs should be stopped if partial remission is not achieved at 6 mo (grade B, moderate recommendation)	We agreed to use CNI therapy for SRNS for a minimum of 6 mo to assess response
4.2.1.2	We suggest CNIs are continued for a minimum of 12 mo when at least a partial remission is achieved by 6 mo (2C)	If complete remission is achieved, CNI dosages should be reduced to the lowest dosage required to maintain remission We also suggest considering discontinuation of CNIs after 12–24 mo in these patients to reduce the risk of nephrotoxicity (grade C, weak recommendation)	We agreed CNI be continued for up to 2 yr when at least partial response is achieved by 6 mo

CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; FR, frequently relapsing; IPNA, International Pediatric Nephrology Association; KDIGO, Kidney Disease: Improving Global Outcomes; N/A, not available; NS, nephrotic syndrome; SD, steroid-dependent; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; uPCR, urine protein to creatinine ratio.

Most nephrologists were managing children/adolescents using the Kidney Disease: Improving Global Outcomes Guideline (KDIGO) for Glomerulonephritis. Adult nephrologists used adult guidelines for adolescents.[4] We agreed that the consensus statement would be applicable in the management of children younger than age 18 years.

Modification of KDIGO definitions/guidelines

The KDIGO recommendation statements on steroid-sensitive and steroid-resistant NS and the agreed upon modifications for low- to middle-income African countries also were compared with the recently published International Pediatric Nephrology Association guidelines (Table 2).[13]

Initial treatment for steroid-sensitive NS. The duration of the initial prednisone treatment varied considerably, although most nephrologists followed the recommended duration of 6 weeks daily and 6 weeks alternate-day corticosteroid as a single daily dose (Figure 1a). The majority of nephrologists used 2 mg/kg or 60 mg/m^2 per day to a maximum of 60 mg. When switching to alternate-day dosing, the majority chose 1.5 mg/kg or 40 mg/m^2 per day, to a maximum daily dose of 40 mg (per day) (Table 1).

We agreed to manage the initial episode of NS with oral prednisone at 60 mg/m^2 per day (maximum, 60 mg) as a single daily dose for 6 weeks, followed by 40 mg/m^2 (maximum, 40 mg) prednisone as a single morning dose on alternate days for another 6 weeks. Prednisone thereafter should be tapered at a rate of 10 mg/m^2 per week to 5 mg on alternate days (total cumulative dose, 3595 mg/m^2 for a total of 16 weeks). Because the lowest dose available is 5-mg tablets, not suspension, we recommended that all doses be rounded to up to 5 mg accordingly, and, if at the lowest dose

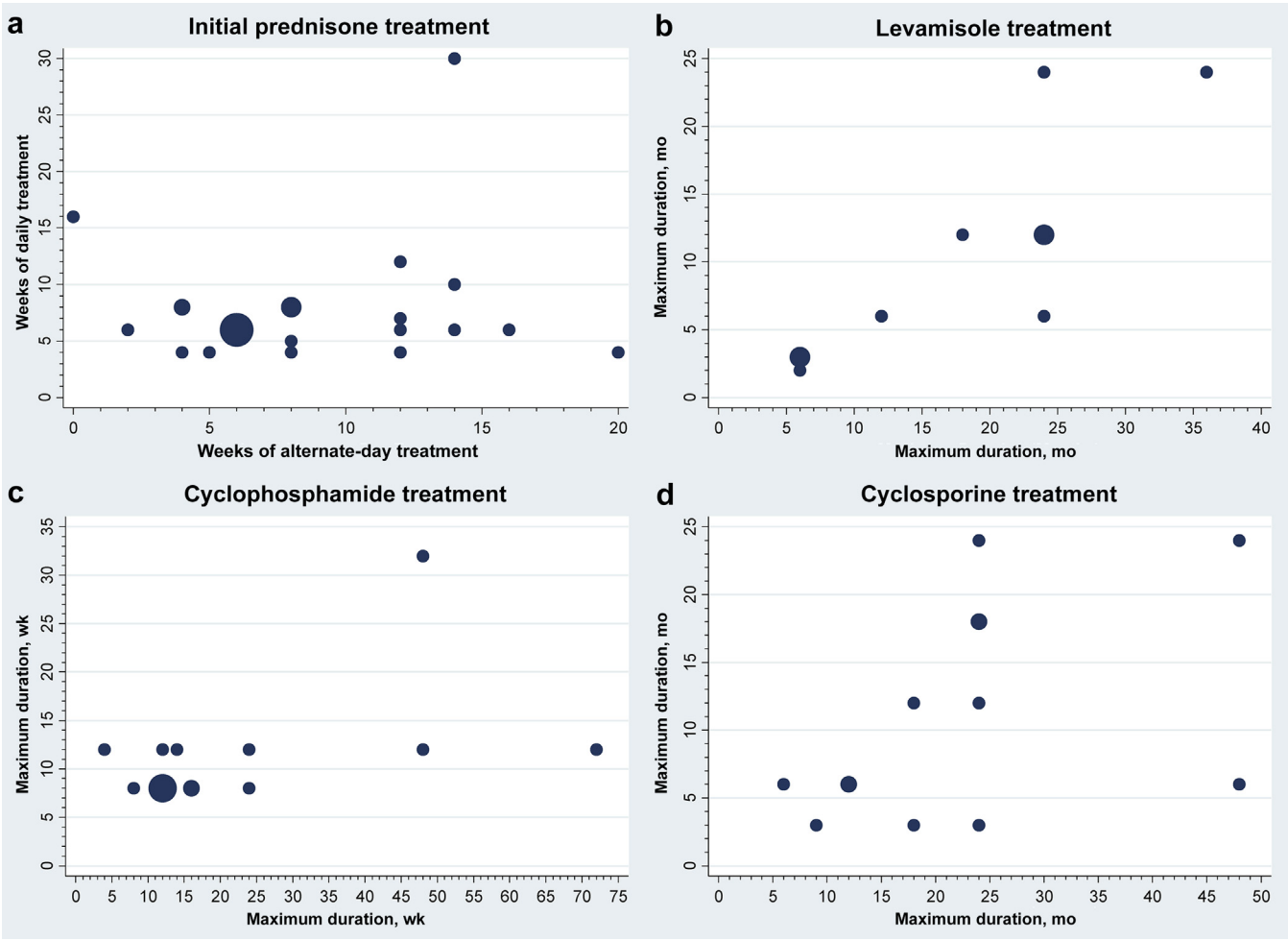

Figure 1 | Bubble plots show the responses from the survey based on the type of therapy used in nephrotic syndrome by the duration of use, and the size of the bubble represents the number of responses. (**a**) Initial prednisone treatment for steroid-sensitive nephrotic syndrome; (**b-d**) treatment with steroid-sparing medications.

of 5 mg, maintain it until the end of the 16th week (different from KDIGO, in which further tapering is specified).[4]

Treatment of relapses. Variations in practice also were noted for treatment of relapses (Table 1). Recommended treatment for relapses should include oral prednisone 60 mg/m^2 (maximum, 60 mg/d) daily until remission. Once in remission, we recommend decreasing to 40 mg/m^2 per day (maximum, 40 mg [per day]) on alternate days for 1 week, and then taper by 10 mg/m^2 per day per week to complete a total of 4 weeks of treatment.

For frequently relapsing (FR)/steroid-dependent (SD) steroid-sensitive nephrotic syndrome, approximately 90% of respondents use maintenance alternate-day prednisone for at least 3 months, with most choosing the lowest dose to maintain remission. In line with current KDIGO guidelines, and similar to the protocol described earlier, we recommend prednisone to treat relapses for up to 3 months at the recommended relapse dosing.

We agreed to not prescribe prophylactic prednisone for relapse prevention in children with FR/SDNS already on low-dose, alternate-day during episodes of malaria, however, we agreed to use it for upper respiratory infections pending results of clinical trials.

Use of steroid-sparing agents in FRNS and SDNS. Choice of steroid-sparing agent, drug route, and dose varied across the continent, and within each country, as described in Tables 1 and 3 and shown in Figures 1b–d and 2a. Steroid-sparing agents should be initiated once the patient is in remission, using either an alkylating agent (cyclophosphamide, chlorambucil), levamisole, calcineurin inhibitors (cyclosporine, tacrolimus), mycophenolate mofetil, or rituximab, based on availability.

The availability of levamisole varies across the continent. If available, it is affordable in resource-constrained regions and in packages of three 40-mg tablets. Doses range from 1.5 to 4 mg/kg, with the most commonly prescribed dose of 2.5 mg/kg on alternate days (Figures 1b and 2a). Mild to moderate reversible neutropenia requires monthly monitoring of white blood cell count. Cost effectiveness, proven efficacy, and a favorable safety profile supports its use as a steroid-sparing agent and led the consensus panel to consider levamisole as

Table 3 | Steroid and steroid-sparing agent cost for treatment of nephrotic syndrome in children

Medication	Used to treat FRNS[a]/ SDNS[b]	Used to treat SRNS[c]	Medication type/ formulation[d]	Cost (USD)/tablet						Average monthly cost, USD[j,k]
				Cameroon[e]	Ghana[f]	Nigeria[g]	South Africa[h]	Tanzania[i]	Uganda[j]	
Steroids[l] (*Prednisone/ Prednisolone*)	✓	✓	Generic 5-mg tablets	0.3	0.02	0.01	0.01	0.03	0.013	15.79 ± 28.68
Levamisole[m]	✓		Generic 50-mg tablets	—	—	0.09	—	—	0.135	1.39 ± 0.39
			Brand name 50-mg tablets	—	—	0.16	—	0.01	—	1.05 ± 1.31
Cyclophosphamide[n]	✓		Generic 25-mg capsules	—	—	—	—	—	—	—
			Brand name 50-mg capsules/tablets	0.38	0.31	0.25	0.265	0.50	0.41	6.98 ± 1.89
			IV 500 mg /vial	—	2.20	3.00	5.50	—	2.80	2.32 ± 1.00
			1 g/vial	—	4.00	4.80	8.00	4.60	4.20	1.76 ± 0.56
Cyclosporine[o]	✓	✓	Generic 50 mg	—	—	0.83	—	1.30	1.40	58.24 ± 15.06
			Brand name 25-mg tablets	—	—	1.84	0.252	1.75	0.69	140.21 ± 97.26
			50-mg tablets	—	1.56	—	—	2.60	—	102.96 ± 36.40
			100-mg tablets	—	—	7.32	—	2.60	2.00	98.34 ± 72.12
Tacrolimus[p]	✓	✓	Generic 0.5-mg tablets	—	—	1.30	—	—	0.55	183.15 ± 105.00
			1-mg tablets	—	2.00	1.72	—	—	0.88	151.80 ± 57.70
			3-mg tablets	—	9.38	—	—	—	—	309.54
			5-mg tablets	—	10.00	—		—	—	198.00
			Brand name 0.5-mg tablets	—	—	—	0.56	2.60	0.67	252.78 ± 227.18
			1-mg tablets	—	—	3.45	2.20	2.60	0.93	227.20 ± 103.82
			5-mg tablets	—	—	—	—	3.30	—	65.34
Mycophenolate Mofetil (MMF)[q]	✓		Generic 250-mg tablets	—	0.354	—	—	—	—	17.51
			500-mg tablets	—	0.416	2.70	0.29	—	1.20	28.48 ± 27.40
			Brand name 250-mg tablets	—	—	—	0.167	—	—	8.26
			500-mg tablets	—	1.875	13.50	—	2.40	1.33	118.13 ± 144.24

FRNS, frequently relapsing nephrotic syndrome; IV, intravenously; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome.
[a]Defined as 2 or more relapses within the first 6 months of diagnosis or 4 or more relapses within any 12-month period.
[b]Defined as 2 or more relapses during the steroid taper or 1 relapse within 14 days of steroid cessation.
[c]Defined as no response to steroids within 8 weeks of treatment.
[d]Multiple medications have different brand names available by country and source of medication; individual names for all countries were not provided. Brand names listed are from Uganda (Prednisolone: Kam Predisol, Kampala Pharmaceuticals Industries 1996 Limited, Kampala, Uganda; Levamisole: Argotrax [Ergamisole], Agog Pharma Ltd, India; Cyclophosphamide: Cytoxan, Baxter Healthcare Corporation, Germany; Cyclosporine: Capimune, Mylan, UK; Neoral, Novartis Pharma Services Inc, Germany; Tacrolimus: Advagraf and Prograf, Astellas Pharma, UK; Mycophenolate Mofetil: Mofilet [Mofetil], Emcure Pharmaceuticals Ltd, India; Cellcept, Roche Pharma, Germany; and Nigeria [Prednisolone: specific brand available; Levamisole: Argotrax, Agog Pharma Ltd, India; Levamisole: Retrax [not mentioned in the manuscript] manufactured by Reals Group located in Lagos, Nigeria; Cyclophosphamide: other brands not mentioned in the manuscript available; Cyclosporine: Neoral, Novartis, Switzerland; Tacrolimus: Prograf, Astellas, Tokyo, Japan; Mycophenolate Mofetil: Teva, Petah Tikva and New Jersey, USA, and Israel; Cellcept, Roche, Basel, Switzerland).
[e]1 USD is approximately 565 XAF (Central African Franc).
[f]1 USD is approximately 4.80 GH¢ (Ghanaian Cedi).
[g]1 USD is approximately 360 ₦ (Naira).
[h]1 USD is approximately 15 R (South African Rand).
[i]1 USD is approximately 2285 TZS (Tanzanian Shilling).
[j]1 USD is approximately 3650 UGX (Uganda Shilling).
[k]Average monthly cost was calculated based on a 4-year-old boy at the 50th percentile for height (103 cm) and weight (16.5 kg) based on World Health Organization guideline growth curves with an estimated surface area of 0.687 m^2.
[l]**Route:** oral; **dose:** 60 mg/m^2 per day (maximum daily dose, 60 mg) until remission for 3 days, then 40 mg/m^2 per day (maximum daily dose, 40 mg/d), alternate days for 1 week, then taper by 10 mg/m^2 per day per week; **duration:** minimum, 3 days (immediate remission) + 4 weeks, maximum, number of days it takes to achieve remission + 4 weeks; monthly cost was calculated based on a full dose daily for 30 days.
[m]**Route:** oral; **dose:** 2.5 mg/kg alternate days; **duration:** 6 months to determine effectiveness, if effective, 2 years.
[n]**Route:** oral; **dose:** 2 mg/kg per day; **duration:** 3 months; **OR route:** i.v.; **dose:** 500 mg/m^2 per month; **duration:** 4 months.
[o]**Route:** oral; **dose:** 3 to 5 mg/kg per day divided twice daily; **duration:** 6 months to assess response, up to 2 years; monthly cost was calculated based on 5 mg/kg per day.
[p]**Route:** oral; **dose:** 0.1 to 0.2 mg/kg per day divided twice daily; **duration:** 6 months to assess response, up to 2 years; monthly cost was calculated based on 0.2 mg/kg per day.
[q]**Route:** oral; **dose:** 600 mg/m^2 per dose twice daily; **duration:** 6 months to determine effectiveness, if effective, 2 years.

the first-line, steroid-sparing agent if available.[3] Children should be prescribed levamisole for at least 6 months to determine its effectiveness, and use for up to 24 months if effective, allowing for repeated courses.

Cyclophosphamide is efficacious in sustaining a remission or reducing relapse frequency when given for 8 to 12 weeks.[3,6] It typically is used at 2 mg/kg per day. Four sites in Uganda, Tanzania, Nigeria, and Ghana use intravenous cyclophosphamide at 10 to 20 mg/kg per dose (maximum, 750 mg), owing to hospital funding. Among 17 nephrologists who prescribe cyclophosphamide, only 3 prescribe it after inducing remission with prednisone. White blood cell count is monitored by all centers, on average, every 4 weeks (range, 1–12 wk).

By consensus, cyclophosphamide is the preferred option for treatment of FR/SDNS if levamisole is not available. The route of administration depends on access and cost. Intravenous cyclophosphamide is an alternative if availability, cost, or adherence to treatment precludes the use of an oral formulation. We agreed to oral cyclophosphamide for a maximum of 12 weeks (total cumulative dose, 168 mg/kg) or intravenous cyclophosphamide 500 mg/m^2 per dose given monthly for a maximum of 4 months (Figure 1c). We suggest close monitoring, with complete blood counts within 2 weeks of therapy, and every 4 weeks thereafter. For intravenous cyclophosphamide, we recommend complete blood counts within 1 to 2 weeks of therapy, and before each infusion. We do not recommend repeated courses of cyclophosphamide.

Cyclosporine is prescribed at a median of 3 mg/kg per dose twice daily, however, the duration of treatment varies (Figure 1d). Only 11 of 19 sites perform a kidney biopsy before starting cyclosporine and only South Africa conducts surveillance biopsies. Drug monitoring is available in only 3 countries. If measured, target trough levels of cyclosporine varied from 20 to 100 ng/ml. Although generic tacrolimus is available, availability across the continent remains limited.

The working group chose cyclosporine as the calcineurin inhibitor of choice, and recommend its use for a minimum of 6 months to assess response, for up to 24 months with monthly serum creatinine measurements, and, if possible, cyclosporine 12-hour trough level monitoring targeting 50 to 100 ng/ml. Relapses after discontinuation of cyclosporine may occur, therefore, if possible, we recommend a kidney biopsy before reinitiating cyclosporine, to assess for nephrotoxicity.

The working group agreed to use mycophenolate mofetil when other steroid-sparing agents have failed. We agreed to use 600 mg/m^2 per dose twice a day with a minimum trial of 6 months to determine responsiveness and continue for up to 24 months of therapy. Repeated courses with mycophenolate mofetil can be used. We agreed to monthly monitoring of white blood count.

Use of immunosuppressive agents in steroid-resistant nephrotic syndrome. Consistent with KDIGO guidelines, steroid resistance was reported as the lack of response to treatment after 8 weeks of therapy by 40% of participants (Figure 2b).

The duration of the calcineurin inhibitor varied considerably from 3 months to as long as 48 months, and in some centers in combination with low-dose prednisone. If children relapsed while on therapy, prednisone often was used to induce remission. Some centers still use cyclophosphamide owing to low cost and availability, despite contrary evidence.[6] The working group agreed that the drug of choice for steroid-resistant nephrotic syndrome (SRNS) is a calcineurin inhibitor, with a similar dosing regimen and duration for FRNS, but not cyclophosphamide.

Kidney biopsies are performed in children with steroid resistance in most centers. Nine centers outsource pathology review to countries within and outside of Africa. All centers agreed that a biopsy should be performed in children with SRNS, even though not routinely accessible.[4] Treatment of SRNS should be guided by biopsy findings based on light, immunofluorescent, and electron microscopy, however, the working group agreed that light microscopy with special immunohistochemistry stains may be used if immunofluorescence and electron microscopy are unavailable (Table 2). Kidney biopsy reports should include the extent of glomerulosclerosis and interstitial fibrosis.

DISCUSSION

International guidelines apply evidence-based medicine to clinical practice with the goal of improved patient outcomes, however, there are region-specific limitations and low-resource–setting issues that need to be considered.

Significant variations in all aspects of clinical practice exist in management of childhood NS among African nephrologists, both between and within participating African countries. The main differences were order of choice for steroid-sparing agents for the treatment of SRNS, and use of intravenous cyclophosphamide for the treatment of FR/SDNS because of financial constraints. Some aspects of care did not align with best available evidence because approximately 40% of nephrologists prescribed cyclophosphamide for SRNS despite well-documented evidence of ineffectiveness in the treatment of SRNS. This practice is driven mainly by cost and availability, key factors in decision making.[3] Designation of the child's age for care by a pediatric nephrologist is based on the health care system and can greatly affect the initial steroid management. Recent randomized clinical trials and systematic reviews do not support a longer initial prednisone course, however, African children were not included in these trials (Supplementary Tables S1 and S2).

For the treatment of the initial episode of NS, consensus was in agreement with the International Pediatric Nephrology Association guidelines for the dose and duration of steroids. The consensus to define steroid resistance as a lack of response to daily prednisone after 8 weeks was based on the possible issues of adherence or access to medications in Africa. This definition does vary from the new International Pediatric Nephrology Association Guidelines on SRNS, which recommends confirming SRNS if no remission is achieved by 6 weeks.[13]

Variations in the duration of steroid therapy before diagnosis of SRNS may explain the wide range of steroid

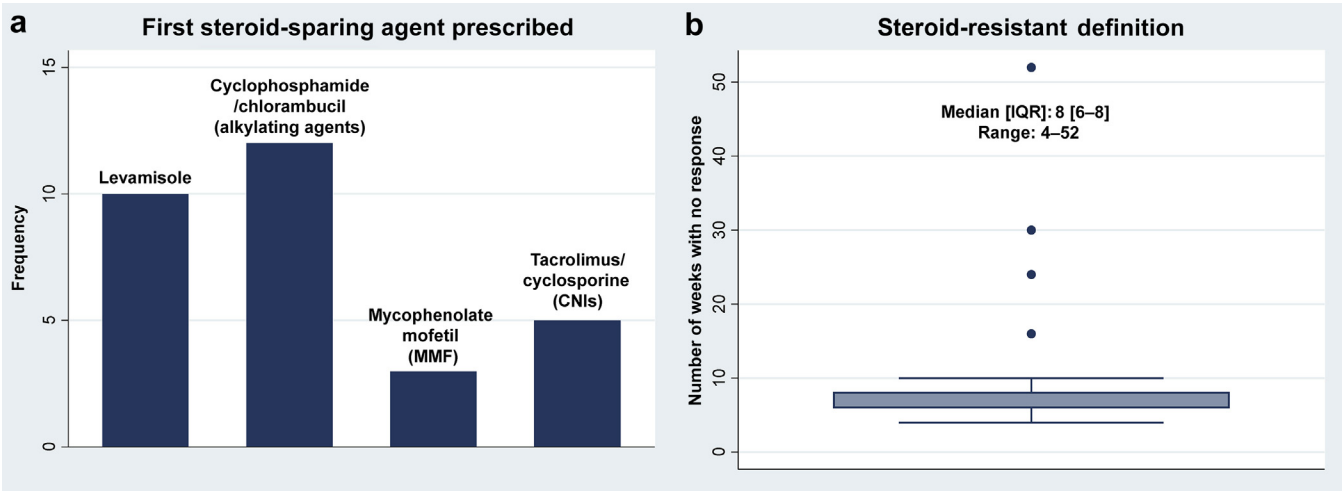

Figure 2 | (**a**) **Steroid-sparing agents in order of most commonly used to least commonly used are cyclophosphamide, levamisole, calcineurin inhibitors, MMF, and chlorambucil.** Cyclophosphamide is used in the majority of centers. Chlorambucil is not available in Uganda, Tanzania, Ghana, or Cameroon, it is used primarily in South Africa and in a few clinical sites in Nigeria. Levamisole is not available in Ghana or Cameroon, and is used more routinely in Nigeria, Tanzania, and Uganda. Cyclosporine is the most commonly used calcineurin inhibitor (CNI). MMF is available only in Uganda, Tanzania, Nigeria, and South Africa. (**b**) African nephrologists used varying definitions for steroid resistance, ranging from 4 to 52 weeks of nonresponse to prednisone, with a median of 8 weeks. IQR, interquartile range.

resistance rates reported within and across countries in Africa.[7–9] Absence of consensus in NS management makes it difficult to study meta-data on the natural history of NS in African children. The consensus meeting also provided a venue for practicing African nephrologists to be engaged in the process, promoting ownership and collaboration, which may improve acceptance and adherence to the guidelines, while improving clinical practice and care for African children. We also included adult nephrologists who manage adolescents as young as 12 years old depending on the region and country.

Adaptability of international protocols to meet local needs, especially in sub-Saharan Africa where health resources are limited and most people pay out of pocket, cannot be overemphasized. Access to steroid-sparing agents, specifically generic formulations, is important. There is no consistency among African countries in purchasing medications *en bloc* because health insurance is almost nonexistent. With the high cost of medications and drug monitoring, most families are unable to afford or sustain these drugs. Lack of facilities and personnel for processing and interpretation of kidney biopsies is a major impediment throughout Africa, and needs to be addressed.

Consensus agreement on the management of NS for sub-Saharan Africa will greatly enhance the adoption of treatment guidelines and may be generalizable to other low-resource regions. The Ibadan consensus guideline on NS will improve the quality of care of children with standardized definitions, pragmatic approaches to dosing and tapering, and a unified consensus on the use, order, and dose of steroid-sparing agents.

METHODS

We addressed all the KDIGO guidelines for childhood NS for steroid-sensitive nephrotic syndrome in children (chapter 3 of the KDIGO guidelines), and steroid-resistant nephrotic syndrome in children (chapter 4 of the KDIGO guidelines).[14] We did not address nephrotic syndrome in adults.

We invited all the H3A-KDRN participating physicians to complete a short survey regarding current clinical management of NS in both children and adolescents. All potential participants were contacted by email to complete a 10-minute survey. The practicing nephrologists completed the survey to determine variability in practice patterns and the definitions used. Some completed the survey as an individual or on behalf of the center because of their common group practice. The survey was sent to 50 nephrologists from 6 countries and 30 completed the survey. Because children older than the age of 12 to 18 often are managed by adult nephrologists, we also included 4 adult nephrologists and 6 combined adult and pediatric nephrologists. We had a 60% response rate for the survey, however, with some nephrologists reporting on behalf of the center, the overall response was 95% across 19 participating centers. The consensus meeting occurred in Ibadan, Nigeria, during the H3A-KDRN 2018 Annual Investigator and Research Team Meeting in January 2018. Each survey question was discussed until consensus was reached. Participants were given equal opportunity to speak and explain their selected responses. In addition, we included 3 faculty who provided the evidence for each guideline statement and reviewed current practice. We used the modified Delphi approach, with repeated rounds of questions and prioritization of statements, to reach consensus on management of NS. An independent senior nephrologist moderated the consensus meeting and if there was no consensus reached, a vote with a simple majority was conducted.

APPENDIX

List of the Human Hereditary and Health in Africa–Kidney Disease Research Network (H3A-KDRN) members

Cameroon: Gloria Ashuntantang and Guemkam Georgette; Ghana: Dwamoa Adu, Victoria May Adabayeri, Vincent Boima, Charlotte Osafo, Elliot Koranteng Tannor, Perditer Okyere, Sampson Antwi, and Jacob Plange-Rhule; Nigeria: Manmak Mamven, Samuel Ajayi, Emmanuel Anigilaje, Ogochukwu Okoye, Ofejiro Okperi, Okiroro Ighosewe, Ifeoma Ulasi, Uzoamaka Muoneke, Odutola Odetunde, Henrietta U. Okafor, Babatunde Salako, Adebowale Ademola, Kemi Amodu, Yemi Raji,

Asinobi O. Adanze, Fatiu Arogundade, Wasiu Olowu, Timothy Olusegun Olanrewaju, Olanrewaju Adedoyin, Patience Obiagwu, Aliyu Abdu, Adaobi Solarin, Oluwatoyin Amira, Christopher Esezobor, Charles Odenigbo, Nonyelum Jisieike-Onuigbo, Adesola Musa, Rosemary Audu, Olanrewaju Jinadu, Adewale E. Adetunji, Muhammad Makusidi, Fatima Nma Jiya Bello, and Jacob Olugbenga Awobusuyi; South Africa: Mignon McCulloch and Peter Nourse; Tanzania: Francis Frederick Furia, Paschal Ruggajo, and Jacqueline Shoo; Uganda: Robert Kalyesubula, Grace Kansiime, and Anthony Batte; Ontario, Canada: Rulan S. Parekh, Damien Noone, Jovanka Vasilevska-Ristovska, and Tonny H.M. Banh; Kansas, USA: Akinlolu O. Ojo, Jillian Wilson, and Donna Smith; Massachusetts, USA: Titilayo Ilori; and North Carolina, USA: Rasheed Gbadegesin

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Figure S1. The survey was completed by 30 nephrologists who received nephrology training either in or outside Africa (mean years of training, 3.0 $\pm$ 1.7) and who have been practicing as a consultant nephrologist for a median of 12 years (IQR, 8–15 y). Some completed the survey for a single center due to common practice.

Table S1. Evidence table for childhood nephrotic syndrome RCT's.

Table S2. Systematic reviews nephrotic syndrome in children.

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