RESEARCH PAPER

Disease Course in Steroid Sensitive Nephrotic Syndrome

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Objective: To review the disease course in patients with steroid sensitive nephrotic syndrome (SSNS) and the factors that determine outcome

Design: Retrospective, analytical

Setting: Pediatric Nephrology Clinic at referral center in North India

Participants/patients: All patients with SSNS evaluated between 1990 and 2005

Intervention: None

Main outcome measures: Disease course, in patients with at least 1-yr follow up, was categorized as none or infrequent relapses (IFR), frequent relapses or steroid dependence (FR), and late resistance. Details on complications and therapy with alternative agents were recorded.

Results: Records of 2603 patients (74.8% boys) were reviewed. The mean age at onset of illness and at evaluation was 49.7±34.6 and 67.5±37.9 months respectively. The disease course at 1-yr (*n*=1071) was categorized as IFR in 37.4%, FR in 56.8% and late resistance in 5.9%. During follow up, 224 patients had 249 episodes of serious infections. Alternative medications for frequent relapses (*n*=501; 46.8%) were chiefly cyclophosphamide and levamisole. Compared to IFR, patients with FR were younger (54.9±36.0 *vs.* 43.3±31.4 months), fewer had received adequate (≥8 weeks) initial treatment (86.8% *vs.* 81.7%) and had shorter initial remission (7.5±8.6 *vs.* 3.1±4.8 months) (all *P*<0.001). At follow up of 56.0±42.6 months, 77.3% patients were in remission or had IFR, and 17.3% had FR.

Conclusions: A high proportion of patients with SSNS show frequent relapses, risk factors for which were an early age at onset, inadequate initial therapy and an early relapse.

Keywords: *Frequent relapses; Minimal change disease; Steroid dependent nephrotic syndrome.*

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The course of illness in children with steroid sensitive nephrotic syndrome varies from a single episode to infrequent or frequent relapses, and rarely the occurrence of late steroid resistance [1,2]. The management of patients with frequent relapses, steroid dependence and late resistance is difficult, often requiring the use of alternative agents. Information on the course of nephrotic syndrome is available from multiple cohorts, including that of the International Study of Kidney Diseases in Children (ISKDC) [1,3-6]. Risk factors for frequent relapses include an early age of onset, short initial therapy, delayed time to remission and brief duration of the first remission [1,7-11]. An understanding of factors that determine the course is useful in decisions regarding therapy and enables counseling.

In 1975, we described our experience on the clinical features and renal histology in 206 consecutive patients with nephrotic syndrome [12]. The findings suggested that clinical and histological features of nephrotic syndrome in Indian children were similar to that reported elsewhere [1]. While the management of the initial episode and choice of alternative medications have changed over the years, there is limited contemporary data on the outcomes. We reviewed the case notes of recent patients, in order to examine the course of illness and its determinants.

Accompanying Editorial: Pages 868-869

Methods

We retrospectively analyzed the records of all patients with idiopathic steroid sensitive nephrotic syndrome, having an Indian ancestry, who presented to this center between 1990 and 2005. Children with onset of illness after 15-years, congenital nephrotic syndrome (onset <3-months of age) or known to be secondary to infections or systemic disease, or estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 at evaluation were excluded.

Disease course

The disease course, use of alternative therapies and complications were described for patients with minimum 12-months follow up at this center (*Study Group*). The course of disease during these 12 months was categorized as single episode, infrequent relapses, frequent relapses, steroid dependence or late resistance. Frequent relapses was defined as the occurrence of ≥2 relapses in 6 months or ≥3 relapses in 12 months, and steroid dependence as the presence of two consecutive relapses while on tapering doses of prednisolone [13]. Failure to show remission of proteinuria despite 4-weeks treatment with prednisolone (2 mg/kg/day) was termed as *initial resistance* when noted at onset of disease, and *late resistance* if occurring in a patient previously responsive to steroids [13].

Hypertension was defined as blood pressure higher than 95th percentile for sex, age and height [14]. Short stature was height less than 2 standard deviations (SD) and obesity was body mass index more than 3 SD of expected [15]. Patients had regular examination for visual acuity, intraocular pressure and cataract. Standard definitions were used for systemic infections [13]. Tuberculosis was diagnosed if the tuberculin test was positive (induration ≥10 mm at 48 hr) in presence of clinical and radiological features.

Therapy

Until 1992, patients at the first episode of nephrotic syndrome were treated with daily prednisolone for 4 weeks followed by alternate day therapy for 4 weeks. Between 1992 and 1995, patients participating in a randomized controlled trial received the aforementioned 8-weeks or prolonged 16-weeks treatment [16]. Thereafter, patients have received therapy with daily and alternate day prednisolone for 6 weeks each. For purpose of this review, *adequate* initial treatment was the use of prednisolone (2 mg/kg/day) for ≥4 weeks followed by 1.5 mg/kg on alternate days for ≥4 weeks. Relapses were treated with prednisolone, 2 mg/kg/d until remission and 1.5 mg/kg on alternate days for 4 weeks.

Patients with frequent relapses or steroid dependence received prednisolone (0.3-0.7 mg/kg) on alternate days for 9-12 months. Those having relapses or steroid toxicity received one or more alternative agents [13], often as follows: (*i*) levamisole (2 mg/kg on alternate days); (*ii*) oral cyclophosphamide (2 mg/kg/d for 12 weeks); (*iii*) mycophenolate mofetil (600-1000 mg/m^2/d); (*iv*) cyclosporine (4-6 mg/kg/d) or tacrolimus (0.1-0.2 mg/kg/d).

Kidney biopsies were done in patients with persistent hematuria, deranged renal function, steroid resistance or prior to therapy with calcineurin inhibitors, and examined by light microscopy and immunofluorescence [17].

Statistical analysis: Data from eligible patients with steroid sensitive illness was used to compute baseline features. Characteristics of patients in the Study Group were compared between the infrequent relapsers (patients with single episode or infrequent relapses) and frequent relapsers (frequent relapses or steroid dependence). Analyses were performed using Stata 11 (Statacorp, College Station, TX). Summary statistics were expressed as means and SD; groups were compared using Student's t test and Chi square test. On logistic regression, risk factors were reported as odds ratio (OR) with 95% confidence interval (CI). For this purpose, certain variables were dichotomized based on information from previous studies [1,3,8,18,19]. These included the age at onset (<4 yr or ≥4 yr); duration of initial therapy (<8 weeks or ≥8 weeks) and duration of remission following therapy of the initial episode (<6 months or ≥6 months).

RESULTS

Of 3299 patients with nephrotic syndrome, 324 were excluded due to inadequate case records, age of onset >15 yr or presumed secondary etiology (***Fig.* 1**). Initial steroid resistance was noted in 372 (12.5% of 2975) patients. Details on baseline characteristics were available in 2603 patients with steroid sensitive nephrotic syndrome **(*Table* I)**. Most patients had received adequate initial therapy with prednisolone and over one-half received treatment for 12 weeks. The duration of initial remission was 4.6±6.4 months. Renal biopsies, in 341

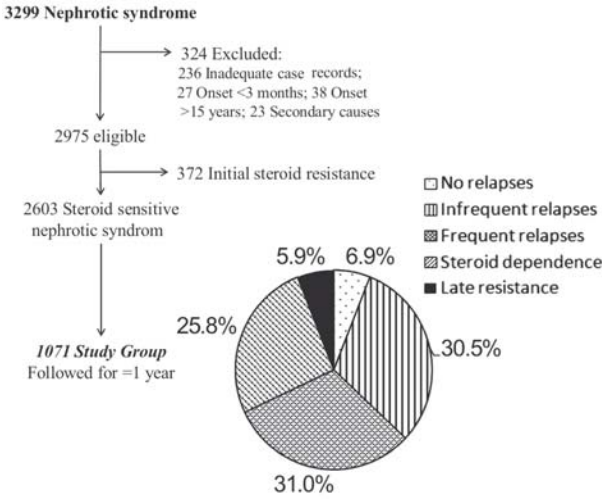


FIG. 1 *Flow chart showing patients with nephrotic syndrome. The course of disease in patients with minimum 12-months follow up at this center (Study Group) is depicted.*

TABLE I BASELINE FEATURES OF PATIENTS WITH STEROID SENSITIVE NEPHROTIC SYNDROME

	All patients; N=2603	*Study Group; N=1071*
Boys	1947 (74.8%)	816 (76.2%)
Age at onset, mo	49.7 ± 34.6	48.7 ± 34.4
Age at evaluation, mo	67.5 ± 37.9	67.4 ± 39.2
Family history of disease	46 (1.8)	15 (1.4)
Hematuria	242 (9.3)	85 (7.9)
Hypertension	97 (3.7)	35 (3.3)
Blood investigations		
Creatinine, mg/dL	0.71 ± 0.34	0.70 ± 0.31
Albumin, g/dL	2.3 ± 0.9	2.2±0.9
Cholesterol, mg/dL	343.2 ± 122.0	344.7 ± 122.6
Initial prednisolone therapy		
Total duration, wks	13.6 ± 6.2	13.2 ± 6.2
Adequate therapy (≥8 wks)	2193 (84.3)	901 (84.1)
8-11 wks	699 (26.9)	318 (29.7)
≥12 wks	1494 (57.4)	583 (54.4)
Duration of initial remission (mo)	4.6 ± 6.4	4.8 ± 7.0

Continuous variables are denoted as mean±standard deviation (95% ci), categorical variables as n (%)

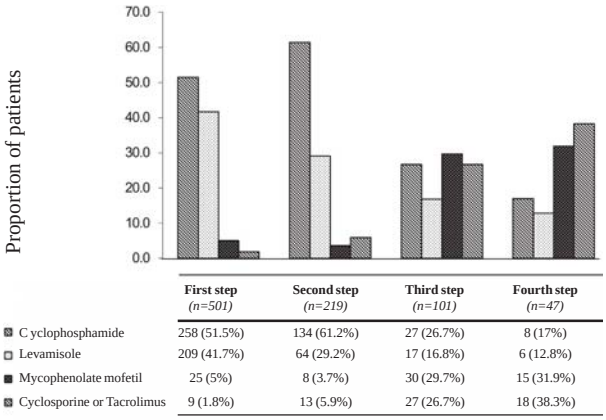
patients, showed minimal change disease in 242 (70.9%), mesangioproliferative glomerulonephritis in 48 (14.1%) and focal segmental glomerulosclerosis in 51 (15.0%).

Study Group

Of all patients with steroid sensitive nephrotic syndrome, 1071 (41.2%) having minimum 12-months follow up at this center constituted the Study Group. Following a mean age of onset of 48.7±34.4 months, and initial remission of 4.8±7.0 months, the age at evaluation was 67.4±39.2 months (Table 1). At follow up of 12 months, the disease course was categorized as none or infrequent relapses in 37.4%, frequent relapses or steroid dependence in 56.8% and late resistance in 5.9% (***Fig.* 1**).

Within the Study Group, 312 patients (237 boys; 76.0%) had been followed since onset of nephrotic syndrome. Their age at onset was 46.7±33.9 months, and disease course during 12-months was defined as none or infrequent relapses in 46.8%, frequent relapses in 49% and late resistance in 4.2%.

Alternative medications: These were administered for frequent relapses in 501 (46.8%) patients. Two, three and four medications were required in 219 (20.5%), 101 (9.4%) and 47 (4.4%) instances respectively (***Fig.* 2).** Most patients received therapy with oral



	First step (*n=501*)	Second step (*n=219*)	Third step (*n=101*)	Fourth step (*n=47*)
C yclophosphamide	258 (51.5%)	134 (61.2%)	27 (26.7%)	8 (17%)
Levamisole	209 (41.7%)	64 (29.2%)	17 (16.8%)	6 (12.8%)
Mycophenolate mofetil	25 (5%)	8 (3.7%)	30 (29.7%)	15 (31.9%)
Cyclosporine or Tacrolimus	9 (1.8%)	13 (5.9%)	27 (26.7%)	18 (38.3%)

FIG. 2 *Alternative medications for patients with frequent relapses or steroid dependence in the Study Group. Heights of individual bars represent the proportions of patients receiving the medication at each step of therapy. The number (%) of patients is shown in the panel below.*

cyclophosphamide or levamisole initially, followed by mycophenolate mofetil or a calcineurin inhibitor.

Complications: A significant proportion of patients in the Study Group showed adverse effects of corticosteroid therapy. During a mean follow up of 56.0±42.6 months, 224 patients had 249 episodes of serious infections, which required hospitalization. These included peritonitis (7.7%), pneumonia (5.3%), cellulitis (3.7%), diarrheal dehydration (2.2%), urinary tract infections (2.1%) and tuberculosis (1.8%). Sequelae of corticosteroid therapy included obesity (*n*=226, 21.1%), hypertension (*n*=62, 5.8%), stunting (*n*=53, 4.9%) and cataract (*n*=17, 1.6%). Behavior abnormalities and thrombosis were observed in 38 (3.6%) and 4 (0.4%) patients. Patients with frequent relapses had a significantly higher risk of serious infections (OR 2.37; 95% CI 1.66, 3.39), obesity (OR 2.70; 1.92, 3.80), stunting (OR 2.64; 1.45, 4.79) and hypertension (OR 2.22; 1.14, 4.33).

Risk factors for disease course: ***Table* II** compares the characteristics of the frequent (*n*=608) and infrequent relapsers (*n*=400). The former were younger at onset of the disease (mean difference 11.5 months; 95% CI 7.3, 15.8 months; *P*<0.001) and the proportion of patients with frequent relapses declined with increasing age (***Fig.* 3**). The duration of initial therapy was short in frequent relapsers compared to those with infrequent relapses (mean difference 0.9 weeks, 95% CI 0.1, 1.6 weeks; *P*=0.02). A significantly lower proportion of frequent relapsers had received adequate (≥8 weeks) initial steroid therapy. Initial therapy for ≥12 weeks was associated with an additional 30% reduced risk of

TABLE II CHARACTERISTICS OF INFREQUENT RELAPSERS, FREQUENT RELAPSERS AND PATIENTS WITH LATE RESISTANCE

	Infrequent relapsers[†] *n=400*	*Frequent relapsers*[‡] *n=608*	*Late resistance, n=63*
Boys	306 (76.5)	474 (77.9)	44 (69.1)
Age at onset, mo	54.9 ± 36.0 (51.6, 58.1)	43.3 ± 31.4 (40.6, 46.0)**	47.9 ± 39.3 (37.2, 58.5)
Family history of disease	6 (1.5)	9 (1.5)	0 (0)
Hematuria at onset	34 (8.5)	41 (6.7)	10 (15.9)#$
Investigations			
Creatinine, mg/dL	0.67 ± 0.23 (0.59, 0.72)	0.64 ± 0.42 (0.57, 0.68)	0.79 ± 0.77 (0.56, 1.03)
Albumin, g/dL	2.3 ± 0.9 (2.2, 2.4)	2.2 ± 0.9 (2.2, 2.3)	2.2 ± 0.8 (1.9, 2.4)
Cholesterol, mg/dL	347.3 ± 123.9 (331, 363)	346.8 ± 121.7 (335, 359)	328.4 ± 129.4 (286, 371)
Initial steroid therapy			
Total duration, wks	13.7 ± 6.2 (13.1, 14.2)	12.8 ± 6.1 (12.2, 13.3)*	14.3 ± 7.4 (12.3, 16.4)
Adequate therapy (≥8 wks)	347 (86.8)	490 (81.7)*	53 (84.1)
Duration of initial remission, mo	7.5 ± 8.6 (6.5, 8.5)	3.1 ± 4.8 (2.6, 3.5)**	3.9 ± 7.7 (1.2, 6.5)##

*[†]Single episode or infrequent relapses; [‡]Frequent relapses or steroid dependence; Continuous variables are denoted as mean±standard deviation (95% CI), categorical variables as n (%); Difference between infrequent relapsers and frequent relapsers: *P<0.05; **P<0.001; Difference between infrequent relapsers and late resistance: #P<0.05, ##P <0.001; Difference between frequent relapsers and patients with late resistance: $P<0.05.*

frequent relapses compared to those treated for 8-11 weeks (OR 0.70; 95% CI 0.51, 0.95; *P*=0.02). Frequent relapsers also had brief initial remission, compared to those with infrequent relapses (mean difference 4.5 months; 95% CI 3.4, 5.5 months; *P* <0.001).

On univariate and multivariate logistic regression, young age at onset (<4 yr), lack of adequate initial therapy (<8 weeks) and short duration of initial remission (<6 months) were each associated with significantly increased risk of frequent relapses **(*Table* III)**.

Late resistance: Of 1071 patients, 63 (5.9%) showed late resistance. The presence of hematuria (gross 7; microscopic 3) **(*Table* II)** was independently associated with late steroid resistance (OR 3.3, 95% CI 1.4, 8.1; *P*=0.007). Compared to patients with infrequent relapses, the duration of initial remission was shorter (mean difference 3.7 months, 95% CI 0.7, 6.7 months; *P*=0.02). Renal histology (*n*=54) showed focal segmental glomerulosclerosis in 25 (46.3%), minimal change disease in 22 (40.7%) and mesangioproliferative glomerulonephritis in 7 (13%). Therapies included cyclosporine or tacrolimus in 40 (63.5%) patients and IV cyclophosphamide in 23 (36.5%) patients; complete or partial remission was seen in 39 (61.9%).

Outcome

***Table* IV** shows the outcome of patients at last follow up at 56.0±42.6 (range 12-160) months. Infrequent relapses or sustained remission was seen in 828 (77.3%) patients, 185 (17.3%) had frequent relapses or steroid dependence, and 42 (3.9%) showed late steroid resistance. Most patients (89.8%) with infrequent relapses at initial evaluation were in remission or had infrequent relapses. The outcome in patients with frequent relapses or steroid dependence was also satisfactory; 72.0% had remission or infrequent relapses and 23.8% persisted with frequent relapses. At last follow up, 53.8% of 145 patients with frequent relapses continued to require alternative immunosuppressive agents, most commonly levamisole (*n*=37) or cyclophosphamide (*n*=23), while others (*n*=67, 46.2%) were receiving low dose prednisolone on alternate days. A small proportion (2%) having late steroid resistance was managed chiefly with calcineurin inhibitors.

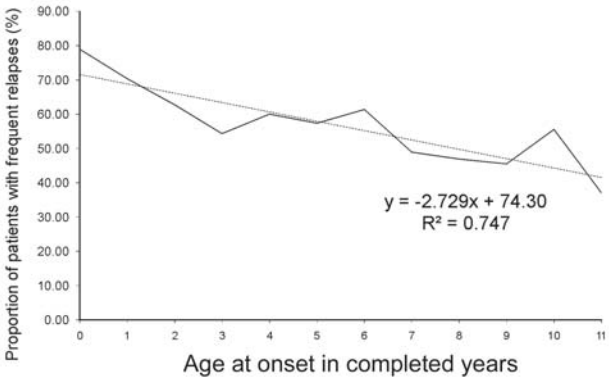


FIG. 3 *Proportion of patients with frequent relapses or steroid dependent nephrotic syndrome in relation to the age at onset of the illness.*

TABLE III RISK FACTORS FOR FREQUENT RELAPSES (*N*=1071)

	Odds Ratio (95% CI)			
	Unadjusted	*P*	*Adjusted*	*P*
Age at onset ≥4 y	0.64 (0.49, 0.85)	0.002	0.62 (0.43, 0.90)	0.01
Initial therapy ≥8 weeks	0.61 (0.41, 0.91)	0.015	0.55 (0.33, 0.92)	0.02
Initial remission ≥6 months	0.17 (0.11, 0.25)	<0.001	0.18 (0.11, 0.27)	<0.001

TABLE IV OUTCOME OF PATIENTS AT LAST FOLLOW UP (*N*=1071) IN RELATION TO INITIAL COURSE.

Outcome at last follow up	*Infrequent relapses (n=400), No (%)*	*Frequent relapses (n=608), No (%)*	*Late resistance (n=63)*
Sustained remission, infrequent relapses	359 (89.8)	438 (72.0)	31 (49.2)
Frequent relapses, steroid dependence	32 (8.0)	145 (23.8)	8 (12.7)
Late steroid resistance	9 (2.3)	12 (2.0)	21 (33.3)
Died	0	13 (2.1)	3 (4.8)

A significant proportion of patients (33.3%) with late resistance had persistent nephrotic range proteinuria. In patients with late resistance, the course of illness was similar in those with focal segmental glomerulosclerosis, minimal change disease and mesangioproliferative glomerulonephritis (data not shown). Sixteen (1.5%) patients, with either frequent relapses or late resistance, died of complications of severe infections. Eleven deaths occurred in patients admitted with refractory septic shock following pneumonia (*n*=5), diarrhea (*n*=3), meningitis with severe pneumonia (*n*=1) or fever without focus (*n*=2). Five children died at home with probable diagnosis of severe pneumonia.

DISCUSSION

We report the course of illness in a large group of patients with steroid sensitive nephrotic syndrome seen at a tertiary care center in India during 1990 to 2005. Data from 1071 patients, with minimum follow up of 12 months, was used to determine the course and risk factors associated with frequent relapses. During this period, practices regarding diagnosis and therapy were relatively constant, except that MMF and tacrolimus were included as alternative agents after 1998. These findings are important since they reflect outcomes of existing practice, as compared to most previous reports that include data on patients diagnosed during 1970-80 [1,3-6,12].

The characteristics of our patients were similar to that reported previously including age at onset, male preponderance and low incidence of familial cases [1,12, 20]. The proportion of patients having initial and late resistance was 12.5% and 5.9% respectively, confirming previous findings [3,5,21]. While the ISKDC reported that just 28.1% patients show frequent relapses in the first 6 months of their illness [3], data from other centers, comprising relatively small numbers of patients, shows that the proportion of frequent relapsers varies from 56-68% [8,10-11]. The present case series suggests that, despite 2-3 years from onset, frequent relapsers constitute more than one-half of all patients. While this information might suggest a referral bias, it is notable that 49% of the 312 patients followed at this center since onset of disease had frequent relapses. The reasons for detecting a high proportion of patients with frequent relapses are unclear, but might reflect biologic variations in disease severity or the increased occurrence of infection induced relapses [22].

There is evidence that adequate initial therapy with corticosteroids is useful in reducing the risk of subsequent relapses [23]. The present study also suggests that extension of initial therapy to 8-11 weeks was associated with reduced proportion of patients with frequent relapses; those receiving therapy for ≥12 weeks had an additional 30% lower risk. While data from prospective studies, reviewed recently [24], emphasize the benefits of prolonged therapy, its optimal duration is not known and is being addressed in randomized controlled trials.

Findings from the present study confirm that an early age at onset of nephrotic syndrome is associated with risk of frequent relapses [8,18,25]. Based on an age cut-off proposed in previous studies, we found that patients with

WHAT IS ALREADY KNOWN?

- Frequent relapses are an important cause of morbidity in children with steroid sensitive nephrotic syndrome.
- Risk factors for relapses are an early age of onset, short initial therapy and delayed time to remission.

WHAT THIS STUDY ADDS?

- More than one-half of all patients with steroid sensitive nephrotic syndrome show frequent relapses. Risk factors include onset at <4 years of age, initial therapy for less than 8 weeks, and brief initial remission lasting <6 months.
- Infections constitute the chief cause for morbidity and mortality.
- The long-term outcome of nephrotic syndrome is satisfactory in the majority.

onset of illness beyond 4-yr had a 38% lower risk of frequent relapses as compared to younger children. However, data from the ISKDC cohort [1] and others [10, 11] do not report an association between age at onset and the occurrence of frequent relapses. Finally, the risk of frequent relapses was reduced by 82% in children with initial remission lasting 6 months of longer, supporting findings of the ISKDC report [1] and of Fujinaga, *et al*. [19].

Almost one-half of the patients, who were followed up, required alternative medications for frequent relapses. Conforming to national guidelines and similar to practices elsewhere, cyclophosphamide and levamisole were the preferred first-line therapies, while the use of calcineurin inhibitors and mycophenolate mofetil was limited [13,26]. The diminishing numbers of patients requiring alternative medications at each step **(*Fig.* 2)** reflects the changes in disease course with therapy and time. Our experience on the impact of these treatment regimens has been reported earlier [27-29].

Long-term follow up of the ISKDC cohort, 9 years from the onset, suggests that the tendency to relapse reduces with time, and that most patients had either sustained remission or infrequent relapses [3]. Five years after diagnosis, almost three-fourth patients in the present study showed such a course, and only one-fifth continued to either relapse frequently or had unremitting proteinuria. The outcomes were similar in patients with frequent relapses and steroid dependence (data not shown). Koskimies, *et al* similarly reported sustained remission in 78.7% of 94 steroid sensitive patients at 5-14 yr follow up [5]. In a cohort of 132 children, followed over 27 years, Wynn, *et al.* found sustained remission in 62.8%; 17% patients had died of renal causes [6].

The limitations of the present analysis are similar to those of any retrospective report, including recall or reporting bias. There was limited information on the time to first remission, precise indications and duration of use of alternative agents, and on morbidities that did not require hospitalization. Patients were referred many months after the onset of symptoms and with a relatively difficult illness, perhaps limiting the scope of these findings. However, similarity of the disease course in patients who had presented at the first episode suggests that these findings were valid and might be generalized to patients with nephrotic syndrome in India.

The present study, on a large and recent group of patients with steroid sensitive nephrotic syndrome, identifies the course of the illness and existing therapeutic practices. It reconfirms the importance of age at onset of nephrotic syndrome, the need for adequate initial steroid therapy and duration of initial remission in predicting the risk of frequent relapses. The outcomes were satisfactory, and on follow up most patients were in sustained remission or had infrequent relapses.

Contributors: RNS, AB and PH were responsible for setting up the database. AS, PKS, AG, MM were involved in retrieval of information from records and its analysis, MK provided statistical inputs, and AKD reported all histological specimens. All authors contributed to the preparation of the manuscript, provided significant inputs during preparation for final publication and approved the final manuscript. AB supervised the study and shall be its guarantor.
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