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ORIGINAL ARTICLE

Variability of diagnostic criteria and treatment of idiopathic nephrotic syndrome across European countries

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Abstract The aim of the surveys conducted by the Idiopathic Nephrotic Syndrome Working Group of the ESPN was to study the possible variability of treatment in Europe at different stages of the disease by means of questionnaires sent to members of the Working Group. Four surveys have been completed: treatment of the first flare, treatment of the first relapse and the issue of steroid dependency, use of rituximab, and the management of steroid-resistant patients. A uniform treatment of the first flare was applied in only three countries, and ten additional centers have adopted one of the three main protocols. Reported treatment of the first relapse was relatively uniform, whereas the use of additional immunosuppressants in steroid dependency was widely variable. Rituximab had already been used in hundreds of patients, although the formal evidence of efficiency in steroid dependency was relatively recent at the time of the survey. The definition of steroid resistance was variable in the European centers, but strikingly, the first-line treatment was uniform throughout the centers and included the combination of prednisone plus calcineurin antagonists.

Conclusion: The variability in the approach of idiopathic nephrotic syndrome is unexpectedly large and affects treatment of the first flare, strategies in the case of steroid dependency, as well as the definitions of steroid resistance.

What is Known:
- *Steroids and immunosuppressants are the universal treatment of idiopathic nephrotic syndrome.*

What is New:
- *The variability of treatments and strategy of treatment in European centers of pediatric nephrology*

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Keywords Proteinuria · Prednisone · Steroid dependency · Steroid resistance · Rituximab · Guidelines

Abbreviations

APN	Arbeitgemeinshaft für Pediatrische Nephrologie
ESPN	European Society of Pediatric Nephrology
GPN	German Society for Pediatric Nephrology
KDIGO	Kidney Disease Improving Global Outcomes
INS	Idiopathic Nephrotic Syndrome
ISKDC	International Study of Kidney Disease in Childhood
IVMP	Intravenous methylprednisolone
MP	Methylprednisolone
SNP	Société de Néphrologie Pédiatrique
WG	Working Group

Idiopathic nephrotic syndrome (INS) is not a frequent disease, but not an orphan disease. The annual incidence in the population below 16 years of age is between 1.2 and 3.4 new cases per 100,000 [6]. It means that 1000 to 1500 new cases are occurring yearly in the European Union. Roughly half of them will be steroid-dependent and will have a median course of 10 years, meaning that 6000 to 16,000 pediatric patients (equivalent to 6 to 18 per 100,000 of the general population <16 years of age) are currently treated with steroids or immunosuppressive drugs. One of the main difficulties in gathering multicenter data for clinical studies on INS is due to the adoption of different treatment protocols as well as the definition of outcomes and resistance to treatment. This issue is particularly important in INS, where elements of the diagnosis and the prognosis are based on the response to the very initial phase of treatment.

The aim of the surveys conducted by the Idiopathic Nephrotic Syndrome Working Group (WG) of the European Society of Pediatric Nephrology (ESPN) was to study the possible variability of treatment in Europe at different stages of the disease by means of questionnaires sent to members of the WG. These questionnaires aimed at exploring different debated issues on INS treatment. The global conclusions are that the variability is unexpectedly large and not always understandable, even when a general consensus had apparently been reached.

Methods

Four surveys have been completed from 2013 to 2015 and sent to the 52 members of the INS Working Group.

Survey 1: first flare

Treatment of the first flare was investigated using a template where the classical protocols were recalled along with a space for the single center's individual approach. Each participant was asked to fill out the available cells of the column space entitled "your protocol" with the local protocol of treatment of the first flare.

Survey 2: first relapse and steroid dependency

Treatment of the first relapse and the management of steroid-dependent patients were investigated using a clinical case. The first query aimed at describing the treatment of the first relapse in each center. According to the answer, a second query was on the timing and choice of additional immunosuppressive treatment in each center.

Survey 3: rituximab

The use of rituximab was investigated using two successive questionnaires. The first questionnaire mainly aimed at defining the criteria to treat with rituximab (steroid dependency, duration, or severe complication of the disease), and the second questionnaire was dedicated to the technical points: dose, number of infusions for the initial cure, duration of B cell depletion, antimicrobial prophylaxis, and withdrawal of conventional immunosuppressive drugs and steroids.

Survey 4: steroid-resistant forms

The management of steroid-resistant patients was investigated using a template to fill out. The template contained open criteria of the definition, use of renal biopsy, and access to genetic testing first-line treatment, duration of the treatment prior to considering failure, and criteria of success.

Results

The surveys were sent to 52 centers and answered by 40 centers from 19 countries. There were 29, 16, 27, and 18 answers for surveys 1, 2, 3, and 4, respectively (Table 1).

Table 1 Number of centers that answered the survey according to countries

Centers	Survey 1	Survey 2	Survey 3	Survey 4
Belarus (Беларусь)	0	0	0	1
Belgium	2	1	1	1
Croatia	3	0	0	0
Denmark[a]	1	0	1	0
Finland	0	0	0	1
France[a]	1	5	5	1
Germany[a]	1	2	2	0
Greece	1	1	1	0
Italy	3	2	5	5
Lithuania	1	1	1	0
The Netherlands	1	1	1	0
Norway	1	0	1	0
Oukraïna (Україна)	0	0	0	1
Poland	1	0	2	1
Russia (Россия)	3	1	1	3
Serbia	2	0	0	0
Spain	2	0	2	2
Turkey	4	1	3	1
UK	2	1	1	1
Total	29	16	27	18

[a] Countries with a uniform nationwide protocol were counted as one center

First flare

The questionnaire was returned by 26 individual centers (Table 2). In addition, three countries—Denmark, Germany, and France—that applied a uniform nationwide treatment were considered as one answer while representing dozens of individual centers. Surprisingly, those three protocols were relatively similar, but differed by the cumulative dose of prednisone (3360 mg/m^2 for Denmark and Germany and 3990 mg/m^2 for France), the use of intravenous methylprednisolone in the case of oral steroid resistance (Germany and France), and the tapering sequence (only in France). In other centers, the variability of the cumulative dose ranged from 2240 to 4245 mg/m^2. Consistently, the duration of treatment also varied from 8 to 24 weeks. Other important results showed that (1) all centers gave 60 mg m^{-2} day^{-1} of prednisone ($n = 14$) or prednisolone ($n = 15$) to start the treatment; (2) all centers were limiting the daily dose during the first weeks of treatment, 18 of them to less than 60 mg/day, meaning that patients over 1 m^2 (about 30 kg body weight) were receiving less than the nominal cumulative dose mentioned in Table 1; (3) 20 of 29 protocols included a sequence of several steps of steroid tapering before withdrawal; and (4) 20 of 29 were using an intravenous (IV) methylprednisolone test in the case of steroid resistance at the end of the period

Table 2 Main parameters of treatment of the first flare in 24 individual centers and three countries

No.	Centers	Drug	Max. daily dose (mg/day)	Duration of daily dose (weeks)	Total duration (weeks)	Cumulative dose of steroids (mg/m^2)	Tapering	IVMP test
01	Spain—2	Prednisone	80	4	8	2240	No	Yes
02	UK—1	Prednisolone	60	4	8	2240	No	No
03	Russia—2	Prednisone	60	6	12	2500	Yes	No
04	Croatia—3	Prednisolone	80	4	14	2660	Yes	No
05	Croatia—2	Prednisolone	80	4	10	2760	No	No
06	Croatia—1	Prednisone	60	4	13	2780	Yes	Yes
07	Serbia—1	Prednisolone	60	4	8	2800	No	Yes
08	Spain—1	Prednisone	80	4	17	3000	Yes	Yes
09	Belgium—1	Prednisone	60	4	16	3010	Yes	Yes
10	Lithuania	Prednisone	60	4	12	3150	Yes	Yes
11	Turkey—4	Prednisolone	60	4	16	3185	Yes	No
12	Turkey—1	Prednisolone	60	4	20	3325	Yes	Yes
13	Denmark[a]	Prednisolone	80	6	12	3360	No	No
14	Germany[a]	Prednisone	60	6	12	3360	No	Yes
15	Italy—1	Prednisone	70	6	12	3360	Yes	Yes
16	Italy—3	Prednisone	60	6	12	3360	Yes	Yes
17	UK—2	Prednisolone	80	6	12	3360	No	No
18	Netherlands	Prednisolone	80	6	12	3360	No	No
19	Serbia—2	Prednisolone	80	6	12	3360	No	Yes
20	Belgium—2	Prednisolone	80	6	16	3555	Yes	Yes
21	Norway	Prednisolone	60	4	16	3570	Yes	Yes
22	Turkey—3	Prednisolone	60	4	12	3570	Yes	No
23	Turkey—2	Prednisone	60	4	18	3900	Yes	Yes
24	France[a]	Prednisone	60	4	18	3990	Yes	Yes
25	Italy—2	Prednisone	75	4	18	3990	Yes	Yes
26	Russia—1	Prednisone	60	6	18	3990	Yes	Yes
27	Greece	Prednisone	60	4	18	3990	Yes	Yes
28	Russia—3	Prednisolone	60	6	18	4095	Yes	Yes
29	Poland	Prednisone	60	4	24	4245	Yes	Yes

Centers and countries have been classified according to the cumulative dose of steroids

IVMP intravenous methylprednisolone

[a] Nationwide protocol adopted by all the centers

of full oral daily dose. Another unexpected fact was the variability of the protocols within large countries (Italy, Russia, Spain, and Turkey) as well as within smaller countries (Belgium, Croatia, and Serbia). Finally, half of the centers (13/26) were following one of the three main protocols emerging from the literature (Table 4): two centers (nos. 01 and 02; Table 1) had a protocol close to the model of the International Study of Kidney Diseases in Children (ISKDC; Table 4), seven centers (nos. 13–19; Table 1) had a protocol close to the model of the German Society for Pediatric Nephrology (GPN; Table 4), and four (nos. 24–27; Table 1) had a protocol close to that of the French Société de Néphrologie Pédiatrique (SNP; Table 4).

First relapse and steroid dependency

The survey adopted the form of a clinical quiz that was compiled by 16 centers. The clinical case presented a typical steroid-dependent patient relapsing 5 days after the withdrawal of prednisone. Reported treatment of the first relapse was relatively uniform and consisted of a short period of daily prednisone limited to the time to obtain a remission in one center, plus 3 days in 9 of 16 centers, and plus 5–7 days in five centers. Only one center reported treating the first relapse similarly to a first flare in the absence of significant steroid toxicity. A single treatment with prednisone lasting from 1 to 6 months without any prevention of further relapses was the choice of seven centers. A systematic prevention of further relapses was undertaken as soon as the first early relapse by eight centers: five gave long-lasting alternate day prednisone therapy, one levamisole, one cyclosporine, and one an unconventional combination of levamisole, mycophenolate, and subcutaneous polyclonal immunoglobulins. In the last center, treatment with mycophenolate was given only in the case of significant signs of steroid toxicity. Three centers also mentioned that cyclophosphamide or rituximab could be an option as soon as the first relapse in the case of relapse prior to the withdrawal of steroids.

At the second relapse, immunosuppressant drugs were systematically given to patients in nine centers. Mycophenolate was the first option in the majority of those centers, and only two considered cyclophosphamide or rituximab at this stage. Four centers did not consider any systematic prevention of further relapses at this stage of the disease, but mycophenolate or levamisole was conditioned to steroid toxicity in three out of four centers and cyclophosphamide in one out of four. The last three centers reported no answer for the second relapse and beyond.

Rituximab

The questionnaire was sent in two parts. Twenty-seven centers answered the first part and 13 the second part. One center had no experience at all. In contrast, several hundreds of patients have been treated with rituximab in the other 26 centers. Three centers reported more than 50 patients each and four other centers reported 20 to 50 patients each. The last 18 centers had a more marginal experience with less than ten patients. The major indication of treatment was steroid dependency. Other frequent indications included steroid resistance (eight centers) and long-lasting treatment with immunosuppressants (eight centers). A minimum of at least a 3-year duration of nephrotic syndrome was reported by seven centers, but two centers had clearly no lower limit for prescription. Rituximab was the last line of treatment for three centers. Either non-compliance or complications were an indication in six centers. Strikingly, costs of rituximab were not covered by healthcare insurance in Belgium and Poland in 2015.

Of the 13 centers that answered the second part of the questionnaire, 12 were initiating the treatment by one (eight centers) or two infusions at 1 week distance (four centers), while only one center followed the classic protocol consisting of four infusions in 4 weeks. The dose of one infusion was 375 mg/m^2 for all centers, except one that reported a unitary dose of 750 mg/m^2. Reinfusion was performed if B cell repletion was observed within 6 months after the first infusion in six centers and only in the case of relapse in four centers. A systematic long-lasting B cell depletion of 12 and 18 months was achieved in two centers. An alternate protocol adopted by one center was to treat any relapses with rituximab in steroid-dependent patients, allowing to rapidly stop the oral treatment. A reinfusion was never done in one center. A withdrawal of all oral drugs was attempted by all centers, with a delay varying from 1 month (in three centers) to 12 months.

Steroid-resistant forms

Eighteen centers answered the survey. The heterogeneity of the definition of steroid resistance is shown in Table 3. The first-line treatment that was adopted by the 18 centers was the association of calcineurin inhibitors, either cyclosporine (15 centers) or tacrolimus (three centers). A patient was considered multidrug-resistant in the case of no response to the association of calcineurin inhibitor and prednisone for a period

Table 3 Definitions of steroid resistance

Resistance according to:	No. of centers
4 weeks oral prednisone	1
6 weeks oral prednisone	1
8 weeks oral prednisone	2
4 weeks oral prednisone + 3MP	5
6 weeks oral prednisone + 3MP	8
8 weeks oral prednisone + 3MP	1

3MP three infusions of methylprednisolone at a dose of 1000 mg/1.73 m^2 each

of 3 months (two centers), 6 months (eight centers), or 9 months (five centers; three centers did not answer the question). Partial response to treatment was considered 50% proteinuria reduction by most centers and combined to serum albumin increase in three centers. In the case of partial response, mycophenolate was added as a second-line treatment in 13 centers. Only isolated centers propose a third-line treatment with apheretic techniques, intravenous high-dose immunoglobulin, and rituximab. One center had no additional treatment in the case of multidrug resistance. All centers decided to withdraw immunosuppressive therapies, shifting to exclusive supportive care based on unequivocal genetic results (all centers) or the development of renal failure (all centers).

Discussion

Idiopathic nephrotic syndrome affects children all over the globe, and one should expect that they should be treated with common and shared protocols. Here, we report the results of surveys that concern the treatment of children with INS in the European area. The data come from a sample of European centers of Pediatric Nephrology belonging to the INS Working Group of the ESPN and that answered the four surveys. Despite the relatively low number of participating centers compared to the total number of centers in Europe, which is clearly a limitation of the study, the surveys show large variations of treatment strategies at all steps of the management of idiopathic nephrotic syndrome in the European area, as already reported elsewhere in the world [16, 21].

Numerous guidelines, meta-analyses [9], and follow-up series on the treatment of the first flare of nephrotic syndrome have been released in the literature by Pediatric Nephrology societies, consortium of centers, or single centers [7, 8, 12, 18, 25]. At least seven randomized prospective trials have tested different protocols of steroid therapy [8]. The fact is that the literature shows substantial differences in the treatment of the first flare according to countries and centers. In addition to the protocol described in the literature as the International Study of Kidney Disease in Childhood [3], the GPN (formerly named Arbeitgemeinshaft für Pädiatrische Nephrologie, APN) protocol [5], and the protocol of the Société de Néphrologie Pédiatrique [2], the US and India guidelines recommend a protocol that is very similar to that of the GPN [1, 8]. The protocol recommended by the Kidney Disease Improving Global Outcomes (KDIGO) is less well defined in terms of duration of treatment and is composed of different sources [14]. The main details of the protocols that are used in Europe are shown in Table 4. They are quite different in terms of duration and cumulated dose of steroid therapy, the tapering protocol, and the option of intravenous methylprednisolone in the case of oral steroid resistance. As a matter of fact, out of the European Centers of Pediatric Nephrology, one half of the centers reported using the ISKDC or the APN or the SNP protocol, while the other half have a local protocol that is more or less a mix of the three main protocols. The variability in the

Table 4 Main recommended protocols for treatment of the first flare

	ISKDC	German GPN	French SNP
Daily full dose	60 mg m^{-2} day^{-1} × 4 weeks	60 mg m^{-2} day^{-1} × 6 weeks	60 mg m^{-2} day^{-1} × 4 weeks
Alternate full dose	40 mg/m^2 e.o.d. × 4 weeks	40 mg/m^2 e.o.d. × 6 weeks	60 mg/m^2 e.o.d. × 8 weeks
Tapering step 1	NA	NA	45 mg/m^2 e.o.d. × 2 weeks
Tapering step 2	NA	NA	30 mg/m^2 e.o.d. × 2 weeks
Tapering step 3	NA	NA	15 mg/m^2 e.o.d. × 2 weeks
Total cumulated dose	2240 mg/m^2	3360 mg/m^2	3990 mg/m^2
Total duration	8 weeks	12 weeks	18 weeks
Type of steroid	Prednisolone	Prednisone	Prednisone
Maximum daily dosage	80 mg/day	80 mg/day	60 mg/day
"MP test" in the case of oral steroid resistance	No	IVMP 1000 mg/1.73 m^2 × 3	IVMP 1000 mg/1.73 m^2 × 3

MP methylprednisolone, *ISKDC* International Study of Kidney Disease in Childhood, *GPN* German Society of Pediatric Nephrology, *SNP* Société de Néphrologie Pédiatrique

dose and duration of prednisone (or prednisolone) has already been reported in Italy, not only in General Pediatrics Units but also in those specialized in Pediatric Nephrology [20]. Noteworthy is that two centers using the classical ISKDC protocol have reported the use of IV methylprednisolone in the case of oral steroid resistance while this option is not classically included in those protocols.. The most surprising finding is that, according to this survey, a total of 13 European centers are treating patients below the KDIGO recommendations of minimum steroid therapy: less than 12 weeks of duration or less than 3360 mg/m^2 of cumulative dose corresponding to the sum of 4 weeks at 60 mg m^{-2} day^{-1} and 6 weeks at 40 mg/m^2 e.o.d. [14]. Nevertheless, two recent prospective randomized trials have shown that a cumulative prednisone dose of 2240 mg/m^2 had the same effect on the outcome as doses of 3500 and 3900 mg/m^2 [24, 26]. In contrast, a less recent prospective trial from Japan also showed that patients under 4 years of age had a strong benefit from a high cumulative dose of prednisolone [11]. At the other end, none of the centers participating in this survey reported steroid overtreatment, contrasting with a recent Italian report where patients in two pediatric nephrology units are treated with a cumulative prednisone dose of over 5000 mg/m^2 [20]. However, our data clearly highlight the need to discuss common and shared European guidelines aimed at optimizing steroid therapy according to one protocol with different options. Based on the data of the literature and on the experience of centers, European guidelines should at least state about a uniform dose of steroids and define one option for the tapering protocol and the test with IV methylprednisolone.

In contrast with the treatment of the first flare, the steroid therapy of the first relapse, which has never been the objective of a randomized prospective trial, is very homogenous in Europe. All but one center treat the first relapse with a shortened duration of daily prednisone and a rapid tapering of the dose from 0 to 7 days after the remission of proteinuria, consistent with the KDIGO recommendations [14]. At this point, differences between centers concern the duration of steroid therapy and the use of an additional second-line treatment. Prevention of relapses by either long-lasting steroid therapy or levamisole was reported by seven centers as soon as the first relapse. Beyond the first relapse, KDIGO recommendations are vague, particularly on the chronology of each possible steroid-sparing treatment. No differences are suggested between the treatments that prevent relapses as long as they are continued but have no remnant effect after withdrawal (levamisole, mycophenolate, and calcineurin inhibitors) and those that clearly show the ability to disrupt the course of the disease in long-term follow-up series (cyclophosphamide and rituximab) [14]. At the second relapse, nine European centers considered an additional treatment and four reported using an additional treatment only in the case of steroid toxicity. Among the nine centers that reported an additional treatment, only two reported the early use of cyclophosphamide or rituximab. The duration of the disease was never explicitly mentioned as an indication of additional treatment.

Rituximab has now been fully recognized as an efficient treatment in steroid-dependent patients, with a high rate of evidence since the end of 2014 and the release of the first randomized controlled trial [13]. Nevertheless, the efficiency of rituximab has been empirically recognized by clinicians for several years [4], while more than 300 patients have been reported in the survey at the end of 2014. Variations in the use of rituximab are somehow limited: most of the centers reported the same unitary dose of 375 mg/m^2, and the number of initial infusion was 1 or 2. Long-lasting B cell depletion [22] has been used by two centers, but one should recall that the risk of life-threatening infections might be proportional to the duration of B cell depletion [23]. An alternative way might be to systematically treat relapses in steroid-dependent patients with one infusion of rituximab in order to stop oral treatments rapidly and to delay the next relapse. Nevertheless, the best way to use rituximab remains to be defined in the near future.

Steroid resistance is a condition of high morbidity leading to end-stage renal failure or to long-lasting and heavy immunosuppressive drug therapy [10, 17, 27]. The definition of steroid resistance is very heterogeneous in the survey. Whereas the prevalence of steroid sensitivity is proportional to the duration and the cumulative dose of steroids [19], the resistance after 4 weeks of oral prednisone might have a different significance in terms of difficulty to treat than the resistance after 8 weeks of oral prednisone plus three intravenous methylprednisolone pulses. Nevertheless, the first-line treatment is similar in all centers regardless of the definition. All centers reported using a first line of prednisone and calcineurin antagonists, consistent with the KDIGO recommendations [15]. Mycophenolate is a common drug included in maintenance treatment, especially in partial response. Positive genetic testing is a major cause of immunosuppressive treatment withdrawal in all centers, suggesting that the first-line treatment is systematically started before genetic results are likely to be delayed in most cases. The other criterion that leads to withdrawal of immunosuppressive therapy is the time to unresponsiveness, which ranges between 3 and 9 months, defining multidrug resistance. In this case, experimental therapeutic options using plasma exchange or immunoglobulin removal are a choice for only two centers.

To conclude, a lot of work remains to be done in order to homogenize the treatment of idiopathic nephrotic syndrome based on high-quality evidence. The choice of treatment remains largely dependent on each physician's clinical experience at all steps. This variability of therapeutic approaches deserves some attention and supports the commitment of the INS Working Group of the ESPN to build guidelines and consensus.

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Authors' contributions Georges Deschênes and Licia Peruzzi conceived the questionnaires and wrote the paper.
Marina Vivarelli wrote the paper with LP and GD.
Coauthors of the ESPN Working Group on Idiopathic Nephrotic Syndrome answered the surveys.
Among coauthors, Olivia Boyer, Detlef Bockenhauer, Etienne Berard, Lutz Weber, and Lale Sever kindly reviewed the paper.

Compliance with ethical standards

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The coauthors in the list declare no conflict of interest and no financial relationship with the ESPN.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

It is clear that this paper obviously reports the routine clinical experience of medical teams on the treatment of human patients affected of a human disease, but this article does not contain any experimental studies with human participants or animals performed by any of the authors. It is

also clear that several thousand human patients are the core of this clinical experience, but this paper does not report any specific information contained in patient files. Consequently, informed consent has not been obtained from individual participants.

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