Steroid Sensitive Nephrotic Syndrome: Revised Guidelines

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ABSTRACT

Justification: Steroid sensitive nephrotic syndrome (SSNS) is one of the most common chronic kidney diseases in children. These guidelines update the existing Indian Society of Pediatric Nephrology recommendations on its management. **Objective**: To frame revised guidelines on diagnosis, evaluation, management and supportive care of patients with the illness. **Process**: The guidelines combine evidence-based recommendations and expert opinion. Formulation of key questions was followed by review of literature and evaluation of evidence by experts in two face-to-face meetings. **Recommendations**: The initial statements provide advice for evaluation at onset and follow up and indications for kidney biopsy. Subsequent statements provide recommendations for management of the first episode of illness and of disease relapses. Recommendations on the use of immunosuppressive strategies in patients with frequent relapses and steroid dependence are accompanied by suggestions for step-wise approach and plan of monitoring. Guidance is also provided regarding the management of common complications including edema, hypovolemia and serious infections. Advice on immunization and transition of care is given. The revised guideline is intended to improve the management and outcomes of patients with SSNS, and provide directions for future research.

Keywords: *Calcineurin inhibitors, Frequent relapses, Levamisole, Minimal change nephrotic syndrome, Mycophenolate mofetil, Rituximab, Steroid dependence.*

Nephrotic syndrome, characterized by edema, heavy proteinuria (>1 g/m^2 daily; >40 mg/m^2/hr) and hypoalbuminemia (serum albumin <3 g/dL), is among the most common kidney diseases in childhood. The condition has an annual incidence ranging from 1.2 to 16.9 per 100,000 children [1,2]. While nephrotic syndrome is usually primary or idiopathic, evaluation might reveal an underlying systemic illness in 5-10% of patients. Kidney biopsy reveals minimal change disease in ~80% patients, and focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis (GN) in 7-8% each. Therapy with prednisolone results in complete remission of proteinuria in 85-90% patients, termed steroid sensitive nephrotic syndrome (SSNS). While the outcome in patients with SSNS is satisfactory, approximately 50% show frequent relapses or steroid dependence, and 3-10% show late steroid resistance [3-5].

OBJECTIVE

Guidelines on management of SSNS, by the Indian Society of Pediatric Nephrology, were first published in 2001 [6] and updated in 2008 [7]. With increasing availability of evidence on various therapies, these guidelines have been revised. Guidance is based on the strength and quality of evidence using the GRADE model proposed by the American Academy of Pediatrics [8]. Ungraded statements (indicated by X) are like practice points, not supported by sufficient evidence. **Table I**

highlights key changes in present guidelines compared to 2008 [7] and those recently proposed by the Kidney Disease Improving Global Outcomes [9].

PROCESS

Workgroups were constituted to address key issues, including: *(i)* Evaluation at baseline and follow up, role of biopsy, genetic testing, and differential diagnosis; *(ii)* Management of the initial episode and subsequent relapses; *(iii)* Management of frequent relapses; and *(iv)* Supportive care and outcomes. Separate workgroups have addressed guidelines on the definition and management of steroid resistant nephrotic syndrome [10]. The workgroups identified gaps in knowledge, formulated questions and developed consensus statements prior to the meeting in New Delhi on 5 April 2019, when the evidence was discussed through alternating breakout and plenary sessions. Research studies were rated from A to D using standard criteria, and each consensus statement was assigned one of two levels of recommendation, based on assessment of relative benefit versus harm, and relevance in context of availability and cost, and the feasibility of monitoring (**Supp. Table I**) [11]. Draft guidelines were again discussed in Pune on 21 December 2019. The final manuscript was circulated to all participants for approval.

DEFINITIONS

Criteria for defining the course of nephrotic syndrome are shown in **Box I** [12-14]. For purpose of this guidelines, unless stated, the term 'frequent relapses' includes patients with 'steroid dependence', and prednisolone and prednisone are used interchangeably. The management of initial and late resistance, defined as lack of remission following 6-weeks' prednisolone therapy (**Box I**) is discussed separately [10].

Patients with frequent relapsing and steroid resistant nephrotic syndrome are at high risk of complications, due to the illness and toxicity of medications. We advise that these patients, and those younger than one year, be managed by pediatric nephrologists.

Guideline 1: Evaluation

1.1 In a patient presenting with recent onset of edema, we recommend the following investigations to confirm the diagnosis of nephrotic syndrome: *(i)* urinalysis; and *(ii)* blood levels of urea, creatinine, albumin and total cholesterol (**Box II**). (X)

1.2 We suggest additional evaluation in selected patients (**Box II**). (X)

1.3 We recommend that parents be taught to maintain a record of proteinuria (by dipstick or boiling), infections and medications received. **(**X)

Rationale

Children with the first episode of nephrotic syndrome require evaluation to confirm the diagnosis and screen for an underlying cause and complications. Family history of nephrotic syndrome, asthma and allergies, and renal diseases are asked for. Features including fever, abdominal pain, rash, arthralgia,

oliguria, hematuria and history of drugs or infections suggest an underlying cause, e.g., systemic lupus erythematosus and IgA vasculitis. Height, weight and blood pressure should be recorded; weight monitoring helps in assessment for edema.

Investigations advised at the initial episode are listed in **Box II**. The diagnosis is based on presence of nephrotic range proteinuria, hypoalbuminemia and edema. Majority of patients show total cholesterol levels exceeding 200 mg/dL. Nephrotic range proteinuria is present if in an early morning urine sample protein is 3-4+ (dipstick/ boiling test), spot protein to creatinine ratio is >2 mg/mg, or the protein excretion is >40 mg/m^2 per hr on a timed-sample. Precise estimation of 24-hr protein excretion is cumbersome, and is seldom necessary. Urine microscopy is normal, except for hyaline or granular casts; occasional microscopic hematuria is not uncommon. Persistent microscopic hematuria or red cell casts suggests disease other than minimal change nephrotic syndrome, like infection related GN, C3 glomerulopathy, systemic lupus or vasculitis [1]. Additional investigations are required for their diagnosis. Since patients with nephrotic syndrome do not have increased prevalence of urinary tract infections, routine urine cultures are not necessary.

With an estimated prevalence of bacteriologically positive pulmonary tuberculosis of 296 per 100,000 population in India, the risk of latent tuberculosis infection in childhood is high [15,16]. Tuberculin test is suggested prior to the first course of steroid treatment, especially with history of contact [16]. Chest radiography is done in patients with positive tuberculin test; those with features of tuberculosis require appropriate therapy. Patients with positive tuberculin reaction, but no radiological or bacteriological evidence of tuberculosis, should receive isoniazid prophylaxis for 6-months [16]. The prevalence of hepatitis B in non-tribal Indian populations is low (2.4%; 95% CI, 2.2-2.7%) [17], and routine screening is not required.

Genome wide association studies have identified variants in multiple MHC class II molecules as risk factors for SSNS [18]. The diagnostic and prognostic utility of various biomarkers of minimal change disease is limited [19]. There is, currently, no role for biomarkers or genetic studies in these patients.

Subsequent evaluation

Parents are instructed to monitor the child's urine at home, using dipstick or boiling test, and are explained the features of a relapse. During remission, they are advised to screen for proteinuria 2-3 times a week; the child is also examined every day during infections, or if edema is present. Frequent assessment of biochemistry is not necessary. Evaluation of patients during relapses also includes screening for complications (**Box II**).

Guideline 2: Kidney biopsy

2.1 We recommend kidney biopsy in nephrotic syndrome, in the presence of: *(i)* persistent microscopic hematuria, gross hematuria, or acute kidney injury not attributed to hypovolemia; *(ii)* systemic features: fever, rash, arthralgia, low complement C3; *(iii)* initial or late corticosteroid

resistance; and *(iv)* prolonged (>30-36 months) therapy with calcineurin inhibitors (CNI), or reduced kidney function during their use.(1B)

2.2 We suggest performing kidney biopsy prior to initiating therapy with CNI. (X)

2.3 We recommend light microscopy and immunofluorescence examination on all kidney biopsies. Electron microscopy is required in patients with gross or persistent microscopic hematuria, low C3 and suspected disorders of glomerular basement membrane. (X)

Rationale

Clinicopathological studies show that kidney biopsy is not routinely required in children with idiopathic nephrotic syndrome prior to therapy with corticosteroids [20-22]. Remission of proteinuria following steroid therapy is the most important predictor of long-term outcome [3,23]. The chief indication of kidney biopsy is in patients who fail to show complete remission of proteinuria despite 6-weeks daily therapy with prednisolone (steroid resistant illness) [10,24]. A biopsy is indicated in patients with gross hematuria or persistent microscopic hematuria at the onset (≥5 red cells per high power field; urine centrifuged at 400 g for 4-5 minutes, on 3 or more occasions); or extrarenal features of a systemic disease [20-23,25].

An age of onset of more than 12-years is often cited as an indication for performing a kidney biopsy. Review of literature in adolescent onset nephrotic syndrome suggests that a combination of features, including persistent microscopic hematuria, low C3 and steroid resistance, detects all patients with membranous nephropathy or proliferative GN [20-22,26,27]. This might obviate the need for a kidney biopsy in adolescents presenting with typical nephrotic syndrome that is steroid sensitive. Since infants (<12-months-old), including those with congenital nephrotic syndrome, are likely to show histological features other than minimal change disease or an underlying genetic change, we advise next-generation sequencing in these patients [10]. Patients with onset of idiopathic nephrotic syndrome beyond infancy should receive therapy with prednisolone, and are advised to undergo kidney biopsy if they show steroid resistance.

The large majority of patients with SSNS show minimal change disease, and less commonly FSGS or mesangioproliferative GN [20-22,28]. More than 90% children with minimal change disease, 50% with mesangioproliferative GN, and 30% with FSGS have steroid sensitive disease. Patients with frequent relapses do not require a biopsy before initiating therapy with steroid-sparing agents like levamisole, cyclophosphamide, mycophenolate mofetil (MMF) or rituximab [29]. The exception is prior to the use of CNI.

While there is limited guidance to support kidney biopsy in patients with SSNS prior to the therapy with CNI [9,30], information on the extent of tubular atrophy and interstitial fibrosis is useful when planning therapy. Therapy with CNI might result in acute nephrotoxicity, manifested as acute tubular injury and isometric tubular epithelial vacuolization [31,32]. Chronic nephrotoxicity, characterized by striped tubulointerstitial fibrosis has been reported in 25-43% biopsies following

therapy (for 2.5-3.5 years) with cyclosporin or tacrolimus [33-35]. While a recent report found low risk of nephrotoxicity despite prolonged use of tacrolimus [36], most reports suggest similar risk with cyclosporine and tacrolimus [34,37]. We therefore suggest considering kidney biopsy before initiating therapy with CNI, particularly in patients with prolonged disease and unclear course, and to inform the clinician regarding baseline histological changes and allow appropriate counseling. In view of long-term risks of nephrotoxicity, kidney biopsy should be performed following prolonged therapy with CNI, or if the therapy is associated with decline in eGFR that persists despite reduction in CNI dose [9,38].

An adequate biopsy specimen should preferably include the corticomedullary junction and approximately 20 glomeruli to exclude the diagnosis of FSGS [39]. Apart from renal histology, the biopsy provides information on extent and morphology of glomerulosclerosis and associated tubulointerstitial changes. The diagnosis of IgA nephropathy, C3 glomerulopathy and early membranous nephropathy is suggested by immunofluorescence studies. While kidney biopsies from all patients with nephrotic syndrome should be examined by electron microscopy, the facility is often not available. Ultrastructural examination helps to confirm the diagnosis of minimal change disease (effacement of podocyte foot processes; no electron dense deposits), differentiate primary from secondary FSGS (diffuse versus focal foot process effacement); categorize membranous nephropathy and C3 glomerulopathy, and identify disorders of glomerular basement membrane [40].

Guideline 3: Therapy for the first episode of nephrotic syndrome

We recommend that therapy for the initial episode should comprise of prednisolone at a dose of 60 mg/m^2/day (2 mg/kg/day, maximum 60 mg in 1-2 divided doses) for 6 weeks, followed by 40 mg/m^2 (1.5 mg/kg, maximum 40 mg as single morning dose) on alternate days for the next 6 weeks, and then discontinued. (1A)

Rationale

In 1981, the International Study of Kidney Disease in Children (ISKDC) proposed that the first episode of nephrotic syndrome be treated with daily prednisone for 4-weeks, followed by intermittent therapy for the next 4-weeks, and then discontinued [41]. Later, a randomized controlled trial (RCT) by the Arbeitsgemeinschaft für Padiatrische Nephrologie showed that therapy with prednisolone for 6-weeks daily and 6-weeks alternate-day was better in terms of reduced incidence of relapses over the next 12-24 months [42]. In efforts to define optimal therapy for the initial episode, several RCTs have investigated the duration and dose of prednisolone, based on which, a meta-analysis, in 2007, concluded that prolonging therapy for 6-months was associated with reduced risk of relapses and of frequent relapses (relative risk, RR 0.55; 95% CI 0.39-0.80) [43]. However, most studies included in this analysis had methodological flaws, resulting in a high risk of bias.

Four large multicenter RCTs published in the last 7 years have challenged the previous results (**Supp. Table II**). These studies, representing outcomes in over 800 patients across Netherlands, UK, Japan and India, show that extending initial therapy beyond 8-12 weeks does not influence either the time to first relapse or the risk of frequent relapses at 1-2 years' follow up. These studies had low risk of bias; three were placebo-controlled. A meta-analysis that included three of these studies, showed that the risk of frequent relapses at 1-2 years' follow-up was lower for 3-months or longer versus 2-months therapy (RR 0.68; 95% CI 0.47-1.0), but not for 5-months or longer versus 3-months therapy (RR 0.78; 95% CI 0.50-1.22) [44]. Subgroup analysis, limited to studies at low risk of bias, indicated similar risk for frequent relapses in patients treated for 2-3 months versus 3-6 months. These findings are confirmed with inclusion of the PREDNOS study (**Supp. Fig. 1**) [45]. While *post-hoc* analyses in two studies suggest a trend for benefit with prolonged therapy in young children, this finding requires confirmation [45,46].

Based on pharmacokinetics and variations by age, prednisolone is preferably dosed by body surface area in children [47]. However, estimation of body surface area involves complex formulae with variable results [48]. Calculation using body weight is convenient, but results in relative underdosing particularly in young children [47,49]. Underdosing, using weight-based calculations, was associated with increased risk of frequent relapses in some [50,51], but not in all studies [52,53]. Experts therefore prefer to administer prednisolone based on body surface area for young children [47].

Daily prednisolone is administered in single or divided-doses, with similar time to remission [54]. There is no evidence to support therapy with preparations other than prednisone or its active metabolite, prednisolone [55]. Use of deflazacort, betamethasone, dexamethasone or methylprednisolone is not advised. Prednisolone is best given following food; therapy with antacids, ranitidine or proton pump inhibitors is not routinely required.

Guideline 4: Therapy of relapses

We recommend that relapses be treated with prednisolone at 60 mg/m^2/day (2 mg/kg/day; maximum 60 mg) in single or divided-doses until remission (protein trace/nil for 3 consecutive days), followed by 40 mg/m^2 (1.5 mg/kg, maximum 40 mg) on alternate days for 4-weeks. (1C)

Rationale

Almost one-half of the relapses are precipitated by minor infections, usually of the upper respiratory tract. Treatment of infection may rarely induce remission, avoiding the need for corticosteroid therapy. A relapse has conventionally, albeit empirically, been treated as outlined above, but guidelines vary in the duration of therapy. Remission is achieved by 7-10 days, and daily therapy is seldom necessary beyond 2 weeks. In case of persistent proteinuria, daily therapy with prednisolone may be extended, to maximum of 6-weeks. Lack of remission despite treatment with 6-weeks' daily prednisolone indicates late steroid resistance that requires specific evaluation and management [10].

Dose based on body surface area and weight is associated with similar time to remission and frequency of subsequent relapses [52,53]. Retrospective studies and small RCTs suggest that reduced dose or abbreviated duration of therapy with prednisolone is effective in inducing and maintaining remission (**Supp. Table III**). Well-powered studies are required to evaluate the optimal dose and duration of prednisolone for relapses.

Guideline 5: Management of frequent relapses and steroid dependence

Definition

Frequent relapses are defined by the ISKDC as occurrence of two or more relapses in the first 6-months after initial response, or four or more relapses in a year [3]. These patients are at risk of morbidity associated with multiple relapses and corticosteroid toxicity. The term has been used for over 40-yr, with minor modifications. Additionally, we propose that patients with three or more relapses in any 6-months be also classified as frequent relapsers (**Box I)**. Steroid dependence, as previously defined, includes patients with two consecutive relapses, while receiving or within 2-weeks of discontinuing prednisolone [3,6].

The occurrence of two or more relapses in the first 6-months is usually associated with high frequency of relapses in the subsequent 12-24 months [3]. Patients experiencing 4 relapses annually receive ~165-200 mg/kg (4.6-5.6 g/m^2) prednisolone, corresponding to 0.45-0.55 mg/kg (12.5-15.5 mg/m^2) daily. As 12-weeks' prednisolone therapy for the initial episode (~115 mg/kg; ~3.4 g/m^2) might be associated with adverse effects [55,56], the risk of steroid toxicity in patients with 3 relapses in any 6-months or 4 relapses annually is considerable [57].

Two additional situations might suggest the need for steroid-sparing therapy. The first is a patient with significant steroid toxicity (**Box I**) and fewer relapses (3 relapses/year; 2 relapses in 6-months). The second is the occurrence of two relapses in 6-months during long-term therapy with corticosteroids or steroid-sparing agents. In both instances, it is rational to manage the patients as frequent relapsers, even if they do not satisfy standard definitions. While infrequent relapses or sustained remission during therapy with steroid-sparing agents is acceptable, the definition of failure of therapy depends on the medication, interval between relapses and need for concomitant corticosteroids.

5.1 Choice of therapy

We recommend that the choice of immunosuppressive strategy for patients with frequent relapses be based on considerations of its efficacy and adverse effects, patient age, steroid threshold, severity of relapses and features of steroid toxicity (**Fig. 1**). (X)

Rationale

In patients with frequent relapses, guidelines recommend that corticosteroid therapy for the relapse be prolonged and tapered over 3 months or longer [9,30,58]. The dose at which relapses occur (steroid

threshold) is a marker of disease severity. Prolonged therapy with alternate-day prednisolone might maintain remission in patients with low threshold relapses (<0.7 mg/kg on alternate days).

Steroid-sparing interventions are necessary in patients who continue to relapse frequently or show evidence of steroid toxicity while on alternate-day prednisolone (**Fig. 1**). There is limited data on relative efficacy of various steroid-sparing agents, and the choice of immunosuppressive strategy is guided by its efficacy, safety, cost and availability, patient age, disease severity, and parental preference (**Table II**). Potent medications are preferred in patients with high threshold (>1 mg/kg on alternate day) relapses, relapses associated with life-threatening complications, or with significant steroid toxicity (**Box I** and **Table II**). Occurrence of infrequent relapses during such therapy is acceptable, and except in severe steroid dependence, prednisolone is tapered and discontinued over few months. Therapy may be modified in patients with frequent relapses or significant adverse effects.

A proportion of patients with SSNS show disease characterized by multiple relapses despite therapy with steroid-sparing agents, and/or medication-associated toxicity. We propose defining *difficult-to-treat nephrotic syndrome* as patients with: *(i)* frequent relapses or infrequent relapses with significant steroid toxicity; and *(ii)* failure of 2 or more steroid sparing agents: levamisole, cyclophosphamide, mycophenolate mofetil (MMF). These patients might merit therapy with agents such as CNI and rituximab.

While the approach to management indicated in **Fig. 1** suffices in most instances, individual situations may require different preference. Patients diagnosed either with steroid dependence soon after initial therapy, or with significant steroid toxicity at diagnosis of frequent relapses may be considered directly for steroid sparing therapies. Therapy with oral cyclophosphamide is avoided in young patients and in pubertal or post-pubertal boys. Therapy with CNI may be preferred to MMF in very young patients with significant steroid toxicity, even though the definition of difficult-to-treat SSNS is not met.

5.2 Long-term corticosteroids

- In patients with frequent relapses, we suggest tapering prednisolone to a dose of 0.5-0.7 mg/kg on alternate days, for 6-12 months. (2B)
- In patients receiving long term alternate-day prednisolone, we recommend administering the same dose daily for 5-7 days during fever or respiratory tract infection. (1B)

Rationale

Therapy with alternate-day prednisolone is the initial strategy for managing patients with frequent relapses [6,58]. Alternate-day prednisolone, often used as the control limb in RCTs, showed satisfactory response in 43-82.5% patients (**Supp. Table IV**). A balance of benefit over harm is lacking, and there are risks of corticosteroid toxicity. Therefore, in patients in remission at prednisolone dose of 0.5-0.7 mg/kg for a few months, the medication may be tapered to ~0.2-0.3

mg/kg on alternate days. The duration of therapy is at physician discretion, based on its efficacy and assessment of toxicity through monitoring of weight, height, blood pressure, ocular toxicity and hyperglycemia (**Table II**).

Daily prednisolone during infections

More than one-half of relapses in SSNS occur following upper respiratory tract infections. Evidence from three studies (**Supp. Table V)** indicates that, beginning with the onset of infection, switching therapy from alternate-day to daily administration of prednisolone for 5-7 days prevents the occurrence of relapses. One cross-over trial also supports the use of low-dose daily prednisolone in preventing infection-associated relapses in patients off corticosteroids [59]. Results of the recently concluded PREDNOS2 trial will clarify the role of these strategies in preventing infection-associated relapses (ISRCTN10900733).

Daily prednisolone in low-dose

Data from an open-label RCT [60] and a case series [61] suggests that low-dose (0.2-0.3 mg/kg) daily prednisolone is associated with fewer relapses than twice the dose (0.5-0.7 mg/kg**)** on alternate days. The strategy led to lower steroid requirement and was not associated with toxicity [61]. These findings require confirmation in studies with longer follow-up that are powered to examine adverse effects, including suppression of the hypothalamo-pituitary-adrenal axis [62].

5.3 Non-corticosteroid therapies

- We recommend use of a steroid-sparing agent in patients failing therapy with alternate-day prednisolone, steroid toxicity or complicated relapses (**Fig. 1**). (1B)
- In patients failing alternate-day prednisolone, we recommend therapy with either levamisole or MMF for 12-24 months. (1B)
- We recommend MMF or cyclophosphamide in patients with significant steroid toxicity, high steroid threshold, complicated relapses, of failure of therapy with levamisole. (1C)

Rationale

Levamisole

Levamisole has been used for almost 4-decades, mainly in Asia and Europe, as a steroid-sparing agent for frequent relapsing nephrotic syndrome [63]. A recent meta-analysis (8 studies, 462 patients; **Supp. Table VI**), suggested 35% reduction in the risk of relapses following 6-12 months' therapy with levamisole (RR 0.65; 95% CI 0.48-0.88) [64]. The medication is more useful in patients with frequent relapses than in steroid dependence [65]. Comparative studies indicate that the risk of relapse in patients receiving levamisole is similar to cyclophosphamide (2 studies, 97 children; RR 2.14; 95% CI 0.22-20.95), or MMF (one study, 149 patients; RR 1.11; 95% CI 0.86-1.43) [64]. Given the efficacy and safety, the agent is being examined in two RCTs when administered at onset of the disease (LEARNS, EudraCT 2017-001025-41; NEPHROVIR3, NCT02818738).

Levamisole is given at the dose of 2-2.5 mg/kg on alternate days (**Table II**). While few retrospective studies report its efficacy when administered daily (**Supp. Table VII**), the safety of this strategy should be examined in controlled studies with close monitoring for adverse effects, including neutropenia, raised transaminases, anti-neutrophil cytoplasmic antibodies and/or small vessel vasculitis [63,66,67].

Mycophenolate mofetil (MMF)

The use of MMF in frequently relapsing nephrotic syndrome is recent. A review of 7 prospective and 6 retrospective series (508 patients) showed that therapy with MMF for 6-19 months lowered relapse rates, and reduced requirement of prednisolone and/or CNI (**Supp. Table VIII**) [68]. While placebo-controlled, blinded RCTs are lacking, MMF was found to be comparable to levamisole but inferior to cyclosporine in maintaining satisfactory remission or reducing the frequency of relapses in 3 open-label RCTs (**Supp. Table IX**) [64]. Likewise, MMF had efficacy similar or inferior to tacrolimus in a non-randomized comparison (**Supp. Table IX**). MMF is perhaps more efficacious in young children [69], and more effective than levamisole in patients with steroid dependence [70].

Therapy with MMF is given in two divided doses, 600 to 1200 mg/m^2 (20-30 mg/kg) per-day [68]. Dose-related adverse effects include leukopenia, abdominal pain and diarrhea. Data from one RCT suggests that patients with higher blood levels of MMF (determined by area under the curve, AUC) show efficacy similar to cyclosporine [71]. Others emphasize the need to achieve mycophenolic acid AUC levels exceeding 45-60 μg*h/mL [72-74] or trough levels >2-3 μg/mL [75-78]. While pharmacokinetics of MMF is variable, adequate levels are achieved with high doses [76-78]. In the absence of facilities for therapeutic drug monitoring, we propose initiating therapy at the lower end of dose range and escalating as tolerated, to 1000-1200 mg/m^2, if the patient continues to relapse.

Cyclophosphamide

Oral cyclophosphamide, at 2-2.5 mg/kg daily for 8-12 weeks, is the most commonly used steroid-sparing agent in SSNS. Its use finds basis in evidence of efficacy and overall safety, as summarized in a systematic review (38 prospective and retrospective studies, 1504 patients) of patients administered cyclophosphamide or chlorambucil [79]. A recent meta-analysis shows reduced risk of relapse at 6-12 months (6 studies, 202 patients; RR 0.44; 95% CI 0.32-0.60) and 12-24 months (4 studies, 59 patients; RR 0.20; 95% CI 0.09-0.46) following therapy with alkylating agents [64]. In comparative studies, the risk of relapse at 12-24 months following cyclophosphamide therapy was similar to levamisole (1 study, 40 patients; RR 1.12; 95% CI 0.86-1.16), but lower than cyclosporine (2 studies, 95 patients; RR 0.51; 95% CI 0.35-0.74) [64]. A Bayesian network analysis (7 reports, 391 patients) showed lowest relapse rates with cyclophosphamide, compared to other medications [80]. Cyclophosphamide is more effective in patients with frequent relapses than in steroid dependence, and in patients older than 5-7 years **(Supp. Table X)**.

Therapy with cyclophosphamide is initiated during remission. Prednisolone is given at a dose of ~1 mg/kg on alternate days during therapy with cyclophosphamide; the medication may subsequently be stopped after 1-2 months. Leukopenia is the chief adverse effect, reported in one-third of patients; other concerns are alopecia and the risk of infections (**Table II**). Leukocyte count is monitored every 2 weeks, and therapy withheld if the count falls below 4000/mm^3. Increased fluid intake and frequent voiding prevents hemorrhagic cystitis which, along with nausea and vomiting, is common with intravenous (IV) dosing. The risk of gonadal toxicity is proportionate to the cumulative dose, and appears to be high in pubertal and post-pubertal boys (Tanner stage 2 or more), and lower in girls [30,79,81]. Therapy with chlorambucil is associated with risk of seizures, and is not recommended.

Given concerns of gonadal toxicity and malignancy, therapy with cyclophosphamide is usually administered after failure of levamisole or MMF, and is limited to one 12-weeks' course (cumulative ~168 mg/kg). Occasionally, cyclophosphamide may be the preferred initial steroid-sparing therapy in patients older than 7-yr, particularly in presence of significant steroid toxicity and/or complicated relapses. Limited evidence indicates that cyclophosphamide (500 mg/m^2 monthly IV pulse; 6-doses) is as effective as 12-weeks' oral therapy [64], and may be considered in patients with likely non-compliance to oral therapy.

5.4 Difficult-to-treat steroid sensitive nephrotic syndrome

- We recommend therapy with CNI, either cyclosporine or tacrolimus, in patients with difficult-to-treat SSNS. (1B)
- We recommend therapy with rituximab in patients who have either failed CNI or have received these agents for a prolonged duration. (1C)
- We suggest that therapy with rituximab be administered during disease remission after ruling out acute and chronic infections, and should target B cell depletion. (2B)

Rationale

Calcineurin inhibitors

Observational studies indicate that CNI (cyclosporine 4-6 mg/kg/day, tacrolimus 0.1-0.2 mg/kg/day, in two divided doses) maintain remission and enable steroid-sparing in 60–90% patients with frequent relapses or steroid dependence who have failed treatment with alkylating agents [82-84]. These agents have not been compared to placebo or to each other in controlled studies for SSNS. While one RCT each found that cyclosporine was associated with reduced risk of relapse as compared to prednisolone (104 children; RR 0.33; 95% CI 0.13-0.83) or MMF (see above), patients relapsed when the therapy was discontinued [64]. In view of the efficacy and significant steroid-sparing, CNI are preferred for patients with high threshold relapses or significant corticosteroid toxicity. While therapy with CNI is usually restricted to patients with difficult-to-treat SSNS (**Box I**), these agents may be considered before MMF or cyclophosphamide in young children with severe steroid dependence and/or

significant steroid toxicity. The choice of the medication should follow discussion with parents about potential toxicities and the need for monitoring.

Chief adverse effects of CNI include acute and chronic nephrotoxicity (with both agents), hirsutism, gum hypertrophy, hypertension and hyperlipidemia (with cyclosporine), and hyperglycemia or seizures (with tacrolimus) [82,83]. While tacrolimus is preferred to cyclosporine due to lack of cosmetic effects, only the latter is available as an oral suspension for young children. Therapy should be administered for at least 12-months, with monitoring of drug levels (**Table II**). Lower target trough levels and once-daily dosing is acceptable during sustained remission [85.86]. The role of protocol biopsies, before initiating therapy with CNI and following their prolonged use, is discussed in Guideline 2.

Rituximab

B cell depletion has emerged as an effective strategy for sustaining remission in patients with steroid- and/or CNI-dependent nephrotic syndrome. Therapy with rituximab (375 mg/m^2 IV once a week for 1-4 doses) in 13 prospective and retrospective series (n=159) led to sustained remission in 25-71% patients, postponement of relapse by (median) 5-11 months, and withdrawal of other therapies [87]. A systematic review confirmed similar efficacy in 86 adults administered rituximab for frequent relapses [88]. In non-randomized comparisons, the efficacy of rituximab was superior to cyclophosphamide (2 studies, 148 patients) and comparable to tacrolimus (1 study, 23 patients) (**Supp. Table XI**). In a prospective study, therapy with 2-3 doses of rituximab in 101 patients was associated with over two-third reduction in relapses, postponement of relapse by median 16-months and reduced steroid requirement [89].

Data from 7 RCTs in patients with frequent relapses and steroid/CNI dependence indicates superior efficacy of rituximab as compared to placebo (2 studies, 71 patients), or no additional therapy (2 studies, 91 patients); the efficacy was similar or superior to CNI in one study each (174 patients) (**Supp. Table XI**). A Cochrane meta-analysis concluded that therapy with rituximab, in combination with CNI and prednisolone, versus the latter alone, reduced the risk of relapse at 6 months (5 studies, 269 patients; RR 0.23, 95% CI 0.12-0.43) and 12 months (3 studies, 198 patients; RR 0.63, 95% CI 0.42-0.93) [64].

Experts advise administering rituximab at a dose of 375 mg/m^2 IV, using B cell depletion (CD19+ <1% of CD45+ cells, or <5 cells/µl) as a marker for adequacy of dosing. While B cell depletion is usual after even one dose [87], a maximum of 4 infusions have been given. Since administration of rituximab during relapse is associated with its urinary excretion and reduced half-life, therapy is preferred during remission [90]. B cell recovery usually occurs by 6-9 months, and is associated with risk of relapses [87,88,90]. Studies comparing response to rituximab in relation to the number of doses and use of maintenance immunosuppression are summarized in **Supp. Table XII**. An international cohort on 511 patients with frequent relapses or steroid dependence showed that

relapse-free survival was significantly shorter for patients given a single dose of rituximab (8.5 months) compared to those given two (12.7 months) or more doses (14.3 months) [91]. Additional immunosuppression, with MMF, was useful in sustaining remission following therapy with a single dose of rituximab. In patients with difficult-to-treat SSNS with satisfactory response to rituximab, repeated doses of the medication, following relapses or repopulation of B cells, is suggested as a strategy to sustain remission (**Supp. Table XII**). Given the concerns discussed below, the optimal strategy is not clear.

Systematic reviews show that therapy with rituximab is associated with infusion reactions (4 studies, 252 children; RR 5.8, 95% CI 1.3-25.3) [64], delayed adverse events and infections [87,88]. A German registry of autoimmune diseases (370 patients) reported serious infections in 5.3 cases per 100 patient-years [92]. Patients with lymphoma treated with rituximab show reactivation of hepatitis B virus infection in 9% (95% CI 5%-15%) patients [93]. In contrast to the reports of normal IgG in adult patients receiving multiple doses of rituximab (**Supp. Table XII**), hypogammaglobulinemia is not uncommon after such therapy in children with nephrotic syndrome and autoimmune diseases. The risk of hypogammaglobulinemia correlates inversely with age, and positively with the number of rituximab doses [94-96].

We recommend that rituximab be used in patients with difficult-to-treat disease, under the supervision of a pediatric nephrologist. Its use should be avoided in young children (<5-7 yr old), and restricted to patients failing other steroid-sparing agents. Active acute infections and chronic viral infections should be ruled out before therapy. We recommend administering two doses of rituximab during disease remission, at 375 mg/m^2 one-week apart, followed by confirmation of B cell depletion, 2-7 days after the second dose. Vigilance for infections and monitoring for leukopenia and hypogammaglobulinemia is essential during follow up. Further doses of rituximab should be avoided in patients with severe infusion-related adverse events, severe infections or with hypogammaglobulinemia. Prophylactic antibiotics are not routinely recommended. We suggest administering cotrimoxazole (150 mg/m^2 or 5 mg/kg of trimethoprim on alternate days) in patients receiving intense immunosuppression, such as those receiving maintenance immunosuppression with CNI or MMF following therapy with rituximab.

SUPPORTIVE CARE

Patients with nephrotic syndrome are at risk of complications of the disease, and side effects of its medications. Principles of management of hypertension, thromboembolism, growth retardation, obesity, dyslipidemia, and hypothyroidism are discussed in the guidelines on steroid resistant nephrotic syndrome [10]. We emphasize that patients who have received oral steroids for more than 2-weeks within the past one-year, should receive additional corticosteroids during conditions associated with physiological stress like systemic infections, inadequate oral intake, lethargy, dehydration, invasive or dental surgery, trauma and large burns [10]. Conditions such as

uncomplicated viral infections, acute otitis media and fever following immunization do not require stress dosing.

Guideline 6: Management of Hypovolemia and Edema

Edema, a cardinal feature of nephrotic syndrome, often requires specific therapy. We propose that edema be empirically classified based on appearance and percentage weight gain from baseline, as mild (≤7% increase), moderate (8-15%) and severe (>15% increase) [97]. If urine protein is monitored regularly, the occurrence of more than mild edema is unusual. Patients with severe edema have marked hypoalbuminemia (serum albumin <1.5 g/dL), along with ascites and anasarca that interferes with daily activities [97,98]. Intravascular volume depletion is common in patients with moderate or severe edema [99,100], and should be assessed before instituting therapy with diuretics.

6.1 Hypovolemia

- We recommend that patients with moderate to severe edema be assessed for intravascular volume status before initiating therapy with diuretics (**Fig. 2**). (X)
- We recommend the use of normal saline and IV albumin in patients with disease relapse and hypovolemia. (1C)

Rationale

A combination of clinical and biochemical features helps estimate intravascular volume (**Box III**, **Fig. 2**) [97,101]. Patients with hypovolemia often have abdominal pain, nausea, vomiting, dizziness and lethargy. Examination shows tachycardia, pallor, cold peripheries, delayed capillary refill and postural hypotension, and rarely shock [97,101,102]. On the other hand, patients with hypervolemia have refractory anasarca, hypertension and dyspnea [99,100]. Two urinary indices may help assess intravascular volume: fractional excretion of sodium (FENa) and potassium index [103,104]. While both underfill and overfill states are associated with sodium retention [105-107], FENa <0.5% and potassium index >0.6 indicate high aldosterone activity, characteristic of hypovolemia [104,105,108]. The indices are not reliable with recent diuretic therapy and while receiving IV fluids. Other parameters of volume status include changes in hematocrit, urea to creatinine ratio, inferior vena cava diameter and collapsibility, and bioimpedance analysis [97,99-101,109,110].

Hypovolemia may occur at disease onset or relapse, particularly in a setting of diarrhea, vomiting or unsupervised diuretic therapy. Therapy with diuretics should be discontinued. Hypotensive patients should receive 1-2 boluses of isotonic saline (10-20 ml/kg infused over 20-30 minutes) and/or 5% albumin (10–15 ml/kg over 30-60 minutes) (**Fig. 2**). Subsequently, patients are managed with IV and oral hydration, and IV albumin (20%; 0.5–1 g/kg over 3-4 hr) [97,99,101].

6.2 Edema

- We recommend oral furosemide as first line therapy for patients with moderate edema without hypovolemia (**Fig. 2**). (1C)

- We suggest that patients with furosemide-refractory edema be managed as follows: *(i)* combination of loop diuretics with thiazide; *(ii)* co-administration of human albumin with IV furosemide. (X)

Rationale

Patients with mild edema do not require diuretic therapy. Corticosteroid therapy for relapse results in diuresis within one-week, enabling loss of retained extracellular fluid [97,101]. Patients are advised to limit sodium intake (1-2 mEq/kg/day; 15-35 mg/kg salt). Foods rich in salt (>10 mEq/100 g; e.g., bread, cornflakes, processed cheese, sauces, potato chips, salted nuts, *papad*, pickles) and preserved foods (canned vegetables, soups and meat) are avoided in presence of significant edema [97,101].

Diuretics are the initial therapy for patients who are volume replete. Patients with moderate edema without hypovolemia are managed with furosemide (2-4 mg/kg/day) that acts on the ascending limb of Henle [101,105]. Sequential nephron blockade, with additional use of hydrochlorothiazide (2-4 mg/kg/day) or metolazone (0.1-0.2 mg/kg q12-24 hr), augments diuresis by reducing distal sodium reabsorption [97,101]. Monitoring for hypovolemia, hypokalemia and alkalosis is essential. Spironolactone has limited diuretic efficacy, but is an effective potassium-sparing agent in patients receiving high-dose furosemide [97,101]. Use of acetazolamide or amiloride is not advised.

Patients with severe edema may fail to respond to maximal doses of furosemide and thiazide diuretics (diuretic resistance) [98]. Factors contributing to diuretic resistance are poor adherence to salt restriction, reduced bioavailability of furosemide, hypoalbuminemia, hypovolemia, and compensatory salt reabsorption in the distal tubule. The bioavailability of oral furosemide is 20-60%, and is impaired by gut edema in nephrotic syndrome [98]. In patients unresponsive to oral furosemide, assessed as absence of diuresis within 2-4 hr of its administration, switching to IV therapy may elicit a response. IV furosemide, given either as 1-2 mg/kg q 8-12 hr, or bolus of 1 mg/kg followed by infusion of 0.1-0.4 mg/kg/hr is effective [97,98,101]. While torsemide has better efficacy and bioavailability than furosemide in adults with heart failure [111], information in nephrotic syndrome is lacking.

Furosemide, tightly bound to blood albumin, is actively secreted *via* organic acid pumps in the ascending limb of Henle. Tubular secretion is impaired in patients with severe hypoalbuminemia, resulting in diuretic resistance [101]. The combination of 20% albumin (0.5-1 g/kg infused over 3-4 hr) and furosemide (1-2 mg/kg at end of infusion) enhances drug delivery to tubules, with increased efficacy in terms of urine output and weight loss [110,112,113]. A meta-analysis confirmed that combination therapy results in diuresis and natriuresis, which declines by 24-hr [101,114]. Therapy with IV albumin may be associated with risk of worsening hypertension, respiratory distress and heart failure, and is therefore avoided in patients with impaired kidney function [97-99,101,112].

Patients with severe edema who are refractory to the above therapies are likely to have fluid overload, usually in presence of steroid resistance or kidney dysfunction. These patients might require

ultrafiltration or kidney replacement therapy. An approach to evaluation and management of edema is shown in **Fig. 2**.

Guideline 7: Infections and Immunization

Bacterial infections

7.1 We suggest that serious bacterial infections associated with nephrotic syndrome be managed as indicated in **Table III**. (X)

Rationale

Infections are the chief complication in patients with SSNS, accounting for 19-44% of hospitalizations [115-120]. Contributing factors include the use of immunosuppressive agents, anasarca, and urinary losses of IgG and complement factors, that predispose to infection with encapsulated organisms [121]. Peritonitis is the most common severe infection, followed by pneumonia and cellulitis [115-119]. Chief pathogens causing peritonitis are pneumococci and *E. coli;* those causing pneumonia include pneumococci, *H. influenzae* and *S. aureus*; and those responsible for cellulitis are staphylococci, group A streptococci and *H. influenzae* [115-119]. The diagnosis and treatment of severe infections should follow standard guidelines [122-124] (**Table III**). Apart from vaccines, there is no evidence of efficacy of other interventions for preventing bacterial infections in patients with nephrotic syndrome [125].

Viral infections

Several viruses, including rhinovirus, adenovirus, influenza, parainfluenza, enterovirus, and respiratory syncytial and Epstein Barr viruses, might trigger disease relapses [126,127]. Infections such as varicella, zoster and influenza might be associated with significant morbidity, and merit specific prevention and management [128-130].

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection

Infection with SARS-CoV2, the etiological agent of coronavirus disease (COVID-19), poses challenges in management of patients with nephrotic syndrome [131]. While children show mild disease, patients on immunosuppression constitute a high-risk group that is predisposed to adverse outcomes. Affected patients are at risk of AKI, particularly if associated with hypovolemia or aggressive use of diuretics. In absence of specific therapy for SARS-CoV-2 infection, most expert groups advise reduction of immunosuppression to acceptable levels, balancing the risk of disease relapses against infection [131,132]. Other considerations include advice through teleconsultation; low threshold for inpatient monitoring of infected patients; and limiting the use of biological agents and antimetabolites [131,132]. Steroid dosing during SARS-CoV-2 infection should follow standard practices regarding stress dosing [10]; relapses may be treated with a lower dose of prednisolone.

7.2 Immunization

We suggest that patients with nephrotic syndrome receive: *(i)* age-appropriate killed, subunit or inactivated vaccines; *(ii)* live vaccines following principles outlined in **Table IV**; *(iii)* vaccines against pneumococcus, varicella, influenza and hepatitis B (**Table V**). (X)

Rationale

Children with nephrotic syndrome should receive vaccines as appropriate for age [133,134]. Killed, inactivated or subunit vaccines are not contraindicated, but may have reduced efficacy during immunosuppression [133-136]. Principles of immunization with live vaccines in immunocompromised children and their household contacts are listed in **Table IV** [124,134,137]. The schedule for administration of specific vaccines that are relevant to patients with nephrotic syndrome is summarized in **Table V** [133,134,138]. The risk of relapse following vaccination is negligible [135,139].

Pneumococcal vaccine

The availability of safe and immunogenic vaccines has reduced the risk of pneumococcal infections in patients with relapsing nephrotic syndrome [140]. Two categories of vaccines are available. The polysaccharide vaccine (PPSV23) is poorly immunogenic in patients younger than 2-years, and does not induce immunological memory. Conjugate vaccines (PCV7-, 10- and 13-valent) induce superior and sustained antibody responses and immune memory even in young infants, with pooled efficacy of 58% (95% CI 29-75%) against invasive disease caused by any pneumococcal serotype [135,141]. The efficacy of PPSV23 and PCV vaccines in patients with SSNS is variable. Information is lacking on the precise impact of vaccination on rates of peritonitis, cellulitis and pneumonia.

Both PCV7/10/13 and PPSV23 elicit satisfactory serological response, even when given during relapse or while on immunosuppressive agents [135]. Nevertheless, we suggest that the vaccine be preferably given during remission, and while on low or no immunosuppression. Antibody responses are ill-sustained in patients with recurrent relapses, justifying re-dosing with PPVS23 after 5 years if the disease remains active; more than 2-doses of PPSV23 are not recommended [134,135].

Varicella vaccine

In view of the risk of severe disease in immunocompromised patients, we recommend that patients with nephrotic syndrome receive two doses of the varicella vaccine, 4-8 weeks apart (**Table V**) [134,138]. Two doses result in seroconversion in ~95% vaccinees; breakthrough varicella might occur in 2.2-7.3% children [142]. The vaccine was safe and immunogenic in 109 patients with nephrotic syndrome, including those receiving low-dose corticosteroids, in two prospective series [143,144] and in an open-label RCT [145].

Severe varicella might follow infection in at-risk individuals exposed to persons with either varicella or herpes zoster. Multiple strategies for post-exposure prophylaxis are used to prevent viral transmission (**Table VI**) [124,133,134,138,146-149]. Unimmunized patients with nephrotic syndrome

who are not immunosuppressed should receive the vaccine within 5-days of exposure [124]. The risk of post-exposure varicella was reduced to one-third in children who were vaccinated following exposure, compared to those unimmunized (3 studies; n=110; 23% *vs.* 78%) [147]. Healthy household contacts should also receive the vaccine to minimize the risk of infecting the patient. In patients in whom vaccination is contraindicated, the Center for Disease Control recommends administration of varicella zoster immune globulin (VARIZIG) within 10-d of exposure [148]. VARIZIG administration was associated with varicella in <10% of 507 high-risk participants, including 231 immunosuppressed children [149]. In view of the low and variable titer of anti-VZV antibodies [150], intravenous immunoglobulin (IVIG) is not recommended [124,134]. If VARIZIG is not available, similar to guidelines from the American Academy of Pediatrics [124] and French Society of Pediatric Nephrology [138], we recommend administering oral acyclovir or valacyclovir for 7-days, starting 6-10 days after exposure, corresponding to the period of secondary viremia (**Table VI**).

Influenza vaccine

Influenza accounts for 13% of all pneumonia, and 7% of severe pneumonia in children <5-yr-old [150,151]. Approximately 1 in 5 unvaccinated children are annually infected by influenza, of which one-half are symptomatic [152]. Given the risk of morbidity in immunosuppressed individuals, annual administration of the inactivated influenza vaccine is recommended for patients with nephrotic syndrome (**Table V**), and their household contacts [124,130,138].

Hepatitis B vaccine

Hepatitis B vaccination coverage rates in India are unsatisfactory, and 45% of 1-6 yr-old children are not vaccinated [153]. Compared to healthy children, fewer patients with nephrotic syndrome show seroprotective (≥10 mIU/mL) antibody titers [154]; one-half of these patients seroconvert after vaccination [136,155]. Seroprotection was lower in patients with steroid resistance, and those on non-steroid therapies [136,154,155]. To overcome vaccine failure, we advise an accelerated schedule using twice the age-appropriate dose, and assessment of serological response to administer booster dose(s) (**Table V**) [156].

Guideline 8: Transition of care

We recommend that patients with nephrotic syndrome who continue to have relapses in adolescence be transitioned into care by adult physicians. (X)

Rationale

SSNS is a self-limiting illness, with the majority of patients outgrowing the illness by puberty. Review of information from multiple cohorts, with median follow-up of 4-30 yr, indicates that the frequency of relapses declines with age [3,4,157-159]. However, 5-42% patients may continue to have active disease in adulthood. Risk factors for illness persisting beyond 18-yr of age include early age at onset, and frequently relapsing or steroid dependent course [3,4,157,158].

Major infections, associated with relapses and intense immunosuppression, are the chief cause of hospitalization and mortality (0-8%) [3,157,158]. Kidney failure is uncommon (≤1%) in patients with SSNS. There is significant risk of short stature (15%), obesity (10%), hypertension (6-46%), metabolic bone disease (9-63%), diabetes mellitus (2%), ocular complications (10%), infertility and malignancies [157,158,160]. Psychosocial concerns, including school-drop out, unemployment and unstable relationships are common.

Given the risk of disease persistence and prevalence of complications, it is advised to transfer the care of adolescents with relapsing disease to 'adult' nephrologists by 18-yr of age. National and international guidelines advocate for smooth transition, with emphasis on shared clinics and consideration of patient and parent perspectives [161].

CONCLUSIONS

The present guidelines, based on best available evidence and expert guidance, provide directions for evaluation and management of SSNS in children. Recommendations, proposed by the Indian Society of Pediatric Nephrology, in 2001 and 2008, have been revised based on systematic reviews, published studies and expert opinion. The management of frequent relapses continues to be challenging, with morbidities associated with the disease as well as therapies. Well-designed prospective studies are required to address issues related to therapy of the initial episode and relapsing nephrotic syndrome **(Table VII)**. We hope that the present guidelines will standardize therapies and improve the quality of care for patients with the disease.

Note: Supplementary material related to these recommendations is available at *www.indianpediatrics.net/_____).*

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Annexure I

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Table I Comparison Between Present and 2008 [7] Guidelines of the Indian Society of Pediatric Nephrology (ISPN), and Kidney Disease Improving Global Outcomes (KDIGO) 2021 [9]

Parameter	***ISPN 2020***	***ISPN 2008 [7]***	***KDIGO 2020 [9]***
Nephrotic syndrome	Nephrotic range proteinuria, hypoalbuminemia (albumin <3 g/dL) and edema	Nephrotic range proteinuria, hypoalbuminemia (<2.5 g/dL), cholesterol >200 mg/dL and edema	Nephrotic range proteinuria and either hypoalbuminemia (<3 g/dL) or edema
Steroid resistance	Lack of complete remission despite daily therapy with prednisolone for 6-wk	Lack of complete remission despite daily therapy with prednisolone for 4-wk	Lack of complete remission despite daily therapy with prednisone at 4-weeks^
Prednisolone for initial episode	6-wk daily and 6-wk AD; surface area (BSA) or weight-based dosing#; no indication for prolonged therapy	6-wk daily and 6-wk AD; weight-based dosing#; no indication for prolonged therapy	4-6 wk daily and 4-6 wk AD; BSA or weight-based dosing#; prolong therapy (16-24 wk) if <4-6 yr-old, or if delayed remission
Frequent relapses	≥2 relapses in first 6-months after initial therapy; ≥3 relapses in any 6-months; ≥4 relapses in 1-yr	≥2 relapses in first 6-months after stopping initial therapy; ≥4 relapses in 1-yr	≥2 relapses in 6-months; ≥4 relapses in 1-yr
Prolonged AD prednisolone	Taper to 0.5-0.7 mg/kg AD for 6-12 months	Taper to 0.5-0.7 mg/kg AD, for 9-18 months	Limited role in view of risk of toxicity
Prednisolone during infections	Daily for 5-7 days, if receiving AD prednisolone	No recommendation	Daily at 0.5 mg/kg for 5-7 days, whether on/off steroids
Steroid sparing therapy: Indications, choice	Failure of AD therapy: Levamisole or MMF Steroid threshold >1 mg/kg AD, toxicity, complicated relapses: Cyclophosphamide, MMF Difficult-to-treat: CNI, then rituximab	Failure of AD therapy, steroid toxicity: Levamisole Steroid toxicity, severe relapses, poor compliance: Cyclophosphamide Failure of above therapies: CNI; MMF an option	Frequent relapses with steroid toxicity; patients with dependence Frequent relapses: Levamisole, cyclophosphamide Dependence: MMF, rituximab, cyclophosphamide, CNI
Supportive	Advice on diet, immunization, management of edema; role of parents		Calcium, vitamin D supplements

AD alternate days; CNI calcineurin inhibitor; MMF mycophenolate mofetil
^Late responder: Partial remission at 4 weeks and complete remission at 6 weeks of daily prednisone
#BSA-based dosing: 60 mg/m^2 daily and 40 mg/m^{2}AD; weight-based: 2 mg/kg/day and 1.5 mg per kg AD; maximum 60 mg daily and 40 mg AD

Table II Immunosuppressive Medications for Frequent Relapses

Medication	***Dose***	***Duration***	***Adverse effects***	***Recommended monitoring***
Prednisolone	0.5-0.7 mg/kg on alternate day[a,b]	6-12 mo	Cushingoid features; short stature; hypertension; raised intraocular pressure; glucose intolerance; cataract; elevated transaminases	Screen for side effects, hypertension Anthropometry q 3-6 mo; eye evaluation q 6-12 mo; blood sugar and transaminases q 3-6 mo
Levamisole	2-2.5 mg/kg on alternate day	2-3 years	Leukopenia, ANCA positive vasculitis, high transaminases, seizures	Blood counts^ q 2-3 mo; transaminases q 4-6 mo
Cyclophosphamide	2-2.5 mg/kg/day orally	8-12 weeks	Leukopenia, alopecia, infections; discolored nails; hemorrhagic cystitis; gonadal toxicity and malignancies	Blood counts q 2 weeks[c] Maintain hydration; discontinue during significant infections Co-administer with prednisolone 1 mg/kg AD
Mycophenolate mofetil	600-1200 mg/m^2/day in divided doses; AUC >45 mg·h/L	2-3 years	Abdominal pain, diarrhea, nausea, weight loss; viral warts; leukopenia; elevated transaminases	Screen for adverse effects Blood counts[c] and transaminases q 3-6 mo
Cyclosporine	4-5 mg/kg/day in divided doses; trough 80-120 ng/mL[a]	2-3 years	Both: Nephrotoxicity, hyperkalemia, hepatotoxicity Cyclosporine: Gingival hyperplasia, hypertrichosis; hypertension; dyslipidemia Tacrolimus: Tremors, seizures, headache; diarrhea; glucose intolerance; hypomagnesemia	Screen for cosmetic side effects, tremors, diarrhea, hypertension Creatinine, potassium at 2-4 weeks, q 3-6 mo Liver function tests, glucose, uric acid, magnesium and lipids q 3-6 mo
Tacrolimus	0.1-0.2 mg/kg/d in divided doses; trough 4-8 ng/mL[a]	2-3 years		
Rituximab	375 mg/m^2, slow IV infusion	2 doses, 1-week apart[d]	Chills, fever; serum sickness; bronchospasm Acute lung injury Neutropenia; *P. jirovecii* pneumonia; reactivation of hepatitis B or JC virus; hypogammaglobulinemia	Pre dose: Blood counts, transaminases; hepatitis and HIV serology; immunoglobulin G (IgG) level Post therapy: CD19 counts; blood counts; IgG; consider cotrimoxazole prophylaxis

AUC area under the curve (therapeutic drug monitoring); mo months

[a]*May reduce dose further if remission is sustained*

[b]*During infections, administer alternate day prednisolone at 0.5 mg/kg every day for 5-7 d to prevent relapse*
[c]*Withhold if total leukocyte count <4000/mm^3*
[d]*One to two additional doses are given at weekly intervals if CD19+ cells are >5/µL (or >1% of CD45+ cells) despite two doses of rituximab.*

Table III Management of Serious Infections

Infections	*Organisms*	*Diagnosis*	*Treatment*
Peritonitis	*S. pneumoniae, S. pyogenes E. coli,* Gram negative bacteria	Ascitic fluid: >100 white cells/mm^3, >50% neutrophils Ascitic fluid: Culture, latex agglutination, PCR	Ceftriaxone or cefotaxime for 7-10 d Ampicillin and gentamicin/amikacin for 7-10 d[a]
Pneumonia	*S. pneumoniae, S. aureus, H. influenzae* Influenza H1N1 *M. tuberculosis*	Chest X ray; blood culture; sputum for Gram stain and culture Throat swab for H1N1 by PCR Tuberculin test; pleural tap, gastric aspirate, sputum: acid fast bacilli, CBNAAT	Oral: Amoxicillin, coamoxiclav, cefuroxime for 10-14 d^ Parenteral: Ceftriaxone; or ampicillin and amikacin for 7-10 d^ Oseltamivir for 5 d Therapy as per National Tuberculosis Elimination Program [16]
Cellulitis	*S. aureus, S. pyogenes* *H. influenzae* Gram negative bacteria	Pus for culture, sensitivity Blood culture	Parenteral: Coamoxiclav; cloxacillin with ceftriaxone for 7-10 d^
Sepsis	*S. pneumoniae*, Gram negative bacteria	Complete blood counts; C-reactive protein, procalcitonin; blood culture	Ceftriaxone and amikacin for 10-14 d
Varicella	Varicella zoster virus	Clinical	IV acyclovir (1500 mg/m^2/day in three doses) or oral acyclovir (80 mg/kg/day in four doses) for 7-10 d

PCR polymerase chain; CBNAAT cartridge based nucleic acid amplification test
[a]*Penicillin allergy: Clarithromycin, azithromycin, clindamycin or vancomycin*

Table IV Principles of Immunization with Live Vaccines in Patients with Nephrotic Syndrome

Immunosuppression	***Advice***
Receiving high dose prednisolone (≥2 mg/kg/d; ≥20 mg/day if >10 kg) for <14 d	Vaccinate immediately after discontinuing treatment
Receiving high dose prednisolone (≥2 mg/kg/d; ≥20 mg/day if >10 kg) for ≥14 d	Vaccinate 1-month after discontinuing corticosteroids
Receiving low-moderate dose prednisolone (<2 mg/kg/d or equivalent; <20 mg/d)	No live vaccines, until discontinuation of steroid therapy
Low-dose alternate day prednisolone and pressing need for vaccine	Live vaccine may be administered
Patients receiving cyclophosphamide	Avoid live vaccines until off therapy for 3 months
Patients receiving calcineurin inhibitors, levamisole or mycophenolate mofetil	Avoid live vaccines until off therapy for 1 month
Therapy with rituximab	Avoid live vaccines until after B-cell recovery (~6-9 months)
Immunocompetent siblings and household contacts	Do not administer oral polio vaccine; may receive measles-mumps-rubella, rotavirus and varicella vaccines
Household contacts older than one year	Administer influenza vaccine annually

Table V Specific Vaccines for Patients with Nephrotic Syndrome[a]

Vaccine	*Age*	*Previously received*	*Vaccine*	*Schedule*
Pneumococcal: Conjugate (PCV, 13-valent preferred to 10-valent) Polysaccharide, (23-valent, PPSV23)	6-72 months	Completely immunized (3 doses at 6, 10, 14 weeks; booster at 12-15 months)	PCV13/10	One dose ≥2-yr-old
			PPSV23	One dose when ≥2-year-old and ≥8 wk after last PCV13/10 dose[b]
		No, incompletely immunized	PCV13/10	Two doses, ≥8 weeks apart[c]
			PPSV23	One dose when ≥2-yr-old and ≥8 wk after last PCV13/10 dose[b]
	≥6 years	Completely immunized	PPSV23	1 dose[b]
		No, incompletely immunized	PCV10/13	1 dose
			PPSV23	1 dose, ≥8 wk after last PCV13/10 dose[b]
Varicella[d]	>15 months	No evidence of immunity[e]	Live attenuated	Two doses 4-8 wk apart
Influenza	>6 months		Inactivated	Annually
Hepatitis B	Any	No, or anti-HBs <10 mIU/mL	Subunit (10 µg/0.5 mL)[f]	3 doses at 0, 1 and 6 mo; or in an accelerated schedule with ≥4 wk gap between doses 1 & 2, ≥8 wk between doses 2 & 3, and ≥16 wk between doses 1 & 3[f]

[a]*Efficacy of vaccines might be attenuated while on high dose corticosteroids or other immunosuppression*
[b]*Repeat after 5-yr if still experiencing disease relapses*
[c]*If the two doses are administered at <1-yr-old, give one additional dose during second year of life*
[d]*Avoid in patients <15 months; administer while off immunosuppression (Table IV)*
[e]*Immunity refers to past diagnosis of varicella or herpes zoster, verified by a physician; documented receipt of 2-doses of vaccine 4-8 weeks apart; or serological evidence of immunity*
[f]*Consider post-vaccination testing for adequacy (anti-HBs antibody ≥10 mIU/mL) and administering higher (20 µg) or additional doses*

Table VI Post-Exposure Management of Unimmunized Patients with Nephrotic Syndrome Exposed to Varicella[a]

Contraindication to live vaccine[b]	***Strategy***	***Timing after exposure***	***Level of evidence***
No	Administer varicella vaccine	As soon as possible, <5 days	A [133,146,147]
Yes	*Options (in order of preference)*		
	Varicella zoster immunoglobulin (VARIZIG)[c], 125 IU per 10 kg body weight (maximum 625 IU) intramuscular	<10 days; prefer <4 days	B [148,149]
	Oral acyclovir, 80 mg/kg in 4 divided doses (maximum 3.2 g) daily for 7 days OR oral valacyclovir (if ≥3-mo-old), 60 mg/kg (maximum 3 g) daily in 3 divided doses for 7 days	Begin 6-10 days after exposure	C [124,134,138]
	Intravenous immune globulin, 400 mg/kg	<10 days	X [124,134]

[a]More than 5 minutes of face-to-face contact with individual with varicella or zoster, while indoors
[b]See Table IV
[c]Available internationally from Serotherapeutic since 2006 when VZIG was discontinued (https://varizig.com/liquid-ordering_info.html); brands marketed in India include Vartiect-CP from Paviour Pharma)

Table VII Areas for Clinical Studies in Steroid Sensitive Nephrotic Syndrome

Therapy of initial episode, relapse
Optimal dose and duration of corticosteroid therapy in young (<4-6 years old) patients
Optimal intensity of therapy with prednisolone (daily and alternate day dose and duration) to induce remission and reduce further risk of relapses
Management of frequent relapses
Efficacy and safety of prednisolone administered on alternate days or daily; minimum effective dose
Relative efficacy and safety of various immunosuppressive agents
Efficacy and long-term safety of therapy with calcineurin inhibitors; lowest effective dose
Efficacy and long-term safety of therapy with rituximab; optimal dosing strategy (redosing at relapses, sequential administration *vs.* maintenance immunosuppression); safe cumulative dose threshold

Box I Definitions of Disease Course and Severity in Nephrotic Syndrome

Nephrotic range proteinuria	Urine protein 3+ or 4+; urine protein to creatinine ratio (Up/Uc) >2 mg/mg in first morning urine disease; proteinuria >40 mg/m^2/hr
Remission	Urine protein nil or trace (Up/Uc <0.2 mg/mg) for 3 consecutive early morning specimens
Relapse	Urine protein ≥3+ (Up/Uc >2 mg/mg) for 3 consecutive early morning specimens, having been in remission previously
Frequent relapses	Two or more relapses in the first 6-months after stopping initial therapy[a]; ≥3 relapses in any 6-months; or ≥4 relapses in one yr
Steroid dependence	Two consecutive relapses when on alternate day steroids, or within 14 days of its discontinuation
Steroid resistance[b]	Lack of complete remission despite therapy with daily prednisolone at a dose of 2 mg/kg (or 60 mg/m^2) daily for 6 weeks
Complicated relapse	Relapse associated with life-threatening complications: *(i)* hypovolemia requiring inpatient care, *(ii)* severe infection (peritonitis, cellulitis, meningitis), or *(iii)* thrombosis
Significant steroid toxicity	Hyperglycemia (fasting glucose >100 mg/dl, post prandial glucose >140 mg/dL, or HbA1c >5.7%) [12]; obesity (body mass index >95th percentile or 1.645 SDS for age [13]); short stature (height <-2 SDS for age [13]) with height velocity (<-3 SDS for age [14]); raised intraocular pressure; cataract(s); myopathy; osteonecrosis; or psychosis
Difficult-to-treat steroid sensitive disease	Both of the following: *(i)* frequent relapses, or significant steroid toxicity with infrequent relapses; and *(ii)* failure of ≥2 steroid sparing agents (including levamisole, cyclophosphamide, mycophenolate mofetil)

[a]*Or during initial therapy*
[b]*Therapy in the last 2 weeks may be given on alternate days in patients with steroid toxicity*
HbA1c glycosylated hemoglobin; SDS standard deviation score

Box II Investigations in Patients with Steroid Sensitive Nephrotic Syndrome

Essential at onset
Urinalysis*
Complete blood counts
Blood urea, creatinine, electrolytes, total protein, albumin, total cholesterol
Tuberculin test
Additional evaluation, at onset or relapse
Chest radiography: Positive tuberculin test or history of contact; suspected lower respiratory tract infection
Renal ultrasonography: Planned for kidney biopsy; presence of gross hematuria; suspected renal vein thrombosis
Complete blood counts: Suspected systemic infection or hypovolemia
Blood urea, creatinine, albumin, electrolytes: Severe edema; hypovolemia/dehydration; oliguria/anuria; prolonged (>72 h) diuretic therapy
Complement C3, C4, antinuclear antibody, antistreptolysin O: Gross, persistent microscopic hematuria; sustained hypertension; suspected secondary cause (systemic lupus, IgA vasculitis, C3 glomerulopathy)
Serum transaminases; hepatitis B surface antigen; antibody against hepatitis C virus: History of jaundice or liver disease
Periodic monitoring, if relapsing illness
Blood creatinine; albumin, electrolytes

**Quantitative estimation of urine protein is required if the diagnosis of nephrotic range proteinuria is uncertain*

Box III Features of Hypovolemia During Relapse of Nephrotic Syndrome

Clinical features
Abdominal pain, vomiting, lethargy
Prolonged capillary refill time; cold extremities
Tachycardia, low volume pulses
Low blood pressure; postural hypotension
Biochemical indices
Elevated hematocrit
Fractional excretion of sodium <0.5%
Urinary potassium index (urine K^+/urine Na^++K^+) >0.6
Ultrasonography: decreased inferior vena cava diameter, increased collapsibility index [110]

Fractional excretion of sodium = $\frac{\text{urine } Na^+ \times \text{serum creatinine}}{\text{serum } Na^+ \times \text{urine creatinine}} \times 100$

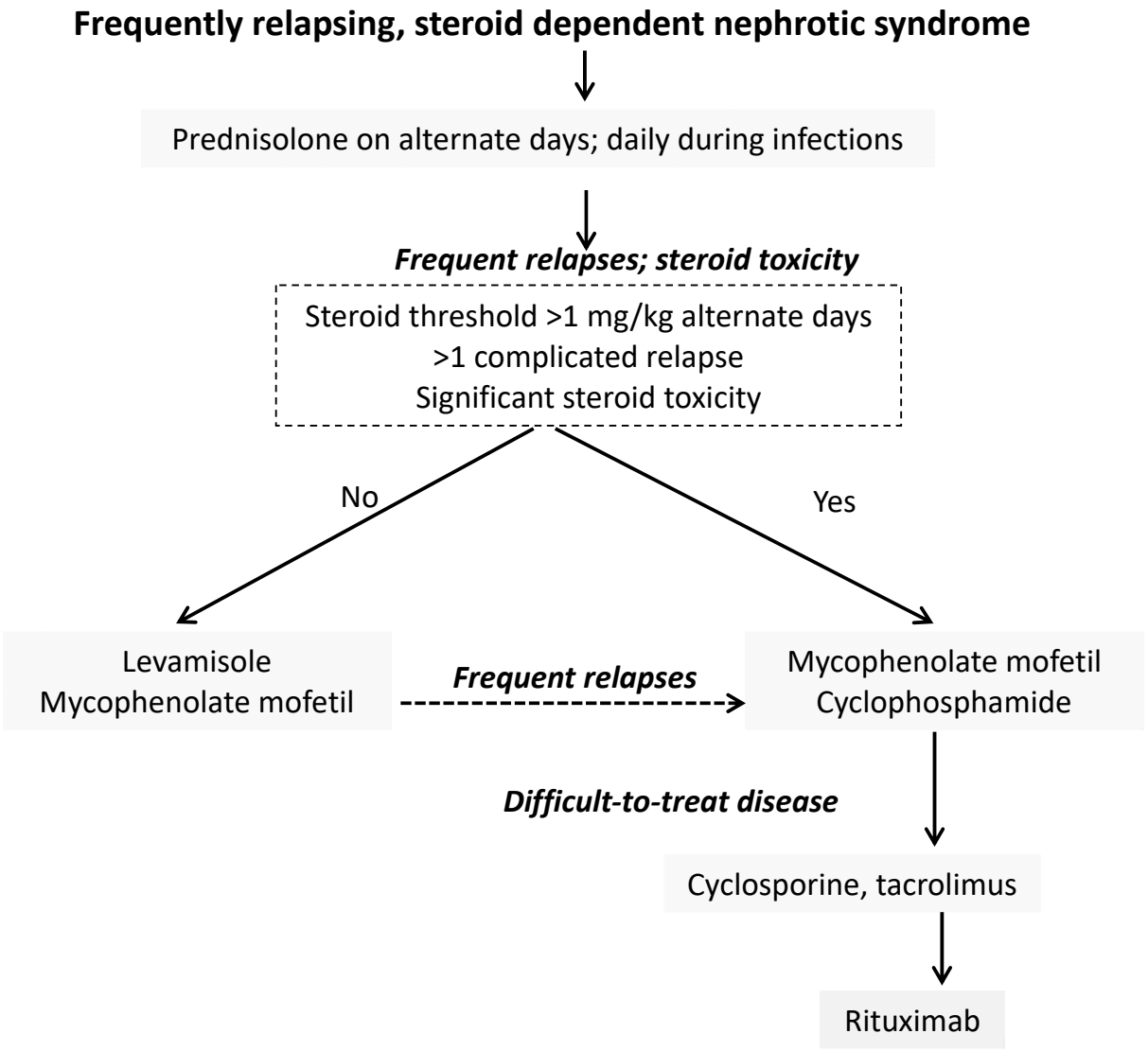


Fig. 1. **Management of frequently relapsing or steroid dependent nephrotic syndrome.**
The initial strategy is to administer prednisolone at a dose of 0.5-0.7 mg/kg on alternate days. In patients with sustained remission or infrequent relapses, therapy may be tapered to 0.2-0.3 mg/kg on alternate days for 6-12 months. Daily therapy at the same dose for 5-7 days, during minor infections, prevents infection-associated relapses. Patients who relapse at steroid threshold >0.7 mg/kg or show steroid toxicity require therapy with steroid-sparing medications (Table II). The choice of agents is based on disease severity, adverse effects, patient age, cost of therapy, and parental preference. Levamisole or mycophenolate mofetil (MMF) are preferred medications for mild disease. Patients with high steroid threshold (>1 mg/kg on alternate days), complicated relapses and those with significant steroid toxicity (Box I) may be treated with MMF at higher doses (1000-1200 mg/m^2/day) or cyclophosphamide. The use of cyclophosphamide is avoided in children <5-7 yr-old and in peri-pubertal boys due to reduced efficacy and risk of gonadal toxicity, respectively. Patients who relapse despite therapy with two or more steroid-sparing agents (difficult-to treat steroid sensitive disease) are considered for therapy with calcineurin inhibitors, and failing that, rituximab. The use of rituximab is avoided in young children due to the risk of hypogammaglobulinemia.

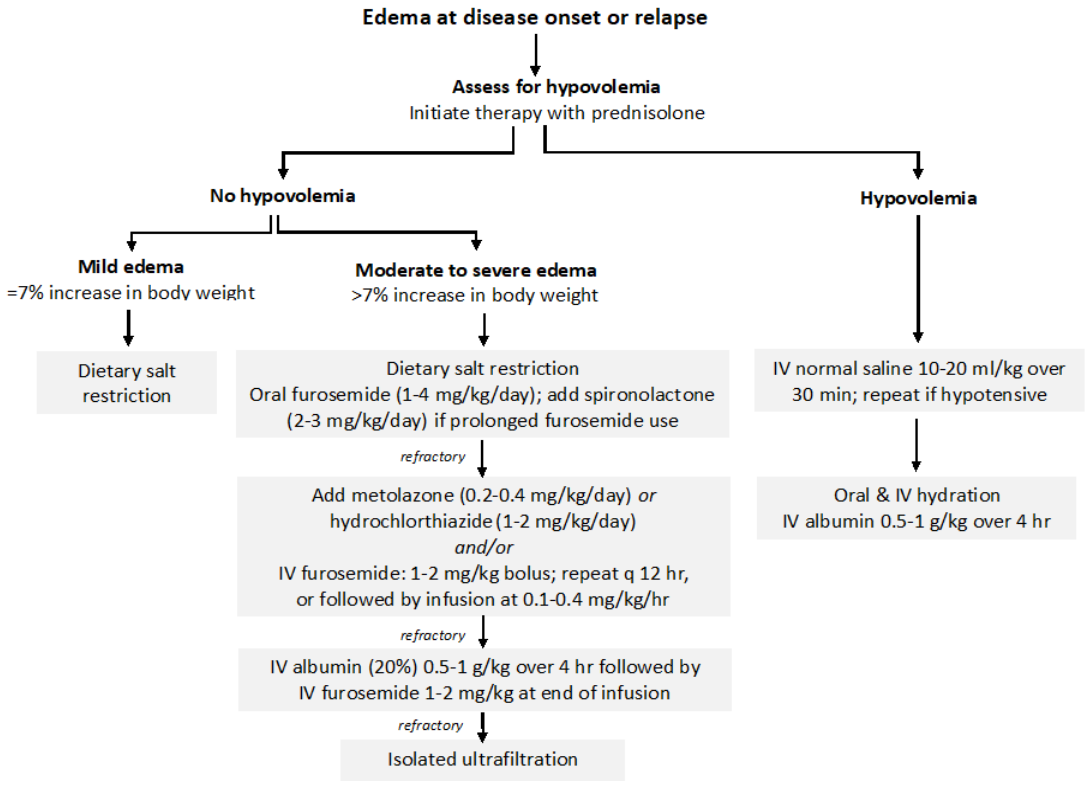


Fig. 2. Management of edema in nephrotic syndrome.

Edema is empirically defined, based on increase in body weight, as mild, moderate and severe (>15% increase). Patients with mild edema are managed with salt restriction alone; prednisolone therapy is associated with spontaneous diuresis within a few days. Hypovolemia should be excluded (Box III) before considering therapy with diuretics. Oral furosemide is the diuretic of choice; patients receiving therapy with furosemide for >48-hr should additionally receive a potassium-sparing diuretic. Edema refractory to furosemide therapy may be treated with additional thiazide diuretics (metolazone or hydrochorthiazide) or IV furosemide, as bolus and/or infusion. Combination therapy with IV albumin (20%) and furosemide enables diuresis in patients refractory to the above measures. IV albumin carries the risk of fluid overload and pulmonary edema in patients with renal dysfunction. Patients with features of hypovolemia require bolus(es) of normal saline if hypotensive, followed by oral and IV hydration, and IV albumin (20%) infused over 2-4 hr.

Supplementary Table I Grading of Evidence [i]

Grade	*Quality of evidence*
A	Well designed and controlled studies; meta-analysis on applicable population; true effect lies close to the estimate of the effect
B	Studies with minor limitations; consistent findings from multiple observational studies; true effect is likely to be close to estimate of the effect, but there is a possibility that it is substantially different
C	Single, few or multiple studies with inconsistent findings or major limitations; confidence in the effect estimate is limited, the true effect may be substantially different from estimate of the effect
D	Expert opinion, case reports; very little confidence in effect estimate, true effect likely to be substantially different from the estimate of effect
X	Situations where validating studies cannot be performed, and benefit or harm clearly predominates
Level	*Strength of recommendation*
1	"We recommend": Most patients should receive the recommended course of action
2	"We suggest": Different choices will be appropriate for different patients

Supplementary Table II Recent Randomized Controlled Trials, with Low Risk of Bias, for Initial Episode of Nephrotic Syndrome

Author, yr	*Type, N*	*Predniso(lo)ne (Intervention)*	*Predniso(lo)ne (Control)*	*Follow up, yr*	*Outcomes at 1-2 yr*			
					% relapsing; time to relapse; HR (95% CI)	*% frequent relapsers; HR (95% CI)*	*Relapse rate; RRR (95% CI)*	*Cumulative prednisone, g/m²/yr; MD (95% CI)*
Teeninga 2013 [ii]	Placebo controlled, randomized N=150	60 mg/m² D till remission; 50 mg/m² D for 6-wk; 40 and 20 mg/m² AD for 4-wk each; 10 mg/m² AD for 10-wk [3.4 g/m² in 24-wk]	60 mg/m² D for 6-wk; 40 mg/m² AD for 6-wk; placebo for 12-wk [3.4 g/m² in 24-wk]	≥1.5	80% *vs*. 77%; 8 *vs*. 6 months; NA	59% *vs*. 50%; 1.1 (0.7, 1.8)	1.0 *vs*. 0.6 per yr; 1.2 (0.9, 1.7)	Not available
Sinha 2014 [iii]	Placebo controlled, randomized N=181	2 mg/kg D for 6-wk; 1.5 mg/kg AD for 6-wk; 1, 0.75 & 0.5 mg/kg AD each for 4-wk [3.5 g/m² in 24-wk]	2 mg/kg D for 6-wk; 1.5 mg/kg AD for 6-wk; placebo for 12-wk [2.8 g/m² in 12-wk]	1	53% *vs*. 63%; 9 *vs*. 7 months; 0.57 (0.36, 1.07)	38% *vs*. 40% 1.0 (0.6, 1.7)	1.3 *vs*.1.5 per yr; 0.7 (0.5, 1.1)	2.3 *vs.* 1.9; 0.45 (-0.12, 1.02)
Yoshikawa 2014 [iv]	Open label, randomized N=255	60 mg/m² D for 4-wk; then 60, 45, 30, 15, 7.5 mg/m² AD for 4-wk each [3.9 g/m² in 24-wk]	60 mg/m² D for 4-wk; 40 mg/m² AD for 4-wk [2.2 g/m² in 8-wk]	2	~70% *vs.* 63%; 8 months each; 1.03 (0.76, 1.39)	~50% *vs*. 45%; 1.16 (0.86, 1.56)	1.3 per person-yr each; 1.1 (0.8, 1.4)	6.5 *vs.* 4.6 in 2-yr; *P*<0.001
Webb 2019 [v]	Placebo controlled, randomized N=237	60 mg/m² D for 4-wk; 60, 50, 40, 30, 20, 10 mg/m² AD, 2-wk each [3.2 g/m² in 16-wk]	60 mg/m² D for 4-wk; 40 mg/m² AD 4-wk; placebo 8-wk [2.2 g/m² in 8-wk]	2	80% *vs*. 81%; ~4.5 *vs*. 3.5 months; 0.87 (0.65, 1.17)	50% *vs*. 53%; 1.04 (0.81, 1.35)	3.6 *vs.* 4.0 at 2-yr; 1.1 (0.9, 1.4)	5.5 *vs.* 6.7 at 2-yr; 1.2 (-0.1, 2.5; *P*=0.07)
Sinha 2019 [vi]	Open label, randomized N=160; <4 yr	60 mg/m² D for 6-wk; 40 mg/m² AD 6-wk; 30, 20, 10 mg/m² AD, 4-wk each [4.6 g/m²]	60 mg/m² D for 6-wk; 40 mg/m² AD for 6-wk [3.4 g/m² in 12-wk]	2	Proportions with relapse, other outcomes; results awaited CTRI/2015/06/005939; NCT03141970			
Xu 2020	Placebo controlled, randomized N=154; 1-6 yr	Daily for 6-wk; AD for 6-wk; taper for 12-wk	Daily for 6-wk; AD for 6-wk; placebo for 12-wk	2	Proportions with frequent relapses, other outcomes; results awaited NCT04536181			

AD alternate days; CI confidence interval; D daily; HR hazards ratio; MD mean difference; RRR relative relapse rate; wk weeks; ^rates adjusted for stratifying variables, where reported

Supplementary Table III Studies on Predniso(lo)ne Therapy of Infrequent Relapses

Author, yr	*Type*	*N*	*Prednisone (Intervention)*	*Prednisone (Control)*	*Follow up, months*	*Time to remission; MD (95% CI)*	*% Frequent relapses*	*Cumulative prednisone*
Raja, 2017 [vii]	Retrospective	50	1 mg/kg/d until remission (minimum 7 d), tapered <1-mo	NA	6	<7 days in 70%; 7-10 days in 7%	NA; 0.9±0.8 relapses in 6-mo	0.75±0.25 mg/kg
Fujinaga, 2018 [viii]	Retrospective	49	60 mg/m^2 until remission; tapered AD <6-mo	Comparison: ≤1.8, 1.8-2 and >2 mg/kg/d	12	7, 7.5 & 7 days	39%, 43%, & 55%	NA
Kainth, 2020 [ix]	Open label, randomized	114	60 mg/m^2/d until remission; 40 mg/m^2 AD for 2-wk	60 mg/m^2/d until remission; 40 mg/m^2 AD for 2-wk	12	Not available	23% *vs*. 22%; RD -1 (-17, 14); HR 1.0 (0.8, 1.2)	1.2 (0.3-1.8) *vs*. 1.8 (1.2-2.4) g/m^2***
Borovitz, 2019 [x]	Open label, not randomized	30	1.5 mg/kg/d (A); 1 mg/kg/d (B) until remission; taper 8-10 wk	2 mg/kg/d until remission; tapered 10-12 wk (C)	6	10±5 (A) & 9±3 (B) *vs*. 7±1 days (C)*	NA	43±26 (A), 25±7 (B) *vs*. 46±3 mg/kg*
Sheikh, 2019 [xi]	Open label, randomized	60	1 mg/kg/d until remission; 1.5 mg/kg AD for 4-wk	2 mg/kg/d until remission; 1.5 mg/kg AD for 4-wk	12	9±2 *vs*. 9±2 days; 0.4 (0.7, 1.6) days	NA	12.5 (9-18) *vs*. 17 (14-21) mg/kg**
Kansal, 2019 [xii]	Open label, randomized	40	2 mg/kg/d until remission; 1 mg/kg AD for 4-wk	2 mg/kg/d until remission; 1.5 mg/kg AD for 4-wk	3	Not available	Relapse at 3 months: HR 1.1 (0.4, 3.2)	NA
Raman, 2017 [xiii]	Open label, randomized, equivalence	52[#]	60 mg/m^2/d until remission; 40 mg/m^2 AD for 4-wk	2 mg/kg/d until remission; 1.5 mg/kg AD for 4-wk	6	6.5 *vs.* 6 days	Similar relapse rate	Similar cumulative prednisolone
PROPINE, [xiv]	Open label, randomized, superiority	78	60 mg/m^2/d until remission; 40 mg/m^2 AD for 36 days	60 mg/m^2/d until remission; 40 mg/m^2 AD for 72 days	6	5 (4-7) *vs*. 6 (5-8) days	Not reported; any relapse: 42% *vs*. 58%	1.29 (1.16-1.64) *vs*. 1.33 (127-1.51) g/m^2
Schijvens, 2018 [xv]	Placebo controlled, randomized	144	60 mg/m^2/d until remission; 40 mg/m^2 AD for 2-wk; placebo at 40 mg/m^2 AD for 4-wk	60 mg/m^2/d until remission; 40 mg/m^2 AD for 6-wk	24	Time to first relapse & other outcomes awaited [Reducing STEroids in Relapsing Nephrotic syndrome, RESTERN; NTR5670, EudraCT 2016-002430-76]		

AD alternate days; /d per day; HR hazard ratio; MD mean difference; mo months; NA not applicable; RD risk difference; RR risk ratio; wk weeks; yr year
P<0.05, **<0.01 and ***<0.0001*
[#]*Number of infrequent relapsers among 100 patients randomized*

Supplementary Table IV Controlled Trials on Efficacy of Predniso(lo)ne on Alternate Days (AD) for Frequent Relapses

Author, yr (reference)	*Type of study*	*N*	*Prednisone AD*	*Comparator*	*Follow up, yr*	*Outcomes at 12-24 mo*				*Adverse events*
						Relapses, n or rate	*Proportion (%) with relapses*	*% with frequent relapses*	*Cumulative predniso(lo)ne*	
APN, 1981 [xvi]	Open label RCT	64[#1]	35 mg/m^2	Prednisone at 40 mg/m^2 on 3 consecutive days each week	0.5 (1)[^]	0.9±0.3 *vs*. 1.9±0.4 in 6 months*	43% *vs*. 72%*		3.9±0.2 *vs*. 3.8±0.2 g/m^2 in 6 months	Obesity 57% *vs*. 52%; hirsutism 13% vs. 20%; psychosis 0% *vs*. 8%; infections 17% *vs*. 12%; 4 in each group withdrawn for steroid toxicity
Broyer, 1997 [xvii]	Open label RCT	40	15-20 mg/m^2	Deflazocort in equivalent dose AD	1	3±2 *vs*. 1±1**	88% *vs*. 42%**		5.1 *vs* 5.7 g/m^2	Mean change in height -0.4 *vs*. -0.2 SDS, weight 3.9 *vs*. 1.7 kg & BMD -12 *vs*. -6%; Cushingoid 7 *vs*. 11
Mattoo, 2000 [xviii]	Prospective study	36	0.5-0.8 mg/kg	Prednisolone at same dose; given daily for 5 days during URTI	2	5.5±1.3 *vs*. 2.2±0.9*	Non-relapsers excluded	Not reported	Not reported	Not reported
Jayantha, 2002 [xix]	Open label RCT	129[#2@]	60 mg/m^2 AD, tapered q 4 wk by 10 mg/m^2 (total 7 months)	Prednisolone 40 mg/m^2 AD for 4 wk (total 2 months)	0.5	0.4±0.5 *vs*. 2.1±1.5*	38% *vs*. 88%*	17.5% *vs*. 40.6%*	3.3±1.2 *vs*. 2.7±1.3	Hypertension 30% *vs*. 12.5%; slow growth 35% *vs*. 28.1%
Al Saran, 2006 [xx]	Open label, not randomized	56	<0.5 mg/kg	Levamisole 2.5 mg/kg AD	1	2.6±1.8 *vs*. 1.0±1.8*	100% *vs*. 37.5%*	50% *vs*. 9.4%*	3.9±1.2 *vs*. 3.1±1.9 g/m^2	None *vs*. gastrointestinal symptoms in one patient
Abeyagunawardena, 2008 [xxi]	Placebo-controlled cross-over RCT	40[@]	0.1-0.5 mg/kg; given 5 mg daily for 7 days in URTI	Prednisone at same dose; given placebo daily for 7 days in URTI	2 URTI	Not reported	48% *vs*. 18%*	Not reported	Not reported	No significant events
Gulati, 2011 [xxii]	Open label RCT	100[!]	0.5–0.75 mg/kg	Prednisolone at same dose; daily during infections	1	1.8±0.5 *vs*. 0.9±0.4*	85% *vs*. 61%*	8% *vs*. 4%	138±22 *vs*. 120±32 mg/kg	Not reported
Yadav, 2019 [xxiii]	Open label RCT	61	0.5–0.7 mg/kg	Prednisolone at 0.2-0.3 mg/kg daily	1	1.94 *vs*. 0.55 per person-yr	71% *vs*. 40%	57% *vs*. 7%[$*]	0.39±0.19 *vs*. 0.27±0.07 mg/kg/day	Cataract & glaucoma 6.5% *vs*. 0% each

BMD bone mineral density; NS not significant; RCT randomized controlled trial; SDS standard deviation score; URTI upper respiratory tract infection
[#]Outcomes reported for [1]48 and [2]90 patients; [^]therapy for 6 months; follow up for 6 months more off therapy; [@]included patients with infrequent relapses; [!]includes 32 patients that also received levamisole; [$]includes patients with infrequent relapses with steroid toxicity
*P *<0.05*

Supplementary Table V Studies on Low-dose Predniso(lo)ne Administered Daily at Onset of or During Infections[@]

Author, yr	*Type of study*	*N*[#]	*Intervention: Prednisone*	*Control*	*Duration*	*Outcomes*	
						Relapse rate [RR (95% CI)] or %	*Proportion (%) with relapses*
Mattoo 2000 [xviii]	Non-randomized, prospective study	36	0.5 mg/kg daily x 5 days	Prednisolone 0.5-0.8 mg/kg AD	2 yr	2.2±0.9 *vs*. 5.5±1.3*	Non-relapsers excluded
Abeyagunawardena 2008 [xxi]	Placebo-controlled cross-over RCT	40[$]	5 mg daily x 7 days[@1]	Placebo for 7 days[@1]	2 URTI	Not available	18% *vs*. 48%*
Gulati 2011 [xxii]	Open label RCT	100[^]	0.5-0.8 mg/kg AD; daily x 7 days[@2]	Prednisolone 0.5-0.8 mg/kg AD[@2]	2 yr	0.9±0.4 *vs*. 1.8±0.5 [0.9 (0.4, 1.4)]***	61% *vs*. 85%*
Abeyagunawardena 2017 [xxiv]	Placebo-controlled cross-over RCT	48[#1]	0.5 mg/kg daily x 5 days	Placebo for 5 days	2 yr	Not available	33% *vs*. 58%*
PREDNOS 2 [xxv]	Placebo-controlled RCT	300[#2]	15 mg/m^2 x 6 days (maximum 40 mg)	Placebo for 6 days	Until first infection: 1 yr	Occurrence of relapse [ISRCTN10900733]	

AD on alternate days; CI confidence interval; RR rate ratio; URTI upper respiratory tract infection; yr year
[@]Refers to URTI, except [@1]viral infections and [@2]any infections
[$]While on prednisolone AD
[#]These studies included patients with frequent relapses, except two that also enrolled patients with [1]infrequent relapses and [2]relapsing nephrotic syndrome (≥2 relapses in previous year) while on/off maintenance immunosuppression
[^]Patients requiring prednisolone AD at >1 mg/kg to maintain remission additionally received levamisole at 2-2.5 mg/kg AD
*P *<0.05, **<0.01, and ***<0.0001*

Supplementary Table VI Randomized Controlled Trials Examining Efficacy of Levamisole Administered on Alternate Days

Author, Year	*Type of RCT*	*Comparison**	*N*	*Follow up, months*	*Outcomes at 6-12 months*		
					Proportion (%) with relapse	*Frequency of relapses*	*Relative risk of relapse (95% CI)*
BAPN, 1991 [xxvi]	Placebo controlled	Placebo	61	6	87.1 *vs*. 93.3	Not reported	0.93 (0.79, 1.1)
Weiss, 1993 [xxvii]	Placebo controlled	Placebo	49	12	93.4 *vs*. 88.9	0.7±0.2 *vs*. 0.6±0.3	1.05 (0.86, 1.3)
Abeyagunawardena, 2006 [xxviii]	Open label	No treatment	76	12	19.0 *vs*. 76.5*	Not reported	0.25 (0.13, 0.48)
Gruppen, 2018 [xxix]	Placebo controlled	Placebo	99	12	66.0 *vs*. 85.7*	Not reported	0.77 (0.61, 0.97)
Dayal, 1994 [xxx]	Open label	Prednisone	61	12	40.9 *vs*. 71.4	Not reported	0.57 (0.31, 1.05)
Rashid, 1996 [xxxi]	Open label	Prednisone	40	10	55 *vs*. 90*	Not reported	0.61 (0.4, 0.93)
Sural, 2001 [xxxii]	Open label	Prednisone	58	12	56.7 *vs*. 82.1*	Not reported	0.69 (0.48, 0.99)
Al-Saran, 2006 [xx]	Open label	Prednisone	56	12	41.2 *vs*. 100*	0.1±0.2 *vs*. 0.2±0.2*	0.42 (0.28, 0.63)
Sural, 2001 [xxxii]	Open label	Oral cyclophosphamide	57	12	56.7 *vs*. 37	Not reported	1.53 (0.85, 2.74)
Donia, 2005 [xxxiii]	Open label	Intravenous cyclophosphamide	40	22	64 *vs*. 72	Not reported	0.89 (0.68, 1.16)
Sinha, 2019 [xxxiv]	Open label	Mycophenolate mofetil	149	12	59.2 *vs*. 65.8	1.3 (1.1, 1.7) *vs*. 1.1 (0.3, 1.3)	1.11 (0.86, 1.43)

*P *<0.05*

Supplementary Table VII Non-Randomized Studies Examining Efficacy of Levamisole Administered Daily

Author, Year	*Type of study*	*Dose of levamisole, mg/kg per day*	*Comparison, if any*	*N*	*Follow up, months*	*Outcomes at 6-12 months*			
						Proportion (%) with relapse; frequent relapses	*Frequency of relapses*	*Cumulative prednisone*	*Adverse events (AE)*
Abeyagunawardena, 2017 [xxxv]	Prospective	2.5[#]	AD levamisole (received historically)	58	12	79.3% *vs*. 100%; not reported	2.8±0.8 vs. 1.3±0.9	Median 154.1 *vs*. 254.2 mg/kg	No major AE
Ekambaram, 2014 [xxxvi]	Retrospective	2	Prior year	97	6-24	Effective in 77%	1.3±0.7 vs. 2.4±0.5	2.5±0.69 g/m^2 *vs*. 4.1±0.1 g/m^2	Not reported
Chen, 2010 [xxxvii]	Retrospective	2-3.3	Other agents	12	NA	93.3%; no effect 66.7%	Not reported	Not reported	Not reported
Sumegi, 2004 [xxxviii]	Retrospective	2	Prior year	34	60	32.4% *vs*. 100%; not reported	0.41 vs. 4.4	1.5±1.7 g/yr; 23 off steroids	Neutropenia in 14.7%
Fu, 2004 [xxxix]	Prospective	2-3[#]	AD levamisole, 2-3 mg/kg	36	4-36	17% *vs*. 49%; response in 69% *vs*. 80%	1.3±2.1 vs. 2.0±2.5	0.2±0.4 *vs*. 0.2±0.3 mg/kg/day	Leukopenia in 20% *vs*. 31.3%
La Manna, 1988 [xl]	Prospective	2.5	Levamisole, 2.5 mg/kg, given 2/wk	8	2-16	Response in 25%	Not reported	Not reported	Minimal

NA not available
[#]*Having failed AD levamisole*

Supplementary Table VIII Non-Randomized Studies on Mycophenolate Mofetil (MMF) in Nephrotic Syndrome

Author, yr (reference)	*Type of study*	*N*	*MMF, mg/m² per day*	*Follow up (range), yr*	*Outcomes at 12-24 months*				*Adverse events (AE)*
					Relapses, n or rate	*Proportion with relapses*	*Frequent relapses*	*Predniso(lo)ne, mg/kg per day*	
Bagga, 2003 [xli]	Prospective	19	29 (27.4-30.7)	1	2 (1.2-2.7)	78/9%	15.8%	0.3 (0.2-0.4)	Abdominal pain 26.3%
Gellermann, 2004 [xlii]	Prospective	6	1000	2.1 (1.3-3.3)	Not reported	16.7%	0%	Not reported	Juvenile conglobate acne in 16.7%
Novak, 2005 [xliii]	Retrospective	21	1200	1±0.5	0.47±0.43 per month	80.9%	24%	Not reported	Gastrointestinal AE common but mild; varicella in 4.7%
Al-Akash, 2005 [xliv]	Retrospective	11	948 (500-1087)	1 (0.3-2)	1.05 (0-4.5)	45.5%	18.2%	Not reported	Herpes stomatitis 9.1%; gastrointestinal AE 18.2%
Hogg, 2006 [xlv]	Prospective	33	1200	0.5	1 per 14.7 months	25%	Not reported	Not reported	Leukopenia 15.6%; varicella 3.1%; gastritis 3.1%
Okada, 2007 [xlvi]	Prospective	11	750-1000	1	Not reported	36.4%	9.1%	3.2±3.1 mg/kg/month	Gastrointestinal AE 18.2%; alopecia 9.1%
Fujinaga, 2007 [xlvii]	Prospective	12	1220±95	0.9 (0.5-6.5)	0.6±0.9	25% at 6 months	Not reported	0.21±0.11	None
Afzal, 2007 [xlviii]	Retrospective	42	26.5 (16.6-31.3) mg/kg	1.2 (0.5-6.8)	2.2 (1.4, 2.9)	78.6%	11.9%	0.3 (0.3, 0.4)	Abdominal pain 21.4%; infections 9.5%
Fujinaga, 2009 [xlix]	Retrospective	26	34±6 mg/kg	1.6 (0.6-6.5)	0.8±1.2	Not reported	Not reported	0.17±0.11	Anemia and herpes labialis in 3.8% each
Baudouin, 2012 [l][$]	Prospective	23	1200	1	Not reported	26.1%	Not reported	264 (196–306) mg/m²/month[^]	Gastrointestinal AE or infections in 26.1%; leukopenia or anemia in 30.4%
Hasan, 2013 [li]	Retrospective	61	1200	3.2 (1.7-4.7)	0.5 (0–0.87)[^]	51%	38%	Withdrawn in 56%	Gastrointestinal AE 13%; leukopenia or infections 11%; arthralgia 3%

Banerjee, 2013 [lii]	Retrospective	46	20-30 mg/g	3.6±1.8	Not reported	57%	No response in 33.3%	Reduced in 70%	Gastrointestinal AE 7.4%; neutropenia and elevated transaminases in 3.1% each
Jellouli, 2016 [liii]	Retrospective	30	1200	Not reported	0.45	Not reported	Not reported	0.2	Not reported
Basu, 2017 [liv]	Retrospective	130	1200	2.5	0.9±0.4	13.1% (at 1 yr)	6.1%	108.8±35.7 mg/kg	Gastrointestinal AE 3.8%; infections 6.2%; other minor 1.5%
Karunamoorthy, 2019 [lv]	Retrospective	87	28.5 mg/kg	3.3 (1.3-6.5)	Not reported	72.4%	17.2%	0.35^	Infections 12%; diarrhea 6%; leukopenia 3%; gastritis 2%

[$]Single limb Bayesian randomized controlled trial; [^]Reported only for patients with response

Supplementary Table IX Randomized Controlled Trials (RCT) on Mycophenolate Mofetil (MMF) in Steroid Sensitive Nephrotic Syndrome

Author, yr [ref]	*Type of RCT*	*N*	*MMF dose, mg/m^2 per day*	*Comparator*	*Follow up, yr*	*Outcomes at 12-24 months*				*Adverse events (AE)*
						Relapses, n or rate (95% CI)	*Proportion with relapses*	*Frequent relapses*	*Cumulative predniso(lo)ne, mg/kg per day*	
Dorresteijn [lvi]	Open label	24	1200	Cyclosporine 4-5 mg/kg/day	1	0.83±1.3 *vs*. 0.08±0.3	41.7% *vs*. 8.3%	8.3% vs. 0%	0.13±0.16 *vs*. 0.08±0.12	First 3 studies: Hypertension 8.3% *vs*. 29.2%; hypertrichosis 6.9% *vs*. 40.3%; leukopenia 2.4% *vs*. 4.8%; gum hypertrophy 0% *vs*. 20.8%; reduced eGFR 0% *vs*. 8.3%; diarrhea 13.3% *vs*. 0%
Gellermann [lvii]	Cross-over, open label	60	1000; titrated to level	Cyclosporine 150 mg/m^2 per day	2	1.1±2 *vs*. 0.4±0.7*	42.9% *vs*. 30%	Not reported	1.83 *vs*. 0.99 g/m^2	
Uddin [lviii]	Open label	60	800-1200	Cyclosporine 4-5 mg/kg/day	0.5	3±2.9 *vs*. 1.4±2.6	Not reported	Not reported	Not reported	
Wang [lix]	Not RCT	72	24.6±3.1 mg/kg/day	Tacrolimus 0.08±0.02 mg/kg/day	1	1.43 *vs*. 0.83	~58% *vs*. ~48%	12.2% *vs*. 0%	0.16±0.02 *vs*. 0.17±0.03	Infections 11.8% *vs*. 7.9%; gastrointestinal AE 11.8% *vs*. 2.6%; leukopenia 2.7% *vs*. 2.6%
Sinha [xlv]	Open label	149	750-1000	Levamisole 2-2.5 mg/kg on alternate days	1	1.1 (0.3, 1.3) *vs*. 1.3 (1.1, 1.7)	65.8% *vs*. 65.7%	16.4% *vs*. 14.5%	0.2 (0.1, 0.4) *vs*. 0.3 (0.2, 0.4)	Increased aminotransferases 2.6% *vs*. 2.7%; leukopenia 1.3% *vs*. none

AE adverse event; eGFR estimated glomerular filtration rate
**P <0.05; one Bayesian RCT is included in Web Table IX, since it lacked a comparator limb*

Supplementary Table X Determinants of Response to Therapy with Cyclophosphamide

Author, yr	*Cyclophosphamide cumulative dose*	*N*	*Age, yr*	*Follow up, yr*	*Proportion (%) in remission at 1, 2, 5 & 10 yr^*	*Factors associated with prolonged remission*
Latta 2001 [lx]	105-588 mg/kg	1504; 38 studies	NA	NA	Frequent relapses/dependence: NA/NA; 72/40; 36/24; NA/NA	Frequent relapses*; cumulative dose of cyclophosphamide
Vester 2003 [lxi]	165±33 mg/kg	106	7.3±3.8	NA	44; 34; 24; 24	Age >5.5-yr; frequent relapses*; cumulative dose >5 g/m^2; leukopenia
Kyrieleis 2007 [lxii]	~168 mg/kg	80	~4 (2-15)	6 (2-27)	NA; 35; ~48; ~60	Age >3-yr
Zagury 2011 [lxiii]	175 mg/kg	108	4.9	9.5 (5-29)	NA; 34; 25; 22	Relapse threshold <1.4 mg/kg; age >7-yr (univariate analysis)
Cammas 2011 [lxiv]	168 (157-197) mg/kg	143	7.9 (4.6-11.2)	7.8 (4-11.8)	44; 27; 13; 11^1	Age >5-yr; cumulative dose >170 mg/kg
Azib 2011 [lxv]#	160 (149–170) mg/kg	90	5.3 (3.2–9.1)	5.5 (3.2-8.5)	57, 42, 31, NA^2	Age >7.5-yr
Berkane 2018 [lxvi]	168 mg/kg	50	8	1.6	52; 48; NA; NA	Age>8-yr; frequent relapses*

NA not available
**versus steroid dependence*
^*Median time to relapse not reported, except* ^1*10 months and* ^2*0.8 (0.4-1.5) years*
#*All patients were steroid dependent*

Supplementary Table XI Controlled Studies Examining Comparative Efficacy of Rituximab in Steroid Sensitive Nephrotic Syndrome

Author, yr	*Rituximab mg/m²; n*	*Control*	*N*	*Follow up, yr*	*Outcomes*				
					Relapse rate (RR)	*Proportion with relapse (HR; 95% CI)*	*Time to relapse, mo*	*% off steroids*	*% off all agents*
Randomized clinical trials									
Iijima 2014 [lxvii]	375, 4	Placebo	24; 24	1	1.5 *vs*. 4.2 per p-yr (0·37; 0·2, 0·6)	71% *vs*. 96% (0.27; 0.1, 0.5)	8.9 *vs*. 3.4	88% *vs*. 79%	NA
Boumediene 2018 [lxviii]	375, 2[#1]	Placebo[#1]	10; 13	0.5	NA	10% *vs*. 100%	NA	NA	NA
Ahn 2018 [lxix]	375, 1[#1]	None[#1]	40; 21	0.5	3.4 *vs*. 9.4 per p-yr	26% *vs*. 69%	9 *vs*. 2.9	NA	NA
Ravani 2020 [lxx]	375, 1[#]	None[#]	15; 15	1	NA	13% *vs*. 7%	NA *vs*. 1.5	NA	NA
Ravani 2015 [lxxi]	375, 1[#]	Prednisone[#]	15; 15	0.25 (1)	NA	20% *vs*. 93%[$] (0.02; 0.01, 0.15)	18 *vs*. NA	NA	NA
Ravani 2011 [lxxii]	375, 1-2	CNI alone	27; 27	0.25 (1)	NA	19% *vs*. 48% at 3-months	NA	78% *vs*. 7.4%	63% *vs*. 3.7%
Basu 2018 [lxxiii]	375, 2	Tacrolimus	60; 60	1	NA	10% *vs*. 37%	10 *vs*. 7	93% *vs*. 79%	NA
Single arm clinical trials									
Ruggenenti 2014 [lxxiv]	375, 1	None	30[^]	1	0.5 (0-1)	70% in children	7.5	NA	60%
Non-randomized prospective (P) or retrospective (R) comparisons									
Kari 2020 (P) [lxxv]	375, 2	Cyclophosphamide	19; 27	1	NA	16% *vs*. 41% (0.36; 0.1, 1.5)	NA[$]	74% *vs*. 30%	NA
Webb 2016 (R) [lxxvi]	750, 2	Cyclophosphamide	42; 79	≥1	NA	50% *vs*. 60%[$]	14 *vs*. 7	NA	69% *vs*. 84%

Sinha 2012 (R) [lxxvii]	375, 2-3	Tacrolimus	10; 13	1	0.8±1.0 *vs*. 0.9±1.1	50% *vs.* 54%[$]	8.5 *vs*. 9.8	80% *vs*. 46%	80% *vs*. 46%
Ongoing randomized clinical trials									
Nagano [lxxviii]	375, 2	Placebo	20; 20	1	Awaited; JMA-IIA00380				
Ravani [lxxix]	375, 1[#1]	Ofatumumab 1500 mg/m^2, 1[#1]	70; 70	2	Awaited; NCT02394119; Eudra-CT 2015-000624-28				
Mathew	375, 2	Tacrolimus	21; 20	1	Awaited; CTRI/2018/11/016342				

NA not available; p-yr person-year; yr year

[#]Steroids and [#1]CNI tapered; ^Includes 10 children; [$]Based on Kaplan Meier estimates of relapse-free survival at 1-yr

Supplementary Table XII Strategies to Maintain Remission Following Rituximab Administration

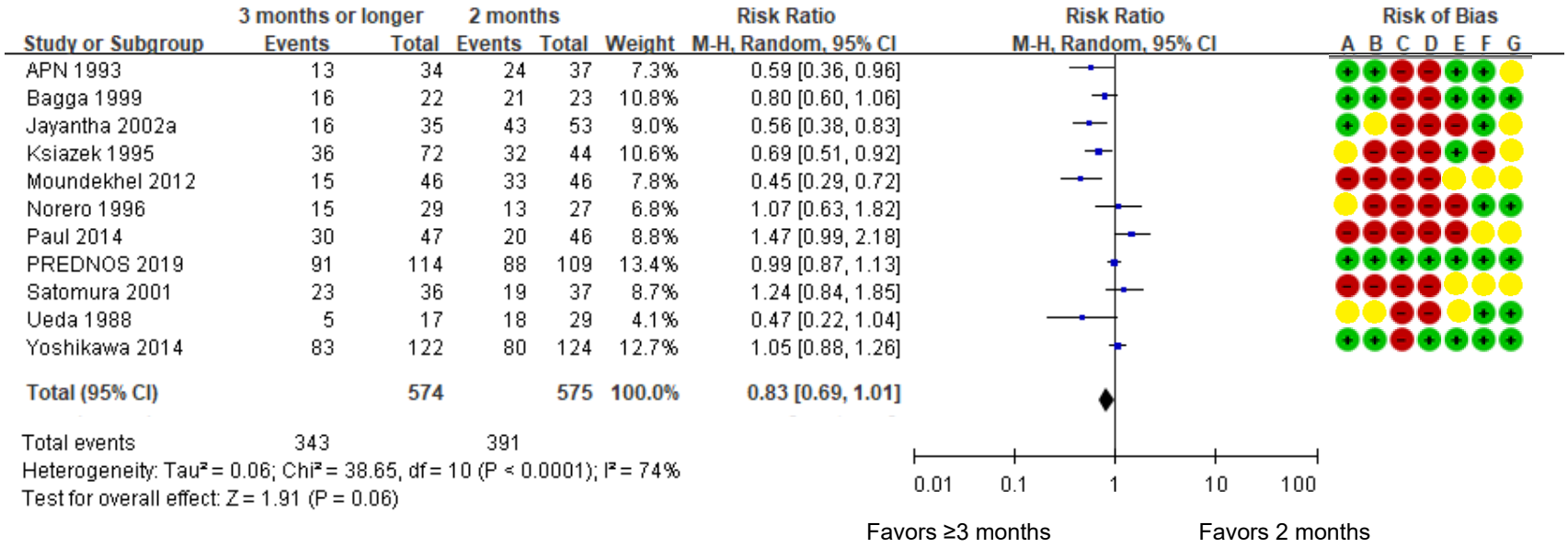
Author, year	*RTX* doses*	*Immunosuppression*	*N*	*Follow up, yr*	*Results*
Maintenance immunosuppression (mIS)					
Ito 2011 [lxxx]	1	MMF *vs*. none	9 *vs*. 7	1 yr	MMF therapy led to fewer relapses (0.4 *vs.* 2.3) and relapsers (33% *vs*. 86%) at 1-yr
Fujinaga 2013 [lxxxi]	1	CsA *vs*. MMF	13 *vs*. 16	1.5 yr	CsA *vs.* MMF led to fewer relapses (0.6±1.4 *vs.* 1.0±0.9); lower rates of relapse (25% *vs*. 45%) and lower treatment failure (15% *vs*. 44%); steroid sparing
Hourinouchi 2018 [lxxxii]	4	MMF *vs*. placebo	40 *vs*.40	1.4 yr	Awaited; UMIN000014347
Number of doses					
Hogan 2019 [lxxxiii]	1[*1] *vs*. 1 *vs*. 2	None	8 *vs*. 35 *vs*. 18	≥1 yr	Proportions in sustained remission at 1-yr higher by dose: 50 (58–77) % for 100 mg/m^2; 59 (42-76) % for 375 mg/m^2 and 72 (46-87) % for 750 mg/m^2 Low *vs.* high dose associated with risk of relapse: HR 5.0 (1.2, 21.6)
Maxted 2019 [lxxxiv]	1 *vs*. 2-3 *vs*. 4[*2]	Details not available	40 *vs.* 5 *vs*. 15	≥1 yr	1, 2-3 or 4 dose equivalents: Similar proportions in sustained remission at 1-yr (47%, 71%, 53%); similar time to relapse (334, >720, 344 days)
Number of doses and maintenance immunosuppression (mIS)					
Chan 2020 [lxxxv]	1 *vs*. 2 *vs*. 3-4	Prednisone, CNI or MMF [Continued *vs*. stopped]	191 *vs*. 208 *vs*. 112	≥0.5 yr	Time to relapse: *(i)* Similar for 1, 2 or 3-4 doses (11.8, 11.9, 13 months); *(ii)* similar among patients on mIS (11.8, 11.9, 13 months); *(iii)* lower for 1 vs. 2 or 3-4 doses if not given mIS (8.5, 12.7, 14.3 months); adjusted HR 0.5 & 0.6 (0.3-0.9)
Sequential administration of doses					
Takei 2013 [lxxxvi]	1 q 6 mo; 2 doses	Prednisone; CNI, MMF or mizoribine	25 adults^	1 yr	Before *vs*. after: Fewer relapses (62 *vs*. 4) and reduced prednisone (8.2±3.4 vs. 3.3±2.3 g/yr); 80% off prednisone and mIS; increased serum IgG (P=0.0005)
Miyabe 2016 [lxxxvii; lxxxviii]	1 q 6 mo; 4 doses	Prednisone; CNI, MMF or mizoribine	25^& 54^adults	2 yr	Before *vs*. after: Fewer relapses and reduced prednisone; all off prednisone and mIS; increased IgG; improved bone mineral density and blood pressure
Iwabuchi 2018 [lxxxix]	1 q 6 mo;4 doses	Prednisone; CNI, MMF or mizoribine	32 children & 19 adults^	2 yr	In children *vs*. adults: Few relapses and minimal prednisone dose (P <0.001); similar frequency of adverse reactions (21% *vs*.20%)
Papakrivopoulou 2016 [xc]	1 q 6 mo; 2-3 doses	Prednisone off by 3-mo; CNI tapered at >1-yr	15 adults	1.7 yr	Before *vs.* after: Fewer relapses (P <0.001); median remission 25 months; IgG levels unchanged

Taguchi 2020 [xci]	1 q 6 mo; 2-4 doses		13 adults	2 (1-5) yr	Before *vs.* after: Reduced relapses, and prednisone and cyclosporine dosage
Kim 2018 [xcii]	At B cell recovery[@1]	Details NA	12 children	2±1 yr	Before *vs.* after: Fewer relapses and off mIS (P <0.01)
Sellier-Leclerc 2012 [xciii]	At B cell recovery[@2]	MMF off; prednisone and CNI off by 3-mo	30 children	≥2 yr	Sustained remission in 63% at 3.2±0.1 yr; 37% relapsed 4.3 months after B cell recovery; 100% off mIS; transient adverse effects

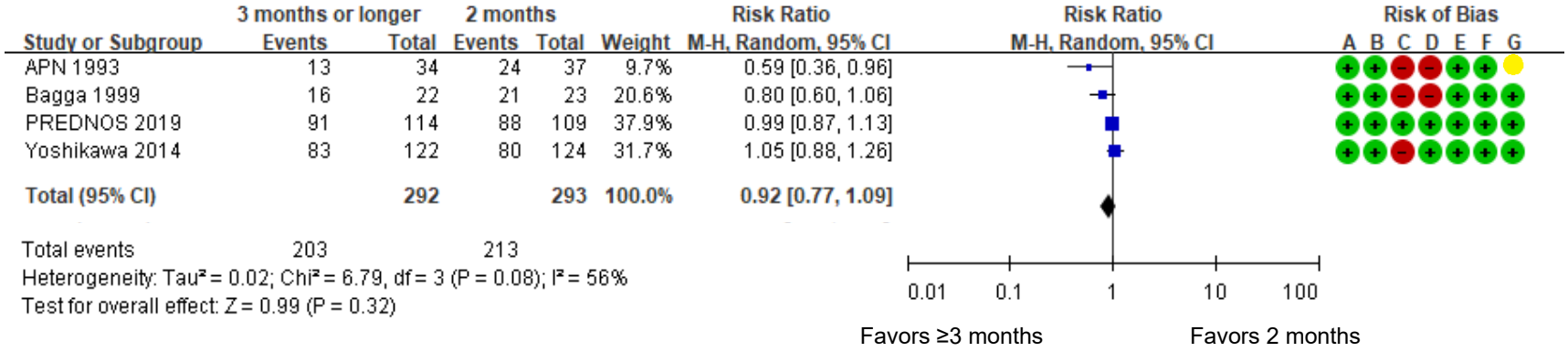
CNI calcineurin inhibitor; HR hazards ratio; IgG immunoglobulin G; MMF mycophenolate mofetil; mo months; NA not available; yr year
**Each dose was 375 mg/m² except[*1] where it was 100 mg/m²or [*2]750 mg/m² x 2 or 375 mg/m² x 4 doses*
[^]Overlap of patients between studies is unclear
[@]Total doses and frequency were [1]3.9±1.6 doses q 6±2 months and [2]5±1.4 doses over 15 months

Supplementary *Figure* I Meta-analyses of Randomized Controlled Trials on Prednisone Therapy for First Episode of Nephrotic Syndrome

Comparison 1.1.1 3-months or longer versus 2-months: Occurrence of relapse (all studies)



Comparison 1.1.2 3-months or longer versus 2-months: Occurrence of relapse in studies at low risk of bias

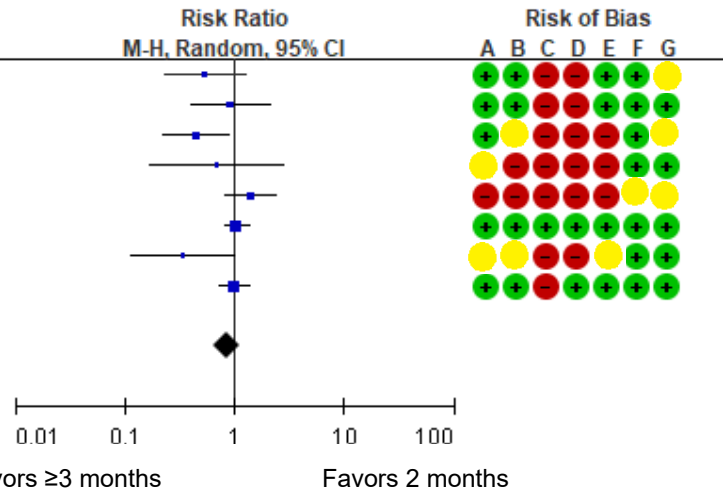


Comparison 1.2.1 3-months or longer versus 2-months: Occurrence of frequent relapses (all studies)

Study or Subgroup	3 months or longer Events	Total	2 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
APN 1993	6	34	12	37	7.9%	0.54 [0.23, 1.29]
Bagga 1999	7	22	8	23	8.4%	0.91 [0.40, 2.10]
Jayantha 2002a	8	48	26	70	10.7%	0.45 [0.22, 0.91]
Norero 1996	3	29	4	27	3.5%	0.70 [0.17, 2.84]
Paul 2014	20	47	14	46	14.6%	1.40 [0.81, 2.42]
PREDNOS 2019	60	114	55	109	26.4%	1.04 [0.81, 1.35]
Ueda 1988	3	17	15	29	5.5%	0.34 [0.12, 1.01]
Yoshikawa 2014	45	122	46	124	23.1%	0.99 [0.72, 1.38]
Total (95% CI)		**433**		**465**	**100.0%**	**0.86 [0.65, 1.13]**
Total events	152		180			

Heterogeneity: Tau² = 0.06; Chi² = 12.50, df = 7 (P = 0.09); I² = 44%

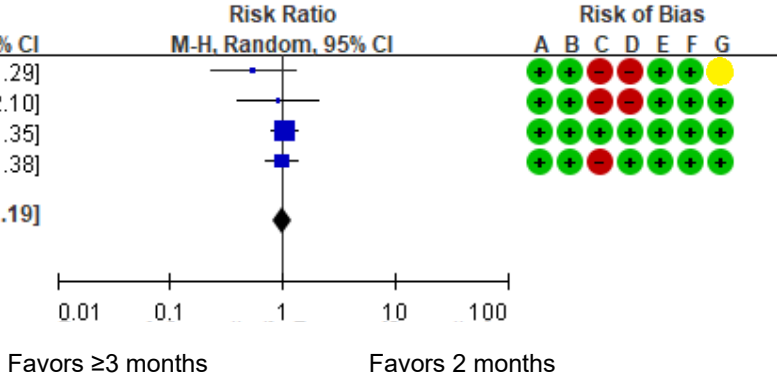
Test for overall effect: Z = 1.09 (P = 0.28)



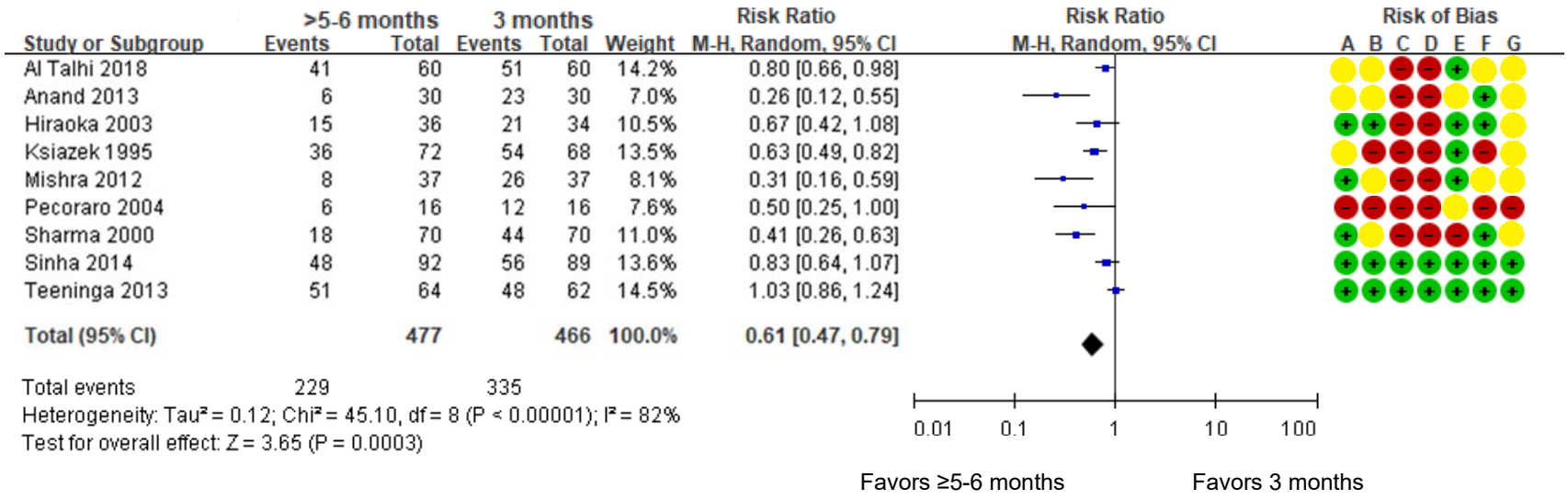
Comparison 1.2.2 3-months or longer versus 2-months: Occurrence of frequent relapses in studies at low risk of bias

Study or Subgroup	3 months or longer Events	Total	2 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
APN 1993	6	34	12	37	4.9%	0.54 [0.23, 1.29]
Bagga 1999	7	22	8	23	5.3%	0.91 [0.40, 2.10]
PREDNOS 2019	60	114	55	109	55.8%	1.04 [0.81, 1.35]
Yoshikawa 2014	45	122	46	124	34.1%	0.99 [0.72, 1.38]
Total (95% CI)		**292**		**293**	**100.0%**	**0.99 [0.82, 1.19]**
Total events	118		121			

Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)



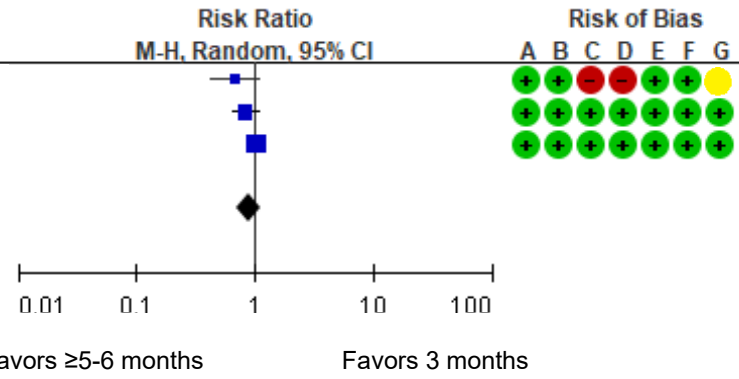
Comparison 2.1.1 5-6 months or longer versus 3 months: Occurrence of relapse (all studies)



Comparison 2.1.2 5-6 months or longer versus 3-months: Occurrence of relapse in studies at low risk of bias

Study or Subgroup	>5-6 months Events	Total	3 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hiraoka 2003	15	36	21	34	17.8%	0.67 [0.42, 1.08]
Sinha 2014	48	92	56	89	36.4%	0.83 [0.64, 1.07]
Teeninga 2013	51	64	48	62	45.8%	1.03 [0.86, 1.24]
Total (95% CI)		**192**		**185**	**100.0%**	**0.88 [0.70, 1.11]**
Total events	114		125			

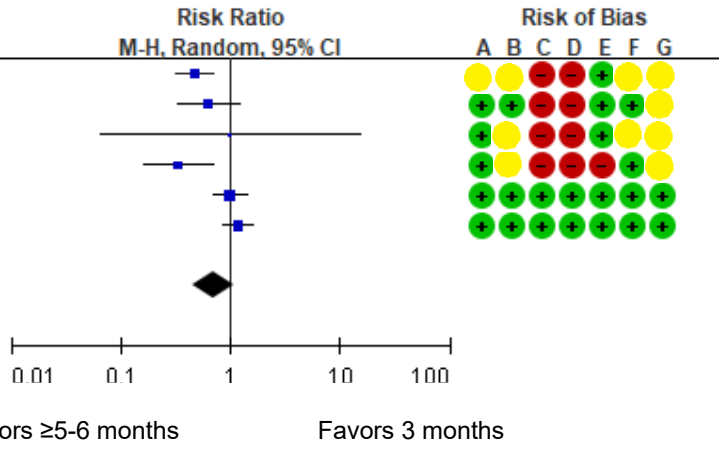
Heterogeneity: Tau² = 0.02; Chi² = 4.29, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 1.05 (P = 0.29)



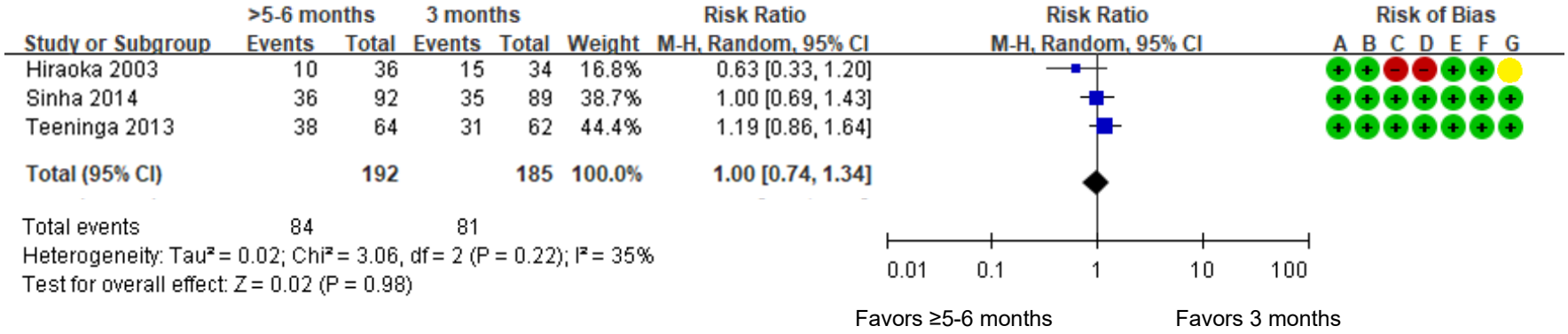
Comparison 2.2.1 5-6 months or longer versus 3-months: Occurrence of frequent relapses (all studies)

Study or Subgroup	>5-6 months Events	Total	3 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Al Talhi 2018	20	60	42	60	21.4%	0.48 [0.32, 0.71]
Hiraoka 2003	10	36	15	34	16.5%	0.63 [0.33, 1.20]
Mishra 2012	1	37	1	37	2.3%	1.00 [0.06, 15.40]
Sharma 2000	8	70	24	70	15.1%	0.33 [0.16, 0.69]
Sinha 2014	36	92	35	89	22.0%	1.00 [0.69, 1.43]
Teeninga 2013	38	64	31	62	22.7%	1.19 [0.86, 1.64]
Total (95% CI)		**359**		**352**	**100.0%**	**0.70 [0.45, 1.08]**
Total events	113		148			

Heterogeneity: Tau² = 0.19; Chi² = 20.47, df = 5 (P = 0.001); I² = 76%
Test for overall effect: Z = 1.63 (P = 0.10)



Comparison 2.2.2 5-6 months or longer versus 3-months: Occurrence of frequent relapses in studies at low risk of bias



Legend for risk of bias assessment

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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