Treatment of idiopathic nephrotic syndrome in children

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INTRODUCTION

The nephrotic syndrome (NS) is caused by renal diseases that increase the permeability of the glomerular filtration barrier. It is classically characterized by three clinical features, but the first two are generally used for a clinical diagnosis.

- Nephrotic range proteinuria – Urine protein excretion >50 mg/kg per day or a spot urine sample with a ratio (U_P/U_{Cr}) greater than 3 mg of protein per mg creatinine (see "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", section on 'Urine protein excretion')f
- Hypoalbuminemia – Serum albumin <3 g/dL (30 g/L)
- Edema

Idiopathic NS is the most common form of NS in children. It is characterized by diffuse foot process effacement on electron microscopy and a variety of findings on light microscopy that include minimal changes, focal segmental glomerulosclerosis (FSGS), or mesangial proliferation. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", section on 'Idiopathic nephrotic syndrome'.)

An overview of the treatment of idiopathic NS in children is presented here. The etiology, clinical manifestations, and diagnosis of NS in children are discussed separately. In addition, specific diseases that cause secondary NS are discussed in greater detail separately. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children" and "Etiology, clinical features, and diagnosis of minimal change disease in adults" and "Focal segmental glomerulosclerosis: Epidemiology, classification, clinical features, and diagnosis" and "Minimal change variants: Mesangial proliferation; IgM nephropathy; C1q nephropathy".)

BACKGROUND

Idiopathic NS is characterized by diffuse foot process effacement on electron microscopy and a variety of findings on light microscopy that include minimal changes, focal segmental glomerulosclerosis (FSGS), or mesangial proliferation. In children, the most common histologic form of idiopathic NS is with minimal changes, referred to as minimal change disease (MCD), occurring in approximately 75 percent of pediatric cases [1].

Prior to 1940, the mortality rate in children with NS was 40 percent, primarily due to infection, but it has been significantly reduced with the introduction of steroid treatment and antibiotics. (See "Complications of nephrotic syndrome in children", section on 'Infection'.)

Patients with MCD are generally responsive to steroid therapy [2]. Because clinical findings are highly predictable in differentiating MCD from other forms of NS, steroid therapy can be initiated in patients who are likely to have MCD based upon clinical criteria without histological confirmation by renal biopsy. Up to one-third of patients with FSGS will also initially respond to steroid therapy. (See "Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children", section on 'Idiopathic nephrotic syndrome'.)

Clinical experience has demonstrated that the response to steroid therapy rather than the histologic features seen on renal biopsy is better at predicting long-term prognosis. Patients who respond to steroids have an excellent prognosis and rarely develop end-stage renal failure. As a result, patients with NS can be defined by their response to steroid therapy as follows:

- Steroid-sensitive nephrotic syndrome (SSNS) – More than 90 percent of patients who respond to steroid therapy have MCD, and FSGS is primarily seen in the remaining patients [3]. Almost all patients with SSNS have an excellent outcome with few patients developing end-stage renal disease (ESRD) or chronic kidney disease (CKD). (See 'Steroid-sensitive nephrotic syndrome' below.)
- Steroid-resistant nephrotic syndrome (SRNS) – One-fourth of patients who fail to respond to steroids will have MCD [3]. Patients who fail an initial course of steroid therapy should undergo renal biopsy to determine the underlying diagnosis to guide further therapeutic choices. (See "Steroid-resistant idiopathic nephrotic syndrome in children: Etiology".)

SOCIETAL GUIDELINES

Several societies have established guidelines to manage pediatric NS that all initiate therapy with corticosteroid therapy (ie, prednisone or prednisolone). The following discussion is consistent with the Children's Nephrotic Syndrome Consensus and the Kidney Disease: Improving Global Outcomes (KDIGO) practice guidelines to treat pediatric NS, which are presented below. Symptomatic support and treatment of complications of NS are discussed separately. (See "Complications of nephrotic syndrome in children" and "Symptomatic management of nephrotic syndrome in children".)

Children's Nephrotic Syndrome Consensus — In 2009, the Children's Nephrotic Syndrome Consensus Conference, which included pediatric nephrologists from the southeast and midwest sections of the United States, developed the following guidelines for the treatment of children with NS [4].

- Initial therapy – Initial prednisone therapy of 2 mg/kg per day for six weeks, followed by alternate-day prednisone of 1.5 mg/kg for an additional six weeks.
- First relapse/infrequent relapse – Prednisone therapy of 2 mg/kg per day until the urine protein tests are negative or trace for three consecutive days, followed by alternate-day prednisone of 1.5 mg/kg for four weeks.
- Frequent relapses – Prednisone therapy of 2 mg/kg per day until the urine protein tests are negative or trace for three consecutive days, followed by alternate-day prednisone of 1.5 mg/kg for four weeks, which is then tapered over two months to 0.5 mg/kg every other day. In this guideline, steroid-sparing agents, such as oral cyclophosphamide, cyclosporine, and mycophenolate mofetil (MMF) may be used to sustain remission and thereby reduce cumulative steroid doses and toxicity. However, in our experience, these patients usually do not require steroid-sparing agents because low dose alternate-day prednisone is effective in preventing frequent relapses and is well tolerated. (See 'Frequent relapsing/steroid dependent NS' below.)
- Steroid-dependent disease – Prednisone remains the preferred therapy in the absence of significant steroid toxicity. Steroid-sparing agents, such as levamisole, cyclophosphamide, MMF, and calcineurin inhibitors (ie, cyclosporine or tacrolimus), may be helpful in reducing steroid dosing. However, there are no data based upon controlled trials in helping to choose among these agents, and drug selection is based upon the risk/benefit ratio of each agent as determined by the clinician. (See 'Nonsteroidal therapy' below.)
- Steroid-resistant disease – Therapy is based upon the histologic findings found on renal biopsy. Additional treatment includes angiotensin antagonism and supportive care focused on managing the complications of NS (eg, edema, hypertension, infection, dyslipidemia, and thromboembolism). (See "Steroid-resistant idiopathic nephrotic syndrome in children: Etiology".)

KDIGO guidelines — Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003 and is an international organization focused on improving the outcome of patients with kidney disease globally. In 2012, a working committee developed the following guidelines to manage children with steroid-sensitive nephrotic syndrome (SSNS) as follows [5].

- Initial therapy – Initial prednisone therapy of 60 mg/m^2 or 2 mg/kg per day for four to six weeks (maximum dose of 60 mg/day), followed by alternate-day prednisone of 40 mg/m^2 or 1.5 mg/kg (maximum dose of 40 mg/day) and continued for two to five months with tapering of the dose.
- Infrequent relapses – Prednisone therapy of 60 mg/m^2 or 2 mg/kg per day (maximum dose of 60 mg/day) until the urine protein tests are negative or trace for three consecutive days, followed by alternate-day prednisone of 40 mg/m^2 or 1.5 mg/kg (maximum dose of 40 mg/day) for at least four weeks. (See 'Initial or infrequent relapse' below.)
- Frequent relapses or steroid-dependent disease – Prednisone therapy of 60 mg/m^2 or 2 mg/kg per day (maximum dose of 60 mg/day) until the urine protein tests are negative or trace for three consecutive days, followed by alternate-day prednisone for at least three months. The dose of alternate-day prednisone should be the lowest dose needed to maintain remission without adverse side effects. In patients in whom alternate-day therapy is not effective in maintaining remission, the lowest possible dose of daily prednisone is given to maintain remission to minimize adverse side effects. Daily prednisone should be given to patients during episodes of upper respiratory tract infection and other infections that are associated with relapse. (See 'Infections as relapse triggers' below.)
- Corticosteroid-sparing agents should be given to children with frequently relapsing or steroid-dependent disease who develop steroid-related adverse effects. Data are insufficient to choose among the following agents. Drug selection is based on the reported efficacy, adverse effects, local availability, and cost.
  - Alkylating agents include cyclophosphamide (dose of 2 mg/kg per day for 8 to 12 weeks [maximum cumulative dose of 168 mg/kg]) **or** chlorambucil(dose of 0.1 to 0.2 mg/kg per day for 8 weeks [maximum cumulative dose 11.2 mg/kg]). (See 'Alkylating agents' below.)
  - Levamisole (dose of 2.5 mg/kg on alternate days for at least 12 months). (See 'Levamisole' below.)
  - Calcineurin inhibitors include cyclosporine (initial dose of 4 to 5 mg/kg per day given in two divided doses) **or** tacrolimus (initial dose of 0.1 mg/kg per day given in two divided doses). (See 'Calcineurin inhibitors' below.)
  - MMF (initial dose of 1200 mg/m^2 per day given in two divided doses for at least 12 months). (See 'Mycophenolate' below.)
  - Rituximab (an anti-CD20 monoclonal) should be considered only in children who have failed combination therapy of prednisone and other corticosteroid-sparing agents and have serious adverse effects of therapy. (See 'Rituximab' below.)
  - Both mizoribine and azathioprine are **not** recommended in the management of children with NS.

Canadian Society of Nephrology — A review of the KDIGO guidelines by a working group of Canadian pediatric nephrologists agreed with most of the KDIGO recommendations, including first-line therapy with steroids [6]. However, several areas of uncertainty were identified including the length of steroid therapy for both the initial presentation and subsequent relapses, definition of steroid resistance, and choice of second-line agents after steroid therapy. As a result, the following modifications were noted based on review of the available literature:

- Longer duration of initial steroid course beyond 12 weeks and up to 6 months.
- Limit the use of daily or alternate-day steroid therapy for children with steroid-dependent disease and move to a second-line steroid-sparing therapy (eg, alkylating agent or calcineurin inhibitor). Most Canadian pediatric nephrologists have used tacrolimus (calcineurin inhibitor) as the first second-line agent. However, the working group noted that the timing and use of alkylating agents versus calcineurin inhibitors remain unresolved.
- Levamisole is not readily available in Canada.
- Drug coverage for mycophenolate is not universally available in Canada.

- The definition of steroid resistance was modified to between four and eight weeks rather than a historical definition of eight weeks.

INITIAL PHARMACOLOGIC THERAPY

As noted above, the most common cause of pediatric idiopathic NS is minimal change disease (MCD), which is generally responsive to steroid therapy. As a result, empirical steroid therapy is given to patients with a high probability of having MCD without confirmation of the diagnosis by renal biopsy. MCD can be clinically differentiated from other causes of NS in children. Thus, therapy can be started in patients who fulfill **all** of the following clinical criteria for MCD [3,7,8].

- Age older than one year and younger than 10 years of age
- None of the following findings: hypertension, gross hematuria, and a marked elevation in serum creatinine
- Normal complement levels
- No extra-renal symptoms such as malar rash or purpura

Although steroid therapy is often started immediately following the diagnosis of NS, it should be stressed that spontaneous remission occurs in 5 percent of cases within one or two weeks. Therefore, the initiation of steroid therapy may be delayed for a few days or a week [9].

In older children, a renal biopsy is recommended because of the increase in prevalence of diagnoses other than MCD in this age group. In these patients, therapeutic decisions are based on the histologic diagnosis, which are discussed separately for each specific disease. (See "Minimal change variants: Mesangial proliferation; IgM nephropathy; C1q nephropathy" and "Focal segmental glomerulosclerosis: Treatment of primary focal segmental glomerulosclerosis" and "Evaluation and treatment of membranoproliferative glomerulonephritis" and "Treatment of idiopathic membranous nephropathy".)

Steroid response — Most children with idiopathic NS will respond to steroid therapy with complete resolution of proteinuria (ie, urinary protein excretion <4 mg/m^2 per hour or 100 mg/m^2 per day) [3,10].

In a multicenter study from the International Society of Kidney Disease in Children (ISKDC) of 334 children with MCD, 92 percent of patients responded to steroids [7]. Six months after steroid therapy, the following outcomes were noted in the steroid-responsive patients:

- Approximately 40 percent of patients did not relapse within six months after the initial course of steroid therapy. In this group of patients, long-term follow-up demonstrated 16 percent had no further relapse, and 60 percent only had rare relapses (defined as no two-year consecutive periods with one or more relapses per year).
- Approximately 30 percent relapsed frequently (defined as two or more relapses within six months after initial steroid therapy).
- 20 percent had a single relapse within the six-month time period.
- Three percent of patients who initially responded to steroid therapy failed to respond to subsequent courses of steroid therapy.

Time to response — Most patients who respond to steroid therapy will do so within the first four weeks of therapy [3,10]. This was illustrated in another report from the ISKDC that demonstrated 90 percent of responding patients had attained complete remission within four weeks after beginning therapy, and the remaining 10 percent responded after an additional two to four more weeks of daily steroid therapy (figure 1) [3]. A short response time of less than seven days is associated with a better prognosis including less likelihood of relapsing within three months, frequent relapses, and steroid dependency [11].

Length of therapy and risk of relapse — The optimal duration of therapy for reducing the risk and frequency of relapses remains uncertain. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines that have adopted a long initial course of steroids are based on systematic reviews that showed initial therapy of at least three to seven months including periods of daily and alternate-day therapy reduced the risk of subsequent relapses [5,12].

In a systematic review and meta-analysis, therapy for three months or more appeared to reduce the risk of frequently relapsing nephrotic syndrome (FRNS) (relative risk [RR] 0.68, 95% CI 0.47-1.00) and of relapse by 12 to 24 months (RR 0.80, 95% CI 0.64-1.00) compared with two months of therapy [13]. However, there was a significant degree of heterogeneity and quality of evidence amongst the included studies. A subgroup analysis of studies with low risk of bias showed no difference in the risk for FRNS between patients given prednisone for two or three months and those who received longer durations of therapy. The authors concluded that older, high risk of bias studies overestimated the effect of longer course therapy as compared with subsequent studies of higher quality, and that the evidence demonstrated no benefit of increasing the duration of prednisone therapy beyond two or three months for the treatment of the initial episode of NS.

A subsequent clinical trial of 237 children (age range from 1 to 14 years) with a first episode of steroid-sensitive nephrotic syndrome reported similar outcome between an extended 16-week course and a standard 8-week course of prednisone regarding time to first relapse and the incidence of FRNS (53 versus 50 percent), steroid-dependent nephrotic syndrome (42 versus 44 percent), or requirement for alternative immunosuppressive treatment (54 versus 56 percent) [14].

As a result of the available evidence, treatment durations of two or three months are recommended for the management of the first episode of steroid-sensitive nephrotic syndrome (SSNS) rather than longer durations, as recommended in the KDIGO guidelines [15,16].Slow tapering to avoid adrenal suppression may be important to maintain long-term remission as demonstrated in a small study that reported moderate to severe post-prednisone adrenal suppression was associated with an increased risk of relapse [17].

Increasing initial immunosuppression by adding cyclosporine to steroid therapy had been proposed as a way to reduce the relapse rate. However, the addition of cyclosporine does not alter the two-year relapse rate, and the combination of cyclosporine and prednisone compared with prednisone alone results in a greater number of side effects [18,19]. As a result, steroids alone are used as the initial therapy for childhood NS.

Our approach — Although there is variation in the dosing and duration of therapy, almost all pediatric nephrologists empirically treat children with idiopathic NS with a course of steroid therapy of at least two to three months [20]. Based upon the available data, we initially treat children with idiopathic NS who are likely to have MCD with oral prednisone at a dose of 60 mg/m^2 per day (maximum of 60 mg/day).

With the initiation of steroid therapy, patients and their parents are taught to monitor urine protein levels by urine dipstick [21]. When proteinuria disappears, prednisone is continued at the same daily dose for an additional 30 days and then switched to alternate-day therapy (at the same dose). Alternate-day therapy is tapered over a one- to two-month time period. As noted above, there is no consensus on the total duration of initial steroid therapy, but based on the available evidence, there is no benefit in extending the duration of steroid treatment beyond 2 or 3 months in the first episode of SSNS [16]. However, it should be noted that these trials used prednisolone [22,23], whereas the earlier meta-analysis [12], which concluded that a prolonged course (greater than three months) was beneficial, was based mostly on data from trials using prednisone. There has been no trial directly comparing prednisone and prednisolone as a first-line treatment and it is unknown whether their dosing, including duration, is equivalent.

In our practice, among patients who are not in remission after four weeks of daily steroid therapy, we administer three pulses of methylprednisolone (1000 mg/1.73 m^2) every other day [10,24]. This regimen is associated with fewer side effects than prolongation of daily high-dose steroids (advocated by others in the field as discussed below), and may produce remission more quickly in the few patients who would have entered the second month of daily glucocorticoid therapy. Patients who have persistence of proteinuria one week after this treatment are considered steroid-resistant. A renal biopsy is performed in these patients with steroid-resistant nephrotic syndrome (SRNS), as there is increased likelihood that they have another glomerular disease [3]. No additional steroid therapy is administered until a histologic diagnosis is made, which aids in making therapeutic choices. (See "Steroid-resistant idiopathic nephrotic syndrome in children: Etiology".)

As noted above, other centers do not administer intravenous (IV) methylprednisolone as standard practice in refractory patients, and may use one of the following alternate approaches in patients who are not in remission after an initial four-week course of daily steroid therapy:

- Biopsy patients without administering the three pulses of methylprednisolone, as there is an increased likelihood that they have another glomerular disease that may not be responsive to additional steroid therapy. (See "Steroid-resistant idiopathic nephrotic syndrome in children: Etiology".)
- Continue daily steroid therapy for another four weeks because an additional 10 percent of steroid-responsive patients will respond after four weeks of therapy [3]. Patients who fail to respond to a maximum eight weeks of daily steroid therapy are considered steroid-resistant and require a renal biopsy to determine the underlying glomerular disease [3]. (See 'Steroid-resistant nephrotic syndrome' below.)
- The approach outlined by the Children's Nephrotic Syndrome Consensus conference uses a daily dose of prednisone (maximum 60 mg/day) for six weeks followed by alternate-day steroids of 1.5 mg/kg for an additional six weeks. (See 'Children's Nephrotic Syndrome Consensus' above.)

Outcome based upon response — In the previously mentioned report from the ISKDC, the long-term outcomes of 389 children with MCD (mean follow-up of 9.4 years) were reported based on their initial response to steroid therapy [7]. The following results were noted:

- Overall, 95 percent of children did well. Only 4 to 5 percent died from complications (eg, peritonitis) or progressed to end-stage renal disease (ESRD).
- Prognosis was best in the steroid-responsive patients who did not relapse in the first six months. Approximately 75 percent either continued in remission during follow-up or relapsed rarely. Only 4 percent became frequent relapsers.
- Patients with persistent proteinuria after eight weeks of steroid therapy (steroid-resistant) had a 21 percent risk of progression to ESRD.

STEROID-SENSITIVE NEPHROTIC SYNDROME

As discussed above, the majority of children with idiopathic NS have minimal change disease (MCD) and will attain complete remission with an initial course of steroid therapy. However, 80 to 90 percent of steroid-responsive patients will experience one or more subsequent relapses [7,10,25]. The risk of relapse is greater in children aged less than five years at onset. As a result, management for patients with steroid-sensitive nephrotic syndrome (SSNS) is focused on early detection and treatment of any relapse to reduce the risk of complications associated with NS. (See 'Frequent relapsing/steroid dependent NS' below.)

One study found that children with GR-9beta polymorphism of the glucocorticoid receptor gene *NR3C1* are at increased risk for relapse, frequent relapses, and steroid dependence as compared with noncarriers [26]. Further studies need to conclusively establish this association and determine how best to use this information for management.

Monitoring — Once a patient responds to steroid therapy, ongoing monitoring for proteinuria is required to detect relapses early, and initiate therapy to prevent significant fluid accumulation (edema) and minimize the complications associated with childhood idiopathic NS. (See "Complications of nephrotic syndrome in children".)

Patients and their parents are taught to routinely measure body weight as well as continue to monitor urine protein levels by urine dipstick [21]. Increased urinary protein concentration typically provides the first indication of a relapse. When this occurs, the family should call its healthcare provider for instructions regarding management.

Steroid therapy — Prednisone remains the preferred therapy in the children with SSNS as long as there is no significant steroid toxicity. The regimen of steroid therapy is dependent on the course of the disease (eg, frequency of relapses).

Initial or infrequent relapse — With the first initial relapses or for infrequent relapses, steroid therapy is typically administered at a dose of 60 mg/m^2 per day (maximum dose of 60 mg/day). The length of steroid therapy varies among pediatric nephrologists. In our practice, daily prednisone is given until proteinuria has disappeared for four to five days. Alternate-day therapy is then begun and the dose tapered to 15 to 20 mg/m^2 every other day for another four weeks.

This is similar to the approach by the Children's Nephrotic Syndrome Consensus group, which suggests treating the first relapse or infrequent relapse with prednisone therapy of 2 mg/kg per day (maximum dose of 60 mg/day) until the proteinuria has resolved for three consecutive days [4]. At that point, alternate-day prednisone is administered at a dose of 1.5 mg/kg per day (maximum dose of 45 mg/day) for four weeks. (See 'Children's Nephrotic Syndrome Consensus' above.)

Frequent relapsing/steroid dependent NS — Approximately 25 to 30 percent of steroid-responsive patients will develop frequently relapsing NS, defined as four or more relapses per year [7,10]. In addition, there is a group of patients who are steroid dependent (defined as relapsing during taper or within two weeks of discontinuation of steroid therapy). A distinction between frequent relapsers and steroid-dependent patients should be made, because FRNS seems to have a better prognosis regarding response to steroid-sparing agents and long-term remission [27].

Although children with frequently relapsing or steroid-dependent NS are at risk for steroid toxicity, prednisone remains the preferred therapy in the absence of significant steroid toxicity. Different steroid regimens have been used to treat patients with frequent relapses and/or who are steroid dependent. In our practice, we administer daily prednisone, 40 to 60 mg/m^2, until proteinuria has disappeared for four to five days, followed by alternate-day therapy with tapering by 15 to 20 mg/m^2 every other day to the patient's steroid threshold (ie, the dose at which the relapse has occurred) [28]. This regimen is continued for 12 to 18 months.

Other regimens include:

- The ISKDC recommends a prednisone dose of 60 mg/m^2 per day (maximum of 60 mg/day) be initiated when a patient has relapsed and continued for three days after the urine has become protein free; thereafter, alternate-day prednisone, 40 mg/m^2, is given for four weeks [29].
- The Children's Nephrotic Syndrome Consensus recommends prednisone therapy of 2 mg/kg per day (maximum of 60 mg/day) until the urine protein tests are negative or trace for three consecutive days, followed by alternate-day prednisone of 1.5 mg/kg for four weeks, which is then tapered over two months on an alternate-day schedule [4].
- An open-label randomized controlled trial reported that daily administration of low-dose prednisolone (0.2 to 0.3 mg/kg per day) is more effective than standard-dose alternate day therapy (0.75 mg/kg every other day) in lowering relapse rates, sustaining remission, and enabling steroid-sparing [30].

The first regimen allows better definition in terms of relapses, but is associated with more relapses because of the shorter duration of therapy resulting in larger cumulative steroid dose. The third approach is associated with fewer steroid side effects, as the duration of high-dose therapy is shorter.

Adrenocorticotropic hormone (ACTH) has been suggested as an alternative to corticosteroids therapy. However, in a study of patients with either frequently relapsing or steroid-dependent NS, ACTH administered twice a week at a dose of 80 international units/1.73 m^2 was ineffective at preventing relapses [31].

It is important to appreciate, especially when considering other therapeutic agents, that almost all frequent relapsers have a progressive decrease in the number of relapses over time and ultimately go into permanent remission [32]. Steroid-sparing agents should be considered in children who have significant steroid toxicity. (See 'Steroid side effects' below and 'Nonsteroidal therapy' below.)

Infections as relapse triggers — Viral infections are a documented trigger for a relapse in children with NS [33]. A short-term increase to daily rather than alternate-day maintenance dosing in patients with frequent relapsing SSNS for five to seven days during an episode of intercurrent infections appears to reduce the risk of relapse [34-37]. A randomized controlled trial involving 100 children with frequently relapsing NS found that daily administration of maintenance doses of steroids for seven days during intercurrent infection significantly reduced relapse rates [36]. A short course of daily prednisoloneduring upper respiratory tract infection reduces the risk of relapse in patients with steroid-sensitive NS who have been off treatment for three months or more [37].

Steroid side effects — Complications secondary to prolonged steroid therapy are well known and are seen in children with NS, especially those with frequent relapses or steroid dependency. The side effects associated with steroid use in children with NS are summarized here. Major side effects of steroids are discussed in greater detail separately. (See "Major side effects of systemic glucocorticoids".)

- Statural growth impairment can be seen with prolonged daily steroid therapy [38]. Low-dose alternate-day therapy can preserve growth [39], and catch-up growth often occurs when steroid therapy is discontinued [40]. One small observational study found that growth was not negatively impacted with doses of prednisolone below 0.75 mg/kg per day [41]. We prefer alternate-day therapy whenever possible to preserve normal growth as much as possible.
- Cataracts [42,43].
- Excessive weight gain, which can persist into adulthood [44].
- Although osteoporosis has been reported in adults who had SSNS as children [44], a study that compared adolescents and children with SSNS with control patients by dual energy x-ray absorptiometry (DEXA) found

no long-term effects of intermittent high-dose glucocorticoid exposure upon bone mineral content of the spine or body [18].

- Suppression of the hypothalamic-pituitary-adrenal axis (HPA). In a case series of patients (mean age of 9.7 years) treated with alternate-day steroids, 20 of 32 patients had evidence of HPA suppression, defined as a peak serum cortisol concentration less than 500 nmol/L (18 mcg/dL) in response to adrenocorticotrophin stimulation given as an injection of tetracosactide (0.5 mcg) [45]. Although the authors suggest that HPA suppression increased the risk of relapse, the contribution of HPA suppression is uncertain because the patients in this small study were treated with several different regimens.

Nonsteroidal therapy — In children with significant side effects of steroid therapy, other steroid-sparing agents (eg, alkylating agents) that prolong remissions and reduce the dose of steroids should be considered. These drugs include alkylating agents, levamisole, cyclosporine, mycophenolate mofetil (MMF), and rituximab [46]. In our practice, our initial steroid-sparing agent of choice is levamisole, if it is available. If this is not the case, MMF is our preferred drug for patients with significant steroid toxicity based on the available evidence.

Alkylating agents — Alkylating agents, such as cyclophosphamide and chlorambucil, can induce longer lasting remissions than prednisone alone in patients who are frequent relapsers or steroid dependent [47-50]. However, these medications, which result in depletion of immune competent cells, have significant side effects. Based upon the efficacy and safety data discussed in the following sections, if we elect to use an alkylating agent, we will administer a 12-week course of oral cyclophosphamide at a dose of 2 mg/kg per day (cumulative dose 168 mg/kg). The maximum daily dose should not exceed 2.5 mg/kg.

Efficacy — In a systematic review of the literature, alkylating agents compared with prednisone alone were more effective in reducing the risk of relapse at 6 to 12 months (relative risk [RR] 0.43, 95% CI 0.31-0.60) and at 12 to 24 months (RR 0.2, 95% CI 0.09-0.49) in children with SSNS [50]. Supporting observational data demonstrated that cyclophosphamide therapy resulted in sustained remission in frequently relapsing and/or steroid-dependent patients of 57 to 93 percent at one year, 31 to 66 percent at five years, and approximately 25 percent at 10 years [47-49,51,52]. However, another case series reported lower remission rates of 44, 27, and 13 percent at one, two, and five years after cyclophosphamide therapy, respectively [53].

Variation in remission rates is likely to be due to differences in the patient population such as the proportion of patients with steroid-dependent NS who appear to have a lower response rate to cyclophosphamide. This was illustrated by the following studies:

- In one prospective study of 50 children, only 30 percent of steroid-dependent patients compared with 70 percent of children with frequent relapses had prolonged remissions after an eight-week oral course of cyclophosphamide [54].
- In a long-term follow-up report (median time six years) of 93 patients with steroid-dependent biopsy-proven MCD, only 35 percent of patients remained in sustained remission after a course of cyclophosphamide [55]. Twenty-eight patients (30 percent) had more than five relapses, 19 (20 percent) had five or less relapses, and 13 were lost to follow-up.
- In another study of 90 patients with steroid-dependent NS, a similar sustained remission rate of 31 percent was seen at five-year follow-up [52].

In addition, the degree of steroid dependency may affect remission rates. This was illustrated in a study of 108 patients with steroid-dependent NS treated with cyclophosphamide who attained overall cumulative sustained remission rates of 25 and 22 percent at 5- and 10-year follow-up [56]. Patients who relapsed on lower doses of prednisone (ie, ≤1.4 mg/kg) were more likely to have sustained remission at 5- and 10-year follow-up compared with those who required higher doses of prednisone (35 and 33 percent versus 13 and 5 percent).

The effect of cyclophosphamide may also depend upon the duration of treatment, especially in steroid-dependent children. This was demonstrated in a German study in which 18 steroid-dependent children received a 12-week oral course of cyclophosphamide (2 mg/kg per day) [57]. Patients treated for 12 weeks had a higher remission rate at two years compared with historical controls treated for eight weeks (67 versus 30 percent). However, other studies found no difference in length of remission between an 8- and 12-week course of cyclophosphamide [50,58,59].

In our practice, when we elect to use an alkylating agent, cyclophosphamide is our drug of choice. We administer a 12-week course of oral cyclophosphamide at a dose of 2 mg/kg per day (cumulative dose 168 mg/kg). The maximum daily dose of cyclophosphamide should not exceed 2.5 mg/kg.

Side effects — Complications associated with the use of alkylating agents include the following [60,61]:

- Neutropenia and infection – Bone marrow suppression by alkylating agents requires monitoring complete blood cell counts (CBC). If the white cell count falls below 3000/mm^3, the drug should be withdrawn until the count rises. Treatment also should be discontinued if infection develops. There are reported cases of significant morbidity and mortality associated with varicella and the administration of cyclophosphamide. If varicella infection occurs, acyclovir should be administered immediately and the alkylating agent discontinued. (See "Complications of nephrotic syndrome in children", section on 'Viral infections'.)
- Gonadal toxicity – The development of gonadal toxicity resulting in infertility generally requires a total dose greater than 200 to 300 mg/kg for cyclophosphamide, which exceeds the recommended cumulative dose used to treat children with NS (168 mg/kg for cyclophosphamide) [62,63]. The gonadal toxicity threshold for chlorambucil is 8 to 10 mg/kg.
- Malignancy – In a 2001 systematic review of the literature that included 1504 patients, 14 cases of malignancies were reported after high doses (greater than the above recommended standard dosing) of either cyclophosphamide or chlorambucil [61]. There was also a single reported case of malignancy (acute lymphoblastic leukemia) associated with cyclophosphamide administered in a child with NS using the above

recommended regimen [64]. The extensive use of the above standard regimen of cyclophosphamide in children with NS and only a single reported associated case of malignancy suggest that there is **not** a clinically significant increased risk of malignancy associated with cyclophosphamide at this dosage used to treat childhood NS compared with the general pediatric population.

- Alopecia and hemorrhagic cystitis rarely occur at the recommended doses used to treat children with NS.
- Seizures – Chlorambucil has been associated with an increased risk of seizures in children with NS [65].

Based upon the above data, a 12-week course of 2 mg/kg per day of cyclophosphamide (cumulative dose of 168 mg/kg) appears to have minimal long-term complications and is the preferred regimen when an alkylating agent is used.

Levamisole — Levamisole, which stimulates the immune system, has been shown to have a steroid-sparing effect in children with SSNS [50,66-73]. In the previously mentioned meta-analysis, levamisole was more effective in reducing relapse than steroids alone (RR 0.47, 95% CI 0.24-0.89) [50]. However, most patients relapsed after cessation of treatment. In a subsequently published multinational clinical trial of children managed with standard steroid therapy, the addition of levamisole for one year compared with placebo increased the time to relapse by 78 percent, and increased the remission rate at 12 months (26 versus 6 percent) [73]. Reversible neutropenia was the most common adverse effect. Other reported rare severe adverse effects of levamisole (eg, hepatitis, seizures, and antineutrophil cytoplasmic antibody vasculitis) were not observed.

In an open-label trial of children with frequently relapsing or steroid-dependent nephrotic syndrome, levamisole (2.5 mg/kg on alternate days) and mycophenolate mofetil (MMF) (750 to 1000 mg/m^2) had similar rates of sustained remission, reduction of steroid use, and the frequency of relapses [74]. The rates of adverse effects were low and also similar in both groups treated with levamisole and MMF.

The results of these two randomized controlled trials suggest that the optimal use of levamisole is for children with frequently relapsing nephrotic syndrome as a first steroid-sparing agent before considering more powerful immunosuppression [75].

The dose of levamisole is usually 2 to 2.5 mg/kg given on alternate days (maximum dose of 150 mg). A prospective study has shown that levamisole at 2.5 mg/kg daily was effective and safe. The mean number of relapses per patients was 2.8 ± 0.8 in patients on alternate day schedule of levamisole and 1.3 ± 0.9 on a daily schedule of levamisole [76]. Regular monitoring of complete blood count (CBC) should be performed because the most serious adverse effect of levamisole is reversible neutropenia.

There is limited availability of levamisole worldwide [77], and it is not available in the United States.

Calcineurin inhibitors — Calcineurin inhibitors (cyclosporine and tacrolimus) block T-cell activation and have been used to treat patients with frequently relapsing or steroid-dependent NS. However, long-term therapy is generally required to maintain remission, which increases the risk for drug-induced nephrotoxicity.

Cyclosporine — Data demonstrate cyclosporine is effective in inducing or maintaining remission in patients with frequently relapsing or steroid-dependent NS [78-84]. A review of the literature, which included 129 children, reported cyclosporine either induced remission or maintained remission in 85 percent of patients, thereby allowing withdrawal of prednisone [79]. However, most patients relapse when the drug is withdrawn, thus necessitating prolonged treatment and increasing the risk of nephrotoxicity [78,85-87].

Because of the concern for nephrotoxicity, the plasma creatinine concentration should be monitored regularly in patients who are maintained on long-term course of cyclosporine. However, serial renal biopsies demonstrate histologic lesions of nephrotoxicity without clinical evidence of renal function impairment. Thus, we routinely perform a renal biopsy in asymptomatic patients after 18 months of cyclosporine therapy [83,85,88]. (See "Cyclosporine and tacrolimus nephrotoxicity".)

In the previously mentioned meta-analysis that reviewed nonsteroidal therapy for SSNS, the effect of cyclosporine was initially the same as that of chlorambucil and cyclophosphamide in maintaining remission [50]. However, after cyclosporine was discontinued, it was less effective in maintaining remission at 12 months compared with either alkylating agent and at 24 months for chlorambucil.

The recommended starting cyclosporine dose is 150 mg/m^2 per day divided into two oral doses. The dose should be adjusted to maintain trough whole blood levels between 100 and 200 ng/mL, and the level should not exceed 200 ng/mL. In order to limit the risk of nephrotoxicity, once remission is achieved, we recommend decreasing the dose to less than 5 mg/kg, if possible.

It has been our experience that patients who relapse on cyclosporine or after cyclosporine withdrawal often respond poorly to a second or third course of treatment. Low-dose alternate-day prednisone in combination with cyclosporine may be a better approach in these patients.

Tacrolimus — Limited data suggest that tacrolimus offers no advantage over cyclosporine on maintaining remission in children with SSNS, and it has the same risk of nephrotoxicity [46,89,90]. However, one advantage of tacrolimus over cyclosporine is the reduced cosmetic side effects (hypertrichosis, gum hypertrophy).

Mycophenolate — MMF inhibits T- and B-cell proliferation. Small studies suggest that MMF is effective in increasing the duration of remission in children with idiopathic NS, which may allow withdrawal of steroids or calcineurin inhibitors [91-97]. However, relapses often occur after the treatment is discontinued.

Side effects of MMF include gastrointestinal disturbances (abdominal pain and diarrhea) and hematological abnormalities. Because MMF is teratogenic, use of contraception is recommended in adolescent females [98].

Mycophenolate versus calcineurin inhibitors — Data comparing MMF with calcineurin inhibitors (specifically cyclosporine) are limited, but suggest that MMF is not as effective as cyclosporine in achieving remission [50,99,100]. Although cyclosporine is more effective at preventing relapses, MMF still may be an attractive alternative therapy, as it is less nephrotoxic. Further studies, including larger controlled trials, are needed to determine whether MMF has a role in the treatment of children with NS. Nevertheless, while awaiting further information, we prefer to administer MMF as the initial steroid-sparing agent and prescribe cyclosporine only if the patient fails to respond to MMF.

It appears that higher mycophenolic acid (MPA, the active metabolite of MMF) exposure in children with NS compared with kidney transplant recipients are needed to sustain remission [101]. For children with NS, target MPA-AUC (area under the curve) exposure should be >45 microg·h/mL, which is not associated with increased side effects compared with lower exposure [102-105].

Rituximab — Rituximab, a chimeric anti-CD20 monoclonal antibody that depletes B-cell lymphocytes, appears to be effective in prolonging remission in steroid-dependent or calcineurin inhibitor-dependent patients [106-113]. Results from observational studies also noted that the administration of rituximab allowed for discontinuation or decrease in the dose of one or more immunosuppressive agents [109,110,114,115]. However, a significant proportion of patients relapse after rituximab administration with the recovery of B-cell lymphocytes [116]. However, because of the risk of severe and potentially life-threatening complications, rituximab use should be restricted to children with frequent relapses and serious adverse effects from their medication(s), as the long-term efficacy and safety of rituximab in this group of patients remain unclear [117-119].

Several small trials, many of them open-label studies, have reported that administration of rituximab alone or with corticosteroid was associated with a longer duration of remission [113,114,120-123]. The best evidence regarding the efficacy of rituximab is provided by a clinical trial involving 48 children with either frequently relapsing or steroid-dependent NS who were randomly assigned to receive either a weekly dose of rituximab (375 mg/m^2) or placebo for four weeks while they were in remission [113]. These patients had severe disease with a mean accumulated prednisolone dose of 18 to 19 mg/m^2 during the year entering the study and two-thirds were treated with cyclosporine. Patients initially received standard steroid therapy and stopped taking immunosuppressive agents 169 days after randomization. At one-year follow-up, median relapse-free duration (primary endpoint) was longer in the rituximab group compared with controls (267 versus 101 days). The relapse rate was lower in the rituximab group (1.54 versus 4.17 relapses per person-year), as was the daily prednisolone dose (8.4 versus 21 mg/m^2). However, by one year, relapse had occurred in 17 of 24 patients who received rituximab and 23 of 24 who received placebo (71 versus 96 percent), and by 19 months, all patients had relapsed. No deaths occurred. In a report that included follow-up of this cohort, 48 of 51 patients subsequently relapsed during the observation period (median 59 months) following initial rituximab therapy, and 44 of these patients received or continued immunosuppressive therapy including additional doses of rituximab in 22 patients [120].

The optimum dosing schedule for rituximab in children with steroid-dependent or frequently relapsing NS has not been established. Low versus high dose and the use of single versus multiple administrations remain areas of controversy [123-125].

Adverse effects — Although rituximab is well tolerated in most patients, it may be associated with adverse effects, including infusion-related reactions (hypotension, fever, skin rashes, diarrhea, and bronchospasm). In patients with severe allergic reactions, ofatumumab, a humanized anti-CD20 monoclonal antibody, may be a therapeutic option [126]. Patients may develop serious infections secondary to leukopenia and/or hypogammaglobulinemia [127,128]. Several cases of progressive multifocal leukoencephalopathy caused by JC polyomavirus have been reported in patients with hematological disorders or lupus treated with rituximab [129]. In addition, one published case study reported death due to lung fibrosis [130] and another reported severe myocarditis requiring heart transplantation [127] in two children with NS treated with rituximab. Other adverse effects occurring in association with rituximab reported in childhood NS include *Pneumocystis carnii* pneumonia and severe immune-mediated ulcerative gastrointestinal disease. There has also been report of two patients who developed anti-rituximab antibodies [131].

Choice of agent: Our approach — In children with SSNS and evidence of steroid toxicity, the optimal steroid-sparing agent should maintain long-term remission in the majority of patients allowing for a reduction in steroid dosing and toxicity, and have no significant side effects. However, there is no clear evidence that any of the currently used immunosuppressive agents provide long-term efficacy without significant side effects.

As noted above, in our practice, we recommend the use of levamisole, if it is available. If this is not the case, MMF is our preferred drug for patients with significant steroid toxicity. Although data are limited, MMF appears to have similar efficacy to other nonsteroidal immunosuppressive agents, but with less toxicity. In patients who fail to maintain remission after treatment with levamisole and MMF, we switch to cyclosporine.

Although cyclosporine is effective in inducing or maintaining remission in patients with frequently relapsing or steroid-dependent NS, sustained remission requires prolonged treatment and increases the risk of nephrotoxicity. As a result, in our practice, cyclosporine is used in patients who fail to maintain remission after a course of MMF or cyclophosphamide without a significant steroid dose. Based on the available data, we reserve rituximab only as a last resort.

Late steroid resistance — In a small subset of cases, patients who were initially steroid-sensitive become steroid-resistant [132-134]. Although data are limited, case reports suggest that complete or partial remission can be achieved in the majority of patients using other immunosuppressive therapeutic agents [132,133]. However, these patients are at risk for renal function impairment and developing end-stage renal disease (ESRD).

This was illustrated in a multicenter retrospective review of 29 patients with late steroid resistance [132]. In this cohort, medications used to treat NS included MMF (n = 18), cyclosporine (n = 15), tacrolimus (n = 13), an alkylating agent (n =

9), and rituximab (n = 4). Two-thirds of the patients received more than one of these agents. Patients also received steroid therapy for more than half of their total treatment time. At a mean follow-up time of 85 months, complete remission was achieved in 14 patients and partial remission in six patients. Six patients continued to have nephrotic range proteinuria and three developed ESRD. Over the study period, there were no deaths, but there were 13 episodes of serious adverse events including infections (encephalitis, bacteremia, and peritonitis), rhabdomyolysis, renal injury, and seizures. In this study with a limited number of patients, no risk factors were identified to predict response failure or ESRD.

Based on the available evidence, we suggest that nonsteroidal therapy be offered in patients who develop late steroid resistance. In our center, we use calcineurin inhibitors.

Long-term outcome of SSNS — Limited data on adult long-term outcome of patients who were children with SSNS suggest that patients who had frequent relapses or steroid dependent NS during childhood are at risk for relapses during adulthood and for drug adverse effects [44,135-137]. Renal function remains normal in adulthood [135,136] and long-term sequelae are generally related to side effects of medications.

STEROID-RESISTANT NEPHROTIC SYNDROME

Some children fail to respond to initial steroid treatment. Evaluation to determine the underlying etiology, including a renal biopsy and screening for genetic disorders, should be performed in this setting as therapeutic decisions are based on the underlying cause.

The causes and management of steroid-resistant nephrotic syndrome (SRNS) in children are discussed separately. (See "Steroid-resistant idiopathic nephrotic syndrome in children: Etiology".)

COMPLICATIONS

Complications in children with NS include:

- Infection including peritonitis
- Thromboembolism
- Renal insufficiency
- Anasarca
- Hypovolemia
- Impaired growth

These complications, including their management, are discussed in detail separately. (See "Complications of nephrotic syndrome in children".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Nephrotic syndrome in children".)

SUMMARY AND RECOMMENDATIONS

- In children with nephrotic syndrome (NS) who have a high probability of having minimal change disease (MCD) based on clinical and laboratory findings, we recommend empiric therapy with oral prednisone, thus avoiding renal biopsy (**Grade 1B**).
  We start with oral prednisone at a dose of 60 mg/m^2 per day (maximum of 60 mg/day). When proteinuria disappears, prednisone is continued at the same daily dose for 30 days, followed by alternate-day therapy (at the same dose). Alternate-day therapy is tapered over a one- to two-month period. (See 'Initial pharmacologic therapy' above.)
- Most children with idiopathic NS will respond to steroid therapy. After six months of initial steroid therapy, approximately 40 percent of children with steroid-responsive NS will not relapse, 10 to 20 percent will have less than four relapses, and the remaining will have frequent relapses and/or relapse while on steroid therapy (steroid-dependent). (See 'Steroid response' above.)
- Approximately 90 percent of responding patients attain complete remission within the first four weeks of steroid therapy, and the remaining 10 percent respond after an additional two to four weeks of steroid therapy. (See 'Time to response' above.)
- Children with steroid-responsive NS, who are frequent relapsers and/or are steroid-dependent, often develop evidence of steroid toxicity. In these patients, we recommend treatment with a nonsteroidal agent to maintain remission while reducing steroid dosing and toxicity (**Grade 1B**). (See 'Nonsteroidal therapy' above.)
  - In our practice, our initial steroid-sparing agent of choice is levamisole, if it is available. If this is not the case, mycophenolate mofetil (MMF) is our preferred drug for patients with significant steroid toxicity. (See 'Levamisole' above and 'Mycophenolate' above.)
  - Other experts in the field have suggested the use of a 12-week course of cyclophosphamide in patients with frequently relapsing NS. However, we suggest not to use this regimen in those with steroid-dependent NS, as the long-term remission rate is much lower and does not warrant the significant potential toxicity compared with other alternative medications (**Grade 2C**). (See 'Alkylating agents' above.)
  - Although cyclosporine is effective in inducing or maintaining remission in patients with frequently relapsing or steroid-dependent NS, sustained remission requires prolonged treatment and increases the

risk of nephrotoxicity. As a result, in our practice, cyclosporine is only used in patients who fail to maintain remission after a course of MMF or cyclophosphamide without a significant steroid dose. (See 'Calcineurin inhibitors' above.)

•Ten percent of children will fail to respond to steroid therapy. These children with steroid-resistant nephrotic syndrome (SRNS) are at increased risk for developing end-stage renal disease (ESRD). (See 'Outcome based upon response' above and "Steroid-resistant idiopathic nephrotic syndrome in children: Etiology".)

REFERENCES

1. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int 1978; 13:159.
2. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal Change Disease. Clin J Am Soc Nephrol 2017; 12:332.
3. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. J Pediatr 1981; 98:561.
4. Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome. Pediatrics 2009; 124:747.
5. Lombel RM, Gipson DS, Hodson EM, Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol 2013; 28:415.
6. Samuel S, Bitzan M, Zappitelli M, et al. Canadian Society of Nephrology Commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis: management of nephrotic syndrome in children. Am J Kidney Dis 2014; 63:354.
7. Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. J Am Soc Nephrol 1997; 8:769.
8. Saadeh SA, Baracco R, Jain A, et al. Weight or body surface area dosing of steroids in nephrotic syndrome: is there an outcome difference? Pediatr Nephrol 2011; 26:2167.
9. Tune BM, Mendoza SA. Treatment of the idiopathic nephrotic syndrome: regimens and outcomes in children and adults. J Am Soc Nephrol 1997; 8:824.
10. Dossier C, Delbet JD, Boyer O, et al. Five-year outcome of children with idiopathic nephrotic syndrome: the NEPHROVIR population-based cohort study. Pediatr Nephrol 2019; 34:671.
11. Vivarelli M, Moscaritolo E, Tsalkidis A, et al. Time for initial response to steroids is a major prognostic factor in idiopathic nephrotic syndrome. J Pediatr 2010; 156:965.
12. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev 2005; :CD001533.
13. Hahn D, Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev 2015; :CD001533.
14. Webb NJA, Woolley RL, Lambe T, et al. Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. BMJ 2019; 365:l1800.
15. Hodson EM, Hahn D, Craig JC. Corticosteroids for the initial episode of steroid-sensitive nephrotic syndrome. Pediatr Nephrol 2015; 30:1043.
16. Larkins N, Kim S, Craig J, Hodson E. Steroid-sensitive nephrotic syndrome: an evidence-based update of immunosuppressive treatment in children. Arch Dis Child 2016; 101:404.
17. Leisti S, Koskimies O. Risk of relapse in steroid-sensitive nephrotic syndrome: effect of stage of post-prednisone adrenocortical suppression. J Pediatr 1983; 103:553.
18. Leonard MB, Feldman HI, Shults J, et al. Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome. N Engl J Med 2004; 351:868.
19. Hoyer PF, Brodeh J. Initial treatment of idiopathic nephrotic syndrome in children: prednisone versus prednisone plus cyclosporine A: a prospective, randomized trial. J Am Soc Nephrol 2006; 17:1151.
20. MacHardy N, Miles PV, Massengill SF, et al. Management patterns of childhood-onset nephrotic syndrome. Pediatr Nephrol 2009; 24:2193.
21. Hogg RJ, Portman RJ, Milliner D, et al. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). Pediatrics 2000; 105:1242.
22. Sinha A, Saha A, Kumar M, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. Kidney Int 2015; 87:217.
23. Yoshikawa N, Nakanishi K, Sako M, et al. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. Kidney Int 2015; 87:225.
24. Murnaghan K, Vasmant D, Bensman A. Pulse methylprednisolone therapy in severe idiopathic childhood nephrotic syndrome. Acta Paediatr Scand 1984; 73:733.
25. Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev 2007; :CD001533.
26. Teeninga N, Kist-van Holthe JE, van den Akker EL, et al. Genetic and in vivo determinants of glucocorticoid sensitivity in relation to clinical outcome of childhood nephrotic syndrome. Kidney Int 2014; 85:1444.
27. Kemper MJ, Valentin L, van Husen M. Difficult-to-treat idiopathic nephrotic syndrome: established drugs, open questions and future options. Pediatr Nephrol 2018; 33:1641.

28. Broyer M, Meyrier A, Niaudet P, Habib R. Minimal changes and focal and segmental glomerular sclerosis. In: Oxford Textbook of Clinical Nephrology, Cameron JS, Davison MA, Grünfeld JP, et al (Eds), Oxford Medical Publications, 1992. p.298.
29. Early identification of frequent relapsers among children with minimal change nephrotic syndrome. A report of the International Study of Kidney Disease in Children. J Pediatr 1982; 101:514.
30. Yadav M, Sinha A, Khandelwal P, et al. Efficacy of low-dose daily versus alternate-day prednisolone in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial. Pediatr Nephrol 2019; 34:829.
31. Wang CS, Travers C, McCracken C, et al. Adrenocorticotropic Hormone for Childhood Nephrotic Syndrome: The ATLANTIS Randomized Trial. Clin J Am Soc Nephrol 2018; 13:1859.
32. Welch TR, Gianis J, Sheldon CA. Perforation of the scrotum complicating nephrotic syndrome. J Pediatr 1988; 113:336.
33. MacDonald NE, Wolfish N, McLaine P, et al. Role of respiratory viruses in exacerbations of primary nephrotic syndrome. J Pediatr 1986; 108:378.
34. Abeyagunawardena AS, Trompeter RS. Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomised controlled trial. Arch Dis Child 2008; 93:226.
35. Mattoo TK, Mahmoud MA. Increased maintenance corticosteroids during upper respiratory infection decrease the risk of relapse in nephrotic syndrome. Nephron 2000; 85:343.
36. Gulati A, Sinha A, Sreenivas V, et al. Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol 2011; 6:63.
37. Abeyagunawardena AS, Thalgahagoda RS, Dissanayake PV, et al. Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome. Pediatr Nephrol 2017; 32:1377.
38. Hyams JS, Carey DE. Corticosteroids and growth. J Pediatr 1988; 113:249.
39. Polito C, Oporto MR, Totino SF, et al. Normal growth of nephrotic children during long-term alternate-day prednisone therapy. Acta Paediatr Scand 1986; 75:245.
40. FLEISHER DS, McCRORY WW, RAPOPORT M. The effects of intermittent doses of adrenocortical steroids on the statural growth of nephrotic children. J Pediatr 1960; 57:192.
41. Simmonds J, Grundy N, Trompeter R, Tullus K. Long-term steroid treatment and growth: a study in steroid-dependent nephrotic syndrome. Arch Dis Child 2010; 95:146.
42. Brocklebank JT, Harcourt RB, Meadow SR. Corticosteroid-induced cataracts in idiopathic nephrotic syndrome. Arch Dis Child 1982; 57:30.
43. Ng JS, Wong W, Law RW, et al. Ocular complications of paediatric patients with nephrotic syndrome. Clin Exp Ophthalmol 2001; 29:239.
44. Fakhouri F, Bocquet N, Taupin P, et al. Steroid-sensitive nephrotic syndrome: from childhood to adulthood. Am J Kidney Dis 2003; 41:550.
45. Abeyagunawardena AS, Hindmarsh P, Trompeter RS. Adrenocortical suppression increases the risk of relapse in nephrotic syndrome. Arch Dis Child 2007; 92:585.
46. Wang W, Xia Y, Mao J, et al. Treatment of tacrolimus or cyclosporine A in children with idiopathic nephrotic syndrome. Pediatr Nephrol 2012; 27:2073.
47. Cameron JS, Chantler C, Ogg CS, White RH. Long-term stability of remission in nephrotic syndrome after treatment with cyclophosphamide. Br Med J 1974; 4:7.
48. Chiu J, Drummond KN. Long-term follow-up of cyclophosphamide therapy in frequent relapsing minimal lesion nephrotic syndrome. J Pediatr 1974; 84:825.
49. McDonald J, Murphy AV, Arneil GC. Long-term assessment of cyclophosphamide therapy for nephrosis in children. Lancet 1974; 2:980.
50. Pravitsitthikul N, Willis NS, Hodson EM, Craig JC. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Database Syst Rev 2013; :CD002290.
51. Vester U, Kranz B, Zimmermann S, Hoyer PF. Cyclophosphamide in steroid-sensitive nephrotic syndrome: outcome and outlook. Pediatr Nephrol 2003; 18:661.
52. Azib S, Macher MA, Kwon T, et al. Cyclophosphamide in steroid-dependent nephrotic syndrome. Pediatr Nephrol 2011; 26:927.
53. Cammas B, Harambat J, Bertholet-Thomas A, et al. Long-term effects of cyclophosphamide therapy in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. Nephrol Dial Transplant 2011; 26:178.
54. Arbeitsgemeinschaft für Pädiatrische Nephrologie. Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. N Engl J Med 1982; 306:451.
55. Kyrieleis HA, Levtchenko EN, Wetzels JF. Long-term outcome after cyclophosphamide treatment in children with steroid-dependent and frequently relapsing minimal change nephrotic syndrome. Am J Kidney Dis 2007; 49:592.
56. Zagury A, de Oliveira AL, de Moraes CA, et al. Long-term follow-up after cyclophosphamide therapy in steroid-dependent nephrotic syndrome. Pediatr Nephrol 2011; 26:915.
57. Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of eight week with 12 week course. Report of Arbeitsgemeinschaft für Pädiatrische Nephrologie. Arch Dis Child 1987; 62:1102.
58. Ueda N, Kuno K, Ito S. Eight and 12 week courses of cyclophosphamide in nephrotic syndrome. Arch Dis Child 1990; 65:1147.
59. Donia AF, Gazareen SH, Ahmed HA, et al. Pulse cyclophosphamide inadequately suppresses reoccurrence of minimal change nephrotic syndrome in corticoid-dependent children. Nephrol Dial Transplant 2003; 18:2054.
60. Trompeter RS. Immunosuppressive therapy in the nephrotic syndrome in children. Pediatr Nephrol 1989; 3:194.
61. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol 2001; 16:271.
62. Guesry P, Lenoir G, Broyer M. Gonadal effects of chlorambucil given to prepubertal and pubertal boys for nephrotic syndrome. J Pediatr 1978; 92:299.
63. Watson AR, Rance CP, Bain J. Long term effects of cyclophosphamide on testicular function. Br Med J (Clin Res Ed) 1985; 291:1457.
64. Müller W, Brandis M. Acute leukemia after cytotoxic treatment for nonmalignant disease in childhood. A case report and review of the literature. Eur J Pediatr 1981; 136:105.

65. Williams SA, Makker SP, Grupe WE. Seizures: a significant side effect of chlorambucil therapy in children. J Pediatr 1978; 93:516.
66. Mongeau JG, Robitaille PO, Roy F. Clinical efficacy of levamisole in the treatment of primary nephrosis in children. Pediatr Nephrol 1988; 2:398.
67. Alsaran K, Grisaru S, Stephens D, Arbus G. Levamisole vs. cyclophosphamide for frequently-relapsing steroid-dependent nephrotic syndrome. Clin Nephrol 2001; 56:289.
68. Barletta GM, Smoyer WE, Bunchman TE, et al. Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome. Pediatr Nephrol 2003; 18:833.
69. Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. British Association for Paediatric Nephrology. Lancet 1991; 337:1555.
70. Boyer O, Moulder JK, Grandin L, Somers MJ. Short- and long-term efficacy of levamisole as adjunctive therapy in childhood nephrotic syndrome. Pediatr Nephrol 2008; 23:575.
71. Sümegi V, Haszon I, Iványi B, et al. Long-term effects of levamisole treatment in childhood nephrotic syndrome. Pediatr Nephrol 2004; 19:1354.
72. Elmas AT, Tabel Y, Elmas ON. Short- and long-term efficacy of levamisole in children with steroid-sensitive nephrotic syndrome. Int Urol Nephrol 2013; 45:1047.
73. Gruppen MP, Bouts AH, Jansen-van der Weide MC, et al. A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome. Kidney Int 2018; 93:510.
74. Sinha A, Puraswani M, Kalaivani M, et al. Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial. Kidney Int 2019; 95:210.
75. Vivarelli M, Emma F. Levamisole for children with nephrotic syndrome: new evidence for the use of an "old" drug. Kidney Int 2019; 95:25.
76. Abeyagunawardena AS, Karunadasa U, Jayaweera H, et al. Efficacy of higher-dose levamisole in maintaining remission in steroid-dependant nephrotic syndrome. Pediatr Nephrol 2017; 32:1363.
77. Davin JC, Merkus MP. Levamisole in steroid-sensitive nephrotic syndrome of childhood: the lost paradise? Pediatr Nephrol 2005; 20:10.
78. Niaudet P, Habib R. Cyclosporine in the treatment of idiopathic nephrosis. J Am Soc Nephrol 1994; 5:1049.
79. Niaudet P, Broyer M, Habib R. Treatment of idiopathic nephrotic syndrome with cyclosporin A in children. Clin Nephrol 1991; 35 Suppl 1:S31.
80. Tejani AT, Butt K, Trachtman H, et al. Cyclosporine A induced remission of relapsing nephrotic syndrome in children. Kidney Int 1988; 33:729.
81. Kano K, Kyo K, Yamada Y, et al. Comparison between pre- and posttreatment clinical and renal biopsies in children receiving low dose ciclosporine-A for 2 years for steroid-dependent nephrotic syndrome. Clin Nephrol 1999; 52:19.
82. Mahmoud I, Basuni F, Sabry A, et al. Single-centre experience with cyclosporin in 106 children with idiopathic focal segmental glomerulosclerosis. Nephrol Dial Transplant 2005; 20:735.
83. Habib R, Niaudet P. Comparison between pre- and posttreatment renal biopsies in children receiving ciclosporine for idiopathic nephrosis. Clin Nephrol 1994; 42:141.
84. Ishikura K, Ikeda M, Hattori S, et al. Effective and safe treatment with cyclosporine in nephrotic children: a prospective, randomized multicenter trial. Kidney Int 2008; 73:1167.
85. Kengne-Wafo S, Massella L, Diomedi-Camassei F, et al. Risk factors for cyclosporin A nephrotoxicity in children with steroid-dependant nephrotic syndrome. Clin J Am Soc Nephrol 2009; 4:1409.
86. Ishikura K, Yoshikawa N, Nakazato H, et al. Two-year follow-up of a prospective clinical trial of cyclosporine for frequently relapsing nephrotic syndrome in children. Clin J Am Soc Nephrol 2012; 7:1576.
87. Ishikura K, Yoshikawa N, Nakazato H, et al. Morbidity in children with frequently relapsing nephrosis: 10-year follow-up of a randomized controlled trial. Pediatr Nephrol 2015; 30:459.
88. Hamasaki Y, Komaki F, Ishikura K, et al. Nephrotoxicity in children with frequently relapsing nephrotic syndrome receiving long-term cyclosporine treatment. Pediatr Nephrol 2017; 32:1383.
89. Dötsch J, Dittrich K, Plank C, Rascher W. Is tacrolimus for childhood steroid-dependent nephrotic syndrome better than ciclosporin A? Nephrol Dial Transplant 2006; 21:1761.
90. Sinha MD, MacLeod R, Rigby E, Clark AG. Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. Nephrol Dial Transplant 2006; 21:1848.
91. Bagga A, Hari P, Moudgil A, Jordan SC. Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. Am J Kidney Dis 2003; 42:1114.
92. Novak I, Frank R, Vento S, et al. Efficacy of mycophenolate mofetil in pediatric patients with steroid-dependent nephrotic syndrome. Pediatr Nephrol 2005; 20:1265.
93. Hogg RJ, Fitzgibbons L, Bruick J, et al. Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: a report from the Southwest Pediatric Nephrology Study Group. Clin J Am Soc Nephrol 2006; 1:1173.
94. Fujinaga S, Ohtomo Y, Umino D, et al. A prospective study on the use of mycophenolate mofetil in children with cyclosporine-dependent nephrotic syndrome. Pediatr Nephrol 2007; 22:71.
95. Afzal K, Bagga A, Menon S, et al. Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. Pediatr Nephrol 2007; 22:2059.
96. Banerjee S, Pahari A, Sengupta J, Patnaik SK. Outcome of severe steroid-dependent nephrotic syndrome treated with mycophenolate mofetil. Pediatr Nephrol 2013; 28:93.
97. Dehoux L, Hogan J, Dossier C, et al. Mycophenolate mofetil in steroid-dependent idiopathic nephrotic syndrome. Pediatr Nephrol 2016; 31:2095.
98. Perez-Aytes A, Ledo A, Boso V, et al. In utero exposure to mycophenolate mofetil: a characteristic phenotype? Am J Med Genet A 2008; 146A:1.
99. Dorresteijn EM, Kist-van Holthe JE, Levtchenko EN, et al. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. Pediatr Nephrol 2008; 23:2013.
100. Gellermann J, Weber L, Pape L, et al. Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. J Am Soc Nephrol 2013; 24:1689.

101. Querfeld U, Weber LT. Mycophenolate mofetil for sustained remission in nephrotic syndrome. Pediatr Nephrol 2018; 33:2253.
102. Gellermann J, Ehrich JH, Querfeld U. Sequential maintenance therapy with cyclosporin A and mycophenolate mofetil for sustained remission of childhood steroid-resistant nephrotic syndrome. Nephrol Dial Transplant 2012; 27:1970.
103. Sobiak J, Resztak M, Ostalska-Nowicka D, et al. Monitoring of mycophenolate mofetil metabolites in children with nephrotic syndrome and the proposed novel target values of pharmacokinetic parameters. Eur J Pharm Sci 2015; 77:189.
104. Tong K, Mao J, Fu H, et al. The Value of Monitoring the Serum Concentration of Mycophenolate Mofetil in Children with Steroid-Dependent/Frequent Relapsing Nephrotic Syndrome. Nephron 2016; 132:327.
105. Hackl Á, Cseprekál O, Gessner M, et al. Mycophenolate Mofetil Therapy in Children With Idiopathic Nephrotic Syndrome: Does Therapeutic Drug Monitoring Make a Difference? Ther Drug Monit 2016; 38:274.
106. Guigonis V, Dallocchio A, Baudouin V, et al. Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. Pediatr Nephrol 2008; 23:1269.
107. Fujinaga S, Hirano D, Nishizaki N, et al. Single infusion of rituximab for persistent steroid-dependent minimal-change nephrotic syndrome after long-term cyclosporine. Pediatr Nephrol 2010; 25:539.
108. Sellier-Leclerc AL, Macher MA, Loirat C, et al. Rituximab efficiency in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol 2010; 25:1109.
109. Ravani P, Magnasco A, Edefonti A, et al. Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol 2011; 6:1308.
110. Ravani P, Ponticelli A, Siciliano C, et al. Rituximab is a safe and effective long-term treatment for children with steroid and calcineurin inhibitor-dependent idiopathic nephrotic syndrome. Kidney Int 2013; 84:1025.
111. Sinha A, Bhatia D, Gulati A, et al. Efficacy and safety of rituximab in children with difficult-to-treat nephrotic syndrome. Nephrol Dial Transplant 2015; 30:96.
112. Webb H, Jaureguiberry G, Dufek S, et al. Cyclophosphamide and rituximab in frequently relapsing/steroid-dependent nephrotic syndrome. Pediatr Nephrol 2016; 31:589.
113. Iijima K, Sako M, Nozu K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2014; 384:1273.
114. Ravani P, Rossi R, Bonanni A, et al. Rituximab in Children with Steroid-Dependent Nephrotic Syndrome: A Multicenter, Open-Label, Noninferiority, Randomized Controlled Trial. J Am Soc Nephrol 2015; 26:2259.
115. Kamei K, Ogura M, Sato M, et al. Risk factors for relapse and long-term outcome in steroid-dependent nephrotic syndrome treated with rituximab. Pediatr Nephrol 2016; 31:89.
116. Kamei K, Ito S, Nozu K, et al. Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children. Pediatr Nephrol 2009; 24:1321.
117. Haffner D, Fischer DC. Nephrotic syndrome and rituximab: facts and perspectives. Pediatr Nephrol 2009; 24:1433.
118. Boyer O, Niaudet P. Nephrotic syndrome: Rituximab in childhood steroid-dependent nephrotic syndrome. Nat Rev Nephrol 2013; 9:562.
119. Hodson EM, Craig JC. Rituximab for childhood-onset nephrotic syndrome. Lancet 2014.
120. Kamei K, Ishikura K, Sako M, et al. Long-term outcome of childhood-onset complicated nephrotic syndrome after a multicenter, double-blind, randomized, placebo-controlled trial of rituximab. Pediatr Nephrol 2017; 32:2071.
121. Basu B, Sander A, Roy B, et al. Efficacy of Rituximab vs Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome: A Randomized Clinical Trial. JAMA Pediatr 2018; 172:757.
122. Ahn YH, Kim SH, Han KH, et al. Efficacy and safety of rituximab in childhood-onset, difficult-to-treat nephrotic syndrome: A multicenter open-label trial in Korea. Medicine (Baltimore) 2018; 97:e13157.
123. Maxted AP, Dalrymple RA, Chisholm D, et al. Low-dose rituximab is no less effective for nephrotic syndrome measured by 12-month outcome. Pediatr Nephrol 2019; 34:855.
124. Hogan J, Dossier C, Kwon T, et al. Effect of different rituximab regimens on B cell depletion and time to relapse in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol 2019; 34:253.
125. Kallash M, Smoyer WE, Mahan JD. Rituximab Use in the Management of Childhood Nephrotic Syndrome. Front Pediatr 2019; 7:178.
126. Vivarelli M, Colucci M, Bonanni A, et al. Ofatumumab in two pediatric nephrotic syndrome patients allergic to rituximab. Pediatr Nephrol 2017; 32:181.
127. Sellier-Leclerc AL, Belli E, Guérin V, et al. Fulminant viral myocarditis after rituximab therapy in pediatric nephrotic syndrome. Pediatr Nephrol 2013; 28:1875.
128. Kamei K, Takahashi M, Fuyama M, et al. Rituximab-associated agranulocytosis in children with refractory idiopathic nephrotic syndrome: case series and review of literature. Nephrol Dial Transplant 2015; 30:91.
129. Pradhan M, Furth S. Rituximab in steroid-resistant nephrotic syndrome in children: a (false) glimmer of hope? J Am Soc Nephrol 2012; 23:975.
130. Chaumais MC, Garnier A, Chalard F, et al. Fatal pulmonary fibrosis after rituximab administration. Pediatr Nephrol 2009; 24:1753.
131. Ahn YH, Kang HG, Lee JM, et al. Development of antirituximab antibodies in children with nephrotic syndrome. Pediatr Nephrol 2014; 29:1461.
132. Straatmann C, Ayoob R, Gbadegesin R, et al. Treatment outcome of late steroid-resistant nephrotic syndrome: a study by the Midwest Pediatric Nephrology Consortium. Pediatr Nephrol 2013; 28:1235.
133. Srivastava RN, Agarwal RK, Moudgil A, Bhuyan UN. Late resistance to corticosteroids in nephrotic syndrome. J Pediatr 1986; 108:66.
134. Kim JS, Bellew CA, Silverstein DM, et al. High incidence of initial and late steroid resistance in childhood nephrotic syndrome. Kidney Int 2005; 68:1275.
135. Rüth EM, Kemper MJ, Leumann EP, et al. Children with steroid-sensitive nephrotic syndrome come of age: long-term outcome. J Pediatr 2005; 147:202.
136. Kyrieleis HA, Löwik MM, Pronk I, et al. Long-term outcome of biopsy-proven, frequently relapsing minimal-change nephrotic syndrome in children. Clin J Am Soc Nephrol 2009; 4:1593.

137. Korsgaard T, Andersen RF, Joshi S, et al. Childhood onset steroid-sensitive nephrotic syndrome continues into adulthood. Pediatr Nephrol 2019; 34:641.

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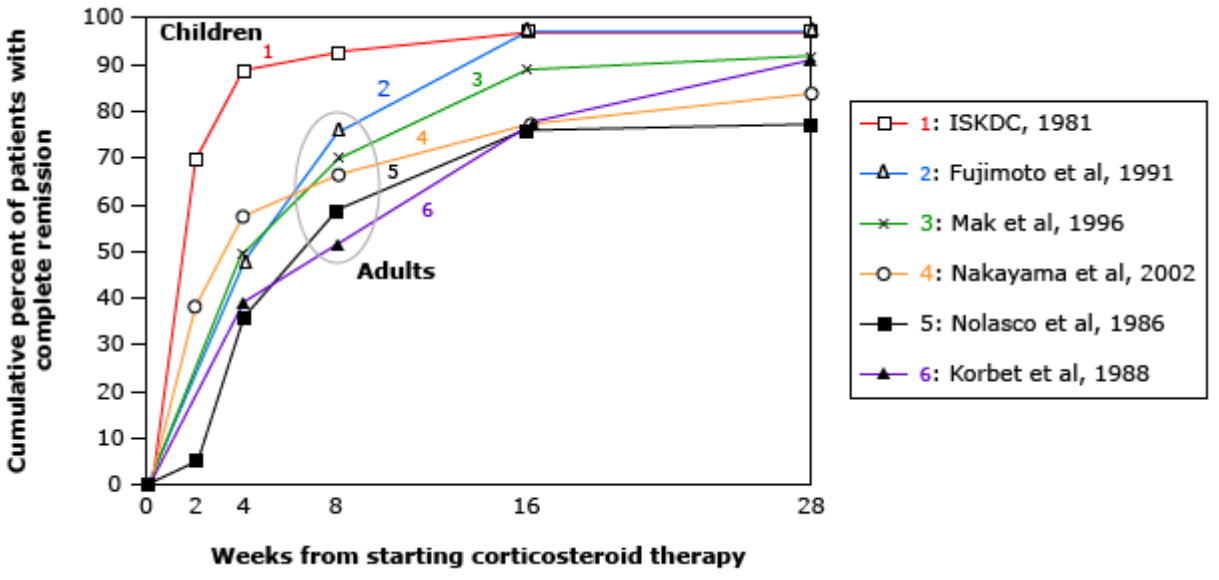
GRAPHICS

Cumulative rate of remission in response to steroids in MCD



The rate of response of minimal change disease (MCD) to corticosteroid therapy is lower in adults compared with children, and more prolonged therapy is required to achieve a remission.

ISKDC: International Study of Kidney Disease in Children.

Adapted with permission from: Nakayama M, Katafuchi R, Yanase T, et al. Steroid responsiveness and frequency of relapse in adult-onset minimal change nephrotic syndrome. Am J Kidney Dis 2002; 39:503.

Graphic 58623 Version 5.0

Contributor Disclosures

Patrick Niaudet, MD Nothing to disclose**Tej K Mattoo, MD, DCH, FRCP**Consultant/Advisory Boards: Kite Medical Limited [Vesicoureteral reflux (Bioimpedance)].**Melanie S Kim, MD**Nothing to disclose

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