Kidney International, Vol. 55, Suppl. 70 (1999), pp. S-3–S-16

Management of minimal lesion glomerulonephritis: Evidence-based recommendations

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Management of minimal lesion glomerulonephritis: Evidence-based recommendations. The treatment of idiopathic minimal lesion disease in children has been extensively studied in randomized controlled trials, however, there is less information available for adults. This article summarizes evidence-based recommendations for management. The first attack should be treated with prednisone or prednisolone at 60 mg/m^2 per day (up to a maximum of 80 mg/day) for four to six weeks, followed by 40 mg/m^2 of prednisone every other day for another four to six weeks (grade A). Relapse should be treated with 60 mg/m^2/day of prednisone (up to 80 mg/day) only until the urine becomes protein free for three days, and then an alternate day regimen of 40 mg/m^2 should be used for another month (grade A). Patients with frequently relapsing disease will have a significant reduction in relapse frequency after eight weeks of an alkylating agent (grade A). Less rigorous studies have suggested benefit with long-term, alternate-day corticosteroid (grade D) or the antihelminthic agent levamisole (grade D). For patients with steroid-dependent disease, an 8- or 12-week course with cyclophosphamide can induce remission (grade D). In true steroid-resistant disease, observational studies have suggested that a course of cyclosporine may sometimes induce remission or restore steroid responsiveness (grade D). Large retrospective studies in adults suggest that therapeutic response is slower than in children, but adults experience fewer relapses and more prolonged remission.

Minimal lesion glomerulonephritis typically presents with the acute onset of nephrotic syndrome, often following a viral upper respiratory tract infection. Complications include thrombosis, acute renal failure, and infections such as cellulitis, peritonitis, and pneumonia [1]. Older literature suggests that spontaneous remissions occur in children with minimal lesion disease, usually after many months of disease compared with a much earlier remission time induced with corticosteroids [2–4].

Histology demonstrates essentially normal-appearing glomeruli on light microscopy, although there may be some expansion of the mesangial matrix. Immunofluorescence is usually negative for immunoglobulins. Some investigators include staining with IgM, and there may be a spectrum of disease between minimal lesion and IgM mesangial proliferative glomerulonephritis. Indeed, this is a potential cause of confusion because some studies allow mesangial proliferation and/or staining with IgM as a variant of minimal lesion, whereas others do not. Although deposition of IgM does not appear to change prognosis, mesangial hypercellularity is associated with late nonresponse [5]. Others have not found an association between histology and postbiopsy course [6].

Key words: prednisone, prednisolone, nephrotic syndrome, acute renal failure, corticosteroids.

Methods

The evidence used in compiling these recommendations was obtained from published trials found in a MEDLINE search of the English language literature. Secondary references from the bibliography of the initial studies were also perused, as were personal files. Recommendations were graded from A to D, based on the level of evidence of the supporting studies.

TREATMENT OF MINIMAL LESION GLOMERULONEPHRITIS IN CHILDREN

Tables 1, 2, and 3 review the levels of evidence of English language studies in children.

Treatment of the first attack

Recommendation 1. Prednisone at 60 mg/m^2 per day (up to a maximum of 80 mg/day) for four to six weeks (grade A) and then 40 mg/m^2 of prednisone every other day for four to six weeks (grade A) are recommended.

Evidence. Minimal lesion accounts for more than 90% of cases of idiopathic nephrotic syndrome in young children. Uncontrolled studies in the 1950s demonstrated that more than 90% of children would respond to corticosteroid treatment. The pioneering studies of the International Study of Kidney Diseases in Children (ISKDC) settled on a regimen of 60 mg/m^2/day prednisone, to a maximum of 80 mg/day for four weeks, followed by intermittent prednisone (40 mg/m^2/day) on three consecutive days out of seven days for the next four weeks [7].

Table 1. Corticosteroids in children, level 1 or 2

Author [Ref]	Study design	*N*	Treatment	Results/comments
APN [8]	RCT frequent relapsers in remission to Pred for 3/7 days or alt days	25 intermittent	Remission induced with daily Pred, then Pred 40 mg/m^2 for 3/7 days or 35 mg/m^{2}q alt day; 6 months total	72% relapse in first 6 months (intermittent)
		24 alt day		43% relapse in first 6 months (alt day) Relapse rate similar after that
ISKDC [14]	Children with early relapse randomized to shorter vs. longer Pred regimens	26 shorter	Shorter: 60 mg Pred until CR (avg 12 days) then 40 mg 3/7 days × 4 weeks	Shorter: 40% relapsed during treatment protocol
		28 longer	Longer: 60 mg Pred/day × 4 weeks then 40 mg/day × 1 week, 30 mg/day × 1 week, etc.	Longer: 8% relapsed during treatment protocol All patients relapsed by 8 months Longer group had 2 × Pred
APN [11]	Children with first attack randomized to shorter vs. longer courses of Pred	32 shorter	Shorter: Pred 60 mg/m^2 until CR × 3 day, then 40 mg/m^2 q 48 hr until serum alb ≥35 g/liter	Shorter course used 50% less Pred but twice the relapse rate, half the relapse free interval
		29 longer	Longer: Pred 60 mg/m^2/day × 4 weeks then 40 mg/m^2 q 48 hr × 4 weeks	Total Pred including relapse rx similar – no advantage to shorter regimen
Ueda [13]	Children with first attack randomized to shorter vs. longer courses of Pred	29 shorter	Shorter: Pred 60 mg/m^2/day × 4 weeks, then 40 mg/m^2/day 3/7 days × 4 weeks	Longer regimen had less relapses while on treatment, so total amount of Pred did not differ between 2 groups
		17 longer	Longer: Pred 60 mg/m^2/day × 4 weeks, then 60 mg/m^2/alt day × 4 weeks, then tapered over 5 months	Longer regimen had fewer patients who became steroid dependent or frequent relapsers
Ehrich [12]	Children with first attack randomized to shorter vs. longer courses of Pred	37 shorter	Shorter: 60 mg/day × 4 weeks then 40/mg/m^2 q 48 hr × 4 weeks	Longer treatment patients more likely to remain in remission, less frequent relapsers in longer treatment group Total Pred dose at one year similar in both groups
		34 longer	Longer: 60 mg/m^2/day × 6 weeks, then 40 mg/m^2 q 48 hr × 6 weeks	

Abbreviations are: alt, alternate; APN, Arbeitsgemeinschaft fur Padiatrische Nephrologie; ARF, acute renal failure; AZA, azathioprine; Chloram, chlorambucil; CR, complete remission; CTX, cyclophosphamide; CsA, cyclosporine; F/U, follow-up; ISKDC, International Study of Kidney Disease in Children; ML, minimal lesion; NS, nephrotic syndrome; PR, partial remission; Pred, prednisone or prednisolone; RCT, randomized controlled trial; stat sign, statistically significant; VAR, variable.

The European collaborative group, Arbeitsgemeinschaft fur Padiatrische Nephrologie (APN), suggested that in the second four weeks of treatment, prednisone given every second day might be more effective in preventing relapses. These two regimens were compared in a randomized controlled study in a group of 48 frequently relapsing patients [8]. Patients receiving alternate-day prednisone had an approximate 50% reduction in relapse rate compared with the controls receiving prednisone three days out of seven. This difference occurred during only the six months of the trial, whereas the later relapse rate was similar. The investigators concluded that the alternate-day regimen was superior for the second four weeks of therapy and have recommended it even for the first attack of minimal lesion disease [9].

Most patients will clear their proteinuria by two weeks of therapy [10]. Investigators have questioned whether a shorter course of initial treatment might be just as effective as the standard regimen. The APN performed a randomized controlled study of their standard regimen (four weeks of daily prednisone plus four weeks of alternate-day prednisone) compared with a short-course group who received 60 mg/m^2/day of prednisone until the urine was clear of protein (about two weeks) and then took alternate-day prednisone until the serum albumin normalized (another two weeks). Although the short-course group initially received only half of the amount of prednisone, they relapsed twice as often and twice as soon, and ultimately received as much steroid as the standard treatment group [11]. The authors concluded that there was no benefit to the shorter therapy.

Several years later, they examined whether longer initial therapy conferred added protection against relapse [12]. Here, children with a first attack were randomly

Table 2. Alkylating and antimetabolite agents in children

Author [Ref]	Study design	*N*	Treatment	Results/comments
Level 1 or 2				
Abramozicz [18]	RCT of 197 children rx Pred 8 weeks	38 nonresponders	Pred + AZA or placebo × 3 months	No difference AZA from placebo
		49 frequent relapsers	Pred + AZA or placebo × 6 months	Trend to less relapses in AZA group but not stat sig
Barratt [19]	RCT of Pred vs. Pred + CTX in frequently relapsing NS, in remission	10 Pred 10 Pred + CTX	Pred taper over 8 weeks "maintenance" Pred + CTX 3 mg/kg/day over 8 weeks then Pred taper over 8 weeks	9/10 relapsed by one year 2/10 relapsed by one year ($P<0.05$)
Barratt [20]	RCT of Pred and either 2 or 8 weeks of CTX in frequently relapsing NS, in remission	16 CTX 2 weeks	"Maintenance" Pred over 8 weeks, taper over 8 weeks + CTX 3 mg/kg/day × 2 weeks	9/16 relapsed by weeks 24
		16 CTX 8 weeks	Same except CTX × 8 weeks	1/16 relapsed by week 24 ($P<0.05$)
ISKDC [21]	RCT "early non-responders" (at 8 weeks of Pred) to intermittent Pred alone or with CTX	33 of which 15 Prd alone 18 Pred + CTX	Intermittent Pred ± CTX (var dose) × 90 days	(not all had ML) Pred alone: 40% CR by 95 days. Pred + CTX: 56% CR by 38 days
	RCT frequent relapsers intermittend Pred alone or with CTX	53 of which 26 Pred alone 27 Pred + CTX	Intermittent Pred ± CTX (var dose) × 42 days	Pred alone: 88% relapse by mean 22 months Pred ± CTX: 48% relapse
Grupe [23]	Steroid-dependent or frequently relapsing NS RCT Pred alone or Pred + chlorambucil	11 Pred alone		All chlorambucil patients went into CR for full F/U (mean 19.6 months) vs. all 11 on Pred had recurrent NS by 7 months
		10 Pred + chlorambucil	Chloram 0.1–0.2 mg/kg/day in divided doses, titrated to WBC × 6–12 weeks total	
APN [17]	Frequently relapsing or steroid-dependent RCT to Pred + chloramb or to Pred + CTX	2 × 2: 16 frequent relapsers 8 chloramb, 8 CTX	After remission, randomized to chloramb 0.15 mg/kg/day × 56 days along with alt day Pred or	CTX or chloram decreased relapse rate in frequent relapsers
		34 steroid dependent 16 chloram, 18 CTX	CTX 2 mg/kg/day × 56 days along with alt day Pred	No difference in time to relapse in steroid dependent group No difference CTX vs. chloramb (small#'s)
Ueda [26]	Steroid-dependent RCT to CTX for 8 or 12 weeks	32 CTX × 8 weeks	After remission, CTX 2 mg/kg/day × 8 weeks or CTX 2 mg/kg/day × 12 weeks	No difference 8 vs. 12 weeks rx (compare with APN 1987 below)
		41 CTX × 12 weeks		
Level 3 or 4				
Chiu [29]	Frequent relapsers rx Pred and CTX compared with historical controls	36 Pred + CTX	CTX 75 mg/m^2/day + Pred 60 mg/m^2/day then tapered; duration 4 months	33% relapse by mean 4 year F/U
	Pred alone	11 Pred alone	Hist controls: Pred same regimen × 4 months	91% relapse by mean 2 year F/U
Barratt [22]	Follow up 1973 study of frequent relapsers	82 CTX	CTX 3 mg/kg/day (most also received Pred) × 8 weeks	Remission lasted longer in older children; better outcome if in CR at onset of CTX rx
Pennisi [30]	Steroid-dependent NS treated with alt day Pred and 6–8 or 12 weeks CTX; retrospective analysis	29 6–8 week CTX	CTX 3–5 mg/kg/day × 6–8 weeks + alt day Pred	42% relapse rate at one year; 21% still in CR at 3.5 years
		24 12 week CTX	CTX 3–5 mg/kg/day × 12 weeks + alt day Pred	8% relapse rate at one year; 63% still in CR at 3.5 years

(*Continued*)

allocated to a long treatment consisting of daily prednisone for six weeks and alternate-day prednisone for six weeks, and the children were then compared with those undergoing the standard regimen. This level 1 study demonstrated that the long-treatment patients were twice as likely to remain in remission compared with the patients

Table 2. (Continued)

Author [Ref]	Study design	*N*	Treatment	Results/comments
Williams [24]	Nonrandom "low" and "high" dose chlorambucil for frequently-relapsing, steroid resistant NS	53	Daily Pred until remission; then alt day Pred and chlorambucil <3 mg/kg/day ("low") or >3.0 mg/kg/day ("high")	Low dose same outcome as high dose. 95% CT at 1 year 85% CR at 4 years. Steroid resistant patients went in CR for 1.3–9.4 years. Young age most important negative prognostic factor
APN [25]	Steroid dependent NS rx 12 weeks CTX compared retro to steroid dependent cohort (APN, 1982) rx 8 weeks CTX	18 12 weeks 18 8 weeks	Daily Pred until remission; then alt day Pred and CTX 2 mg/kg/day $\times$ 12 weeks (historical CTX 2 mg/kg/day $\times$ 8 weeks)	67% sustained remission in 12 week CTX; 22% sustained remission in 8 weeks CTX (12 week group older and received more Pred)
Level 5 or 6				
West [27]	Review of experience with CTX in NS	14	CTX 3–4 mg/kg/day with reduced doses of Pred	Long-term remissions in steroid dependent and frequently relapsing NS
Drummond [28]	Observational study	12	CTX 75 mg/m^2/day	Long therapy with CTX (up to 12 months) decreased relapse rate and associated with clearing of proteinuria in "steroid resistant" NS

Abbreviations are in Table 1.

receiving the standard regimen. Furthermore, fewer patients with the long initial therapy ultimately became frequent relapsers [12]. Even though the total amount of prednisone taken for the first attack was greater than in the standard regimen, steroid side-effects were no more severe. The benefit was that less steroids were subsequently taken because of the fewer relapses. A similar result was found by investigators in Japan in another level 1 study, in which children at first presentation were randomized to either the ISKDC protocol or a longer protocol involving a taper over five months. Again, the longer treatment group had fewer relapses, and fewer of the patients became frequent relapsers. Although the long-treatment group took more prednisone, the cumulative dose over the entire period of follow-up was not different [13].

The difficulty in determining the trade-off between a cumulative steroid dose versus a relapse-free internal is well illustrated in a randomized ISKDC study that examined a long versus shorter steroid regimen in children who had relapsed within six months of their initial response. In this study, the long-treatment group received approximately twice as much prednisone as the other group, but stayed in remission for a mean of 3.27 months compared with 1.48 months. In the end, it was not clear, even to many of the investigators, whether the extra steroid was worth the longer duration of remission [14].

A recent retrospective analysis of nearly 400 children with minimal lesion disease found that if the children responded to the first eight weeks of therapy with complete remission and maintained remission over the next six months, the long-term outlook was excellent with no further, or very rare, relapses. A relapse in the first six months was predictive of further relapses for the next three years. Perhaps not surprisingly, the failure to achieve remission in the first eight weeks of therapy predicted progression to renal failure in 21% of the children. The authors suggest that more aggressive therapy should be used to achieve remission in these children who are slow to respond; however, it is possible that the delayed or lack of response to standard therapy itself is a marker for more aggressive disease [15].

In summary, the intensity of initial therapy for minimal lesion disease appears to determine the rate of subsequent relapse and perhaps also the chances of becoming a frequent relapser. The optimization point of initial dose of prednisone with its cumulative toxicity, versus morbidity involved in relapse and its retreatment, appears to lie at an initial treatment with daily prednisone for four to six weeks and a course of alternate-day prednisone for four to six weeks. Alternatively, a tapering course can be given over several months.

Treatment of relapse

Recommendation 2. For patients with minimal lesion disease who relapse after initial treatment, prednisone should be given at 60 mg/m^2 per day (up to 80 mg/day) until the urine is protein free; then 40 mg/m^2 should be given every other day for four weeks (grade A).

Evidence. Most children will have a relapse of their nephrosis. The mean duration of corticosteroid therapy to clear the urinary protein is similar for the relapse as for the initial attack [11]. However, the intensity of

Table 3. Cyclosporine studies in children

Author [Ref]	Study design	*N*	Treatment	Results/comments
Level 1 or 2				
Garin [48]	Steroid-resistant NS Randomized crossover of CsA vs. no treatment	(ML) 4	CsA 5 mg/kg/day × 8 weeks or no treatment	No change in proteinuria with CsA; small #'s
Tejani [36]	NS (1st episode in 50%) randomized CsA + low dose Pred or high dose Pred alone	6 CsA + Pred	CsA 7 mg/kg/day × 4 weeks + 20 mg/m^2 Pred then lower doses × 4 weeks	6/6 remission—duration of remission same as Pred alone
		7 Pred alone	Pred 60 mg/m^2/day × 4weeks then alt day × 4 weeks	6/7 remission
Ponticelli [37]	RCT CsA vs. CTX for steroid-dependent and frequently relapsing NS	18 CsA	5–6 mg/kg/day × 9 months then tapered × 3 months	25% of CsA relapse free at 2 years; 63% of CTX relapse free at 2 years. Adults same as children
		13 CTX	1.5–2.5 mg/kg/day × 8 weeks	
Level 5 or 6				
Niaudet [35]	Multi-center uncontrolled study CsA in "steroid resistant" NS (Pred × 4 weeks + 3 pulses)	ML: 45	CsA 150 mg/m^2/day + Pred 30 mg/m^2/day × 4 weeks then alt day. Total rx 6 months	23/45 CR or PR in minimal lesion group (? inadequate initial Pred treatment—not really steroid resistant?)
Gregory [50]	Retrospective analysis CsA in steroid-dependent and steroid-resistant NS	ML: 3	CsA 5–10 mg/kg/day + volume expansion in same; alt day Pred	2/3 maintain remission on CsA alone; minimal toxicity with long-term CsA monotherapy
Kitano [33]	Frequent relapsers or steroid dependent rx CsA × 6 months	17	After remission, CsA 3–5 mg/kg/day × 6 months and then tapered	No relapses during CsA; all patients able to come off Pred; but 40% relapsed by 1 month after CsA D/C'ed, 16/17 relapsed by one year
Tanaka [34]	Frequent relapsers or steroid dependent rx "high dose" CsA × 6 months then "low dose" × 12 months	18	"High dose" CsA 3–5 mg/kg/day × 6 months, then 2.5 mg/kg/day × 12 months and then tapered. Also received Pred prn	All patients able to come off Pred; 8 growth, wt loss. Marked 9 relapse rate during CsA 7/18 relapse free × 18 months, 14/18 relapsed within 6 months of stopping CsA

Abbreviations are in Table 1.

prednisone treatment for a first relapse had no influence on the subsequent relapse rate [14, 16].

The current relapse regimen consists of 60 mg/m^2/day (up to 80 mg/day) of prednisone until the urine is free of protein for three days, followed by four weeks of alternate day prednisone at 40 mg/m^2 [9]. This regimen is associated with fewer relapses in the first six months of treatment, compared with administering prednisone three out of seven days in the second four weeks of therapy [8]. The ISKDC demonstrated that treating a relapse for four weeks with daily prednisone rather than just until the urine cleared of protein (average 12 days) was associated with a more prolonged remission (3.27 vs. 1.48 months) but at the cost of double the amount of prednisone [14]. Because all patients in both groups relapsed by eight months anyway, it is recommended to treat a relapse with daily prednisone only until the urine is protein free or for a few more days, and then proceed with the tapering regimen as described earlier in this article.

Treatment of frequently relapsing minimal lesion disease

Recommendation 3. Patients with minimal lesion disease who relapse frequently should be treated with one of these regimens: cyclophosphamide or chlorambucil for eight weeks (discussed in the text; grade A); repeat relapse therapy with prednisone (grade D); symptomatic treatment only (Na restriction, diuretics; grade D); long-term alternate-day prednisone (grade D); and/or levamisole (discussed in the text; grade B).

Treatment of steroid-dependent minimal lesion disease

Recommendation 4. Children with steroid-dependent minimal lesion disease should be treated with 2 mg/kg/day of cyclophosphamide for 12 weeks (grade D) or 6 mg/kg/day of cyclosporine for children and 5 mg/kg/day for adults, with the duration being uncertain (grade A).

Evidence. Ten to 20% of children will experience three or four steroid-sensitive attacks, and half will be-

come frequent relapsers or steroid dependent. Given the cumulative toxicity associated with long-term corticosteroid therapy, treatment has evolved to include alkylating agents, antimetabolites, and cyclosporine in these more difficult patient groups. A frequent relapser is a patient who responds to corticosteroid treatment but experiences two relapses within the first six months after the initial response or has four relapses within any one year [17]. Up to one quarter of relapses in frequent relapsing minimal lesion may remit spontaneously [2]. Steroid dependency is defined as two consecutive relapses occurring during therapy or within 14 days of completing steroid therapy [16]. Therapeutic options for frequent relapsers include repeated relapse treatment with corticosteroid, prolonged tapering of alternate-day or daily steroid, or symptomatic treatment with salt restriction and diuretics. Unfortunately, there are no good studies to compare outcomes of these regimens. The repeated or prolonged use of corticosteroids in either frequently relapsing or steroid-dependent children carries with it the risk of side-effects, including growth retardation, osteoporosis, obesity, and cataracts.

Antimetabolites and alkylating agents

The ISKDC studied prednisone with placebo compared with prednisone and azathioprine for primary nonresponders and for frequent relapsers. This treatment had no benefit for the steroid-resistant group (10 of whom ultimately showed focal sclerosis on renal biopsy) or for the frequent relapsers [18].

Cyclophosphamide is more effective. A randomized controlled trial in children with frequently relapsing minimal lesion disease showed a statistically significant decline in relapse rate in those given cyclophosphamide in addition to prednisone, even though there were just 10 children in each group [19]. The same investigators then compared two weeks of treatment and eight weeks of treatment with cyclophosphamide in a randomized controlled trial in frequent relapsers. Two weeks of cyclophosphamide led to more prolonged remission compared with historical controls who received prednisone alone, whereas eight weeks of cyclophosphamide was even more effective [20]. A level 1 ISKDC study of cyclophosphamide in frequent relapsers showed the clear superiority of cyclophosphamide and prednisone (48% relapse after a mean of 22 months) compared with prednisone alone (88% relapse after a mean of 22 months) [21]. Barratt et al extended their follow-up of cyclophosphamide in frequent relapsers to four years in a level 4 study, which showed that the eight-week course conferred a prolonged benefit to these patients [22].

Chlorambucil led to prolonged steroid-free remission in children with frequently relapsing or steroid-dependent (not steroid-resistant) nephrotic syndrome, with low doses (less than 0.3 mg/kg/day) as effective as high doses (more than 3.0 mg/kg/day) [23, 24]. The APN studied the effect of eight weeks of treatment with cyclophosphamide at 2 mg/kg/day versus chlorambucil at 0.15 mg/kg/day in 16 children with frequent relapsing and 34 children with steroid-dependent disease. In the frequent relapsers, the rate of relapse after treatment declined, although actual rates of relapse prior to therapy were not formally compared. In contrast, the eight weeks of treatment did not apparently benefit the steroid-dependent cohort, although once again, relapse rates were not compared statistically before and after alkylating therapy. There was no difference between chlorambucil and cyclophosphamide, although the numbers were small for that intergroup comparison [17]. In a subsequent prospective study, steroid-dependent patients (similar to the patients who failed the eight weeks of alkylating therapy previously) were instead given 12 weeks of therapy with 2 mg/kg/day of cyclophosphamide. The 12 week group was compared retrospectively with the steroid-dependent children who had received eight weeks of cyclophosphamide. The cumulative rate of sustained remission was 67% in the 12 week trial compared with 22% in the 8 week trial. However, the children who received 12 weeks of cyclophosphamide were older than the historical cohort, who received eight weeks, and may have had a better prognosis because of this age difference [25]. In contrast, a randomized controlled study from Japan comparing 8 versus 12 weeks of cyclophosphamide head-to-head in steroid-dependent nephrotic syndrome found that 12 weeks did not confer any advantage. The relapse rate was similar in both groups and similar to the eight-week treatment group of the APN [26]. The better outcome with the 12 weeks may be confounded by the fact that the children were older and compared with historical controls.

Other retrospective or observational studies have confirmed the effectiveness of cyclophosphamide in frequently relapsing or steroid-dependent nephrotic syndrome [27–30].

Cyclosporine

Very few of the studies of cyclosporine in pediatric nephrosis are controlled, and most are small [31]. The first such study, in the late 1980s, found that cyclosporine treatment reduced relapses and total corticosteroid dose [32]. Subsequent uncontrolled studies found complete remissions in steroid-dependent or frequently relapsing nephrotic syndrome, whereas many children were able to stop corticosteroids [33, 34]. The largest study involved 65 children with nephrotic syndrome, 45 of whom had minimal lesion disease. These patients were classified as steroid resistant if they did not show remission after just four weeks of daily corticosteroids followed by three

pulses of solumedrol. Of the 45 patients with minimal lesion, 21 entered complete remission on cyclosporine treatment in combination with prednisone. Seventeen of these patients remained in remission after a mean three-year follow-up once stopping the cyclosporine, and most patients became steroid sensitive [35]. It may have been premature, however, to classify these children as steroid resistant after just four weeks of therapy. Some of the patients who went into remission with cyclosporine may have actually been demonstrating a delayed response to corticosteroid treatment.

Most patients experience relapses of their disease when cyclosporine is tapered or discontinued, becoming cyclosporine dependent in the same way they were once steroid dependent [31]. Furthermore, with subsequent courses of cyclosporine treatment, the patients appear to become progressively less responsive.

In one of the few randomized studies, children in their first year of nephrotic syndrome were randomized to receive low-dose prednisone and cyclosporine or high-dose prednisone alone (in half of each group, this was instituted with their first presentation). Children in both groups went into remission, and there was no difference in the duration of remission once treatment was stopped [36].

When compared with alkylating agents, cyclosporine was not as successful in maintaining a prolonged remission in steroid-dependent nephrosis [31]. In a randomized controlled trial in both adults and children, cyclophosphamide and cyclosporine were equally successful in inducing remission in steroid-dependent and frequently relapsing nephrotic syndrome. However, remissions lasted longer in the group that received the alkylating agent [37].

A recent uncontrolled retrospective study of the use of cyclosporine (2.5 to 5.0 mg/kg/day starting dose) in steroid-dependent and steroid-resistant nephrosis in children (some of whom had focal sclerosis) reported good results. There was halving of the steroid dependence in the first group and restoration of steroid responsiveness in approximately one fourth of the patients in the latter group. After a median follow-up of 7.5 years in the steroid-dependent cohort and 5.0 years in the steroid-resistant group, there was no change in plasma creatinine with the exception of some of the patients with focal sclerosis. A small number underwent follow-up renal biopsy, and striped interstitial fibrosis and tubular atrophy were found, suggesting cyclosporine nephrotoxicity. However, these were not accompanied by changes in renal function (as judged by serum creatinine, though). The authors concluded that cyclosporine therapy in this setting was effective adjunctive therapy with minimal long-term nephrotoxicity [38].

In summary, for patients with steroid-dependent or frequently relapsing minimal lesion disease, alkylating agents are as effective as cyclosporine and produce a longer remission.

Levamisole

The antihelminthic agent levamisole has immunomodulatory effects and has been used in a number of diseases, such as cancer. Levamisole has been used alone or in combination therapy in minimal lesion disease in children. Unfortunately, few of these studies were either randomized or controlled [39]. A level 5 study used 2.5 mg/kg twice weekly in frequently relapsing minimal lesion disease. Half of the children had already received other immunosuppressive agents besides prednisone, which confuses the issue. Sixteen of the 30 patients stayed relapse free while on levamisole, but many relapsed when it was stopped; however, the follow-up was short [40]. A recent study from India used alternate-day levamisole therapy in steroid-dependent nephrotic syndrome once remission was obtained with corticosteroids. The subsequent relapse rate decreased from a mean of 3 per year to 0.9 per year [41]. Other small studies found that treatment with levamisole induced or maintained remission [42–44]. In one of only two controlled studies of levamisole in pediatric nephrotic syndrome, an increased remission rate compared with placebo was found, but most children relapsed within three months of stopping levamisole [45]. In the other controlled study, 21 of 33 patients receiving levamisole were still in remission compared with 12 of 28 patients receiving no treatment, a nonsignificant difference [46].

Levamisole is well tolerated. The side effects noted include neutropenia, rash, and liver toxicity [47]. However, a review of the literature reveals no new large-scale studies using this agent in nephrosis of children in the last few years. Perhaps others find this agent less effective than published trials suggest; otherwise, it is unclear why this agent has not been more widely accepted for this indication.

Treatment of steroid-resistant minimal lesion disease

Recommendation 5. Management of steroid-resistant minimal lesion disease can include rebiopsy to rule out focal sclerosis (grade D), cyclophosphamide 2 mg/kg/day $\times$ 12 weeks (grade D), or cyclosporine at 6 mg/kg/day for children or 5 mg/kg/day for adults for an uncertain duration (grade D).

Evidence. Patients with steroid-resistant minimal lesion disease are the most difficult to treat. These patients suffer the ill effects not only of corticosteroid toxicity, but of unremitting nephrosis with the attendant risks of sepsis, malnutrition, growth retardation, and thrombosis. The patient with steroid-resistant nephrotic syndrome also has a greater chance of progressive renal insufficiency culminating in end-stage renal disease.

Studies in these children have been limited by small numbers and short follow-up times. The only controlled study had eight children, four with minimal lesion and four with focal sclerosis. The patients received eight weeks of cyclosporine in a randomized cross-over design; there was no difference compared with no treatment [48].

Given the paucity of evidence for cyclosporine, alkylating agents should be used first in children with frequently relapsing, steroid-dependent, and steroid-resistant minimal lesion disease. Cyclosporine should be reserved for those cases in which alkylating agents have failed, especially in which there is unacceptable corticosteroid toxicity and a holiday from prednisone is needed, to allow catch-up growth or puberty. Unfortunately, most children continue to relapse when cyclosporine is withdrawn. The alternative, chronic cyclosporine therapy, carries the risk of nephrotoxicity, with the extent of damage to the kidneys out of proportion to the rise in serum creatinine. Serial renal biopsies have been recommended [49]. Progressive nephrotoxicity in children on long-term cyclosporine therapy may be avoided if the patients are kept volume expanded, low doses are used, and levels are closely monitored [50].

TREATMENT OF MINIMAL LESION DISEASE IN ADULTS

Corticosteroids

Few randomized controlled studies have examined the treatment of adults with minimal lesion disease (Tables 4 and 5). Observational studies from the 1950s showed rapid remissions after corticosteroid treatment of adult patients with minimal lesion disease. No controlled clinical trial was undertaken until 1970 when Black, Rose, and Brewer performed a multicenter controlled trial of steroid treatment in 125 adult nephrotic patients, including 31 patients with biopsy-proven "minimal lesion" disease (it is possible that patients with stage 1 membranous glomerulonephritis could have been included in this group) [3]. The treatment group received prednisone, at least 20 mg/day, for at least six months, compared with a control group. In the patients with minimal lesion disease, prednisone therapy gave an early and rapid decrease in proteinuria. Control patients showed a tendency for remission of the proteinuria, although this occurred much more slowly. By two and a half years, the difference with respect to proteinuria and serum albumin concentrations was not statistically significant between the prednisone-treated and control group.

Another multicenter randomized trial examined whether adults and children with minimal lesion disease could be more effectively treated with pulse methylprednisolone compared with the usual treatment. The group receiving methylprednisolone reached remission sooner only in children, not in adults. The relapse rate was no different between the methylprednisolone and the oral prednisone group. Corticosteroid-related side effects were more prevalent in the group receiving oral prednisone. The investigators suggested that pulse methylprednisolone followed by low-dose oral prednisone was less effective than the usual regimen of high-dose oral steroid, but was associated with less corticosteroid-related side effects. In patients who are at risk for corticosteroid side effects (for example, adult patients with osteoporosis), pulse steroid followed by low-dose oral prednisone might be more appropriate compared with longer term high-dose oral steroid treatment. No studies have directly addressed this question [51].

An uncontrolled level 4 study of alternate-day corticosteroid treatment in adults with idiopathic nephrotic syndrome used 60 to 120 mg of prednisone every other day for 9 to 12 months, followed by a gradual taper. Eighty-three percent of patients with minimal lesion disease sustained a complete or partial remission. Although this regimen was effective, the prolonged duration of therapy meant that the total amount of corticosteroids given was at least as great as in patients receiving more conventional therapy [52].

Antimetabolites and alkylating agents

Few studies have examined antimetabolites or alkylating agents in adults with minimal lesion disease. A level 5 study of long-term azathioprine in patients with steroid-resistant minimal lesion disease showed that all of the patients had remission of their nephrotic syndrome and increased creatinine clearance by one year. Unfortunately, the patients had previously received very large doses of steroids, and in this uncontrolled study, it is unclear whether the remission was actually a late effect of large doses of prednisone or whether this was just spontaneous remission [53].

Few studies have examined the use of cyclophosphamide without corticosteroids in adult patients with minimal change disease. In one study, 2 of the 10 patients treated with cyclophosphamide alone went into remission [54]. In another study, very high doses of cyclophosphamide were used alone in a heterogeneous group of eight patients with minimal lesion disease. Their gonadal status was not followed. In this study, nine weeks of therapy with this alkylating agent induced remission in seven of these patients by five months. After a mean follow-up of six years, none of the patients relapsed. Once again, however, this is a level 6 study, and it is difficult to make firm conclusions in a condition that has a tendency to remit if followed long enough [55].

Cyclosporine

Cyclosporine induces complete or partial remissions in adults with minimal lesion disease. Two level 1 studies

Table 4. Corticosteroids and alkylating agents antimetabolites in studies of adults

Author [Ref]	Study design	*N*	Treatment	Results/comments
Level 1 or 2				
Black [3]	Multicenter RCT Pred 20–30 mg/day >6 months	61 Pred 64 controls (31/125 had ML)	Pred "not less than" 20 mg/kg/day × 6 months	Early response in most ML Pred compared to controls; but gradual tendency to remission in ML controls over 2 years
Imbasciati [51]	Multicenter RCT children + adults pulse IV methyl prednisolone vs. high dose oral Pred	67 children 22 adults	Solumedrol 20 mg/kg/i.v. daily × 3, oral Pred × 4 weeks, taper over 5 months vs. Pred 60 mg/m^2 or 1 mg/kg/day × 4 weeks, alt Pred × 5 months	Children receiving pulses had CR earlier than oral Pred; no difference in adults. Tendency to earlier and more frequent relapses in pulse group; more steroid side effects in oral Pred group
Level 3 or 4				
Bolton [52]	Observational alt day steroids in different GN's	29 (ML)	Pred 60–120 mg q alt day × 9–12 months, then taper	CR or PR in 83% of ML. Some also receive cytotoxics. Short F/U
Nolasco [1]	Retrospective review of adult onset ML (F/U of Cameron 1974)	89	Pred 60 mg/day tapered over 8 weeks; CTX (*N* = 36) for initial rx, steroid "resistance" or frequent relapses	Adults have lower + slower response to Pred (?relatively lower dose c/w children), relapse less often, more stable remission with CTX (66% remission at 5 years). Adults more 8 BP, ARF c/w children. 6/8 no rx went into remission slowly
Level 5 or 6				
Sharpstone [76]	Observational Pred vs. Pred + AZA in different primary GN's	8 ML	Pred 60 mg/day × 3 days tapered to 20 mg/day × 8 weeks; Pred 20 mg/day + 150 mg AZA/day × 8 weeks	ML all started with Pred alone 6/8 CR. In 2/8 changed to Pred + AZA—one improved, one did not
Uldall [54]	Observational CTX for adult ML	10	CTX 1.5 mg/kg/day, titrated to WBC 2.5–24 months	2 patients received CTX only and went into CR; 8 patients had PR or relapses on Pred, on CTX all went into CR or near CR. Alopecia and ovarian toxicity
Idelson [77]	Review of steroid rx in various 1E adult GN's	28 ML	Corticosteroids (dose?)	CR or PR predictive of long-term renal outcome, also persistence of normal renal function for at least 3 years predictive of good outcome
Al-Khader [55]	Review of CTX alone for "adult" ML (ages 13–68) c/w diuretics alone	8 CTX 8 diuretics	CTX 8 mg/kg body wt and tapered to WBC	7/8 CTX CR by 14 weeks (mean 10 weeks) 2/8 diuretic only group CR spontaneously by 12 months. None of 9 CR's had relapses by 6 year F/U
Cade [53]	Steroid-resistant ML given AZA	13	Pred 60 mg/day × 4 weeks, then very slow taper over months; if failed rx or frequent relapses that were failing Pred changed to AZA 2.0–2.5 mg/kg/body wt × years	All 13 showed 9 proteinuria, 8 C_{Cr}. All in CR, but took up to one year to respond. Effect of AZA or late effect of Pred?
Lim [78]	Idiopathic NS	11 ML	Pred in various doses, ACTH or no rx	4/11 had spontaneous remission. Steroid induced CR in 5

Abbreviations are in Table 1.

involving adults are multicenter studies from Italy. The first is a randomized controlled study in steroid-resistant nephrotic syndrome comparing 5 mg/kg/day of cyclosporine in adults and 6 mg/kg/day in children to placebo [56]. Corticosteroid resistance was defined as persistence of nephrotic syndrome after six weeks of prednisone (1 mg/kg/day) for adults or five weeks of prednisone (60 mg/m^2/day) for children. Unfortunately, eligibility included focal sclerosis in addition to minimal lesion disease. Most of these steroid-resistant patients had focal sclerosis. Of the two adults studied with minimal change disease, one went into complete remission, and the other had no response. The sample was too small to draw any conclusion. Of the six children with minimal change disease, four experienced reduction or remission of proteinuria, and two had continuing nephrosis [56].

The other randomized, controlled trial involved patients with steroid-dependent (as opposed to steroid-

Table 5. Cyclosporine in studies of adults

Author [Ref]	Study design	*N*	Treatment	Results/comments
Level 1 or 2				
Ponticelli [37]		See Table 3 (Children and Adults)		
Level 3 or 4				
Meyrier [61]	CsA alone for GN with steroid resistance or dependency	29 ML	CsA 5mg/kg/day; duration depended on response	Pooled results: 72% chance of remission with steroid dependent ML Longest remission 12 months
	CsA + Pred for Gn with steroid resistance or dependence	29 ML	CsA 5mg/kg/day titrated to lower trough levels and tapering Pred; duration depended on response	
Lee [62]	Uncontrolled prospective study steroid dependent or resistant or frequent relapsing NS	22 ML (final)	CsA up to 7 mg/kg/day up to 8 months; Pred 10 mg/kg/day	CR in 19/22; PR in 2/22 Failure in 1; relapses in 68% by 10 months
Level 5 or 6				
Lagrue [57]	Uncontrolled CsA for steroid resistant or dependent NS	10 ML	CsA 3 mg/kg–5 mg/kg × 3 months	CR in 7/10; PR in 2/10 Failure in 1 (also steroid resistant). All relapsed within 2–6 weeks
Maher [59]	Uncontrolled CsA in steroid dependent or resistant NS; some failed CTX	10 ML 1 IgM	CsA 5–12 mg/kg/day for 40–230 days	CR within 14 days. All patients relapsed within 180 days of discontinuation of CsA
Clasen [58]	CsA for frequent relapsing or steroid resistant ML	7	CsA 3–5 mg/kg BID and tapered to blood levels. Pred tapered off when therapeutic CsA levels reached	CR in 5/7. All relapsed with tapering or discontinuation of CsA. Remission could be reinduced with CsA. No response in 2/7 up to 10 months
Green [60]	NS resistant to Pred ± CTX given CsA (details of prior rx not given)	3 ML	CsA 6–10 mg/kg/day	3/3 CR within one month. All relapsed within 1–3 months of stopping CsA. Remission could be reinduced.

Abbreviations are in Table 1.

resistant) nephrotic syndrome or frequently relapsing disease [37]. These patients were randomly allocated to 2.5 mg/kg/day of cyclophosphamide for eight weeks or 5 mg/kg/day of cyclosporine in adults (6 mg/kg/day in children) for up to 12 months. Patients had to be in remission already, and prednisone was tapered off by the first five weeks of the protocol. The majority of the patients were children (55 out of 64), but the results were similar through all ages. Unlike the previous study, the majority of patients had minimal lesion disease (31 out of 34). The population was similar to the ones in studies by the European and ISKDC groups discussed earlier. As in those reports, cyclophosphamide was quite effective in producing a long-lasting remission. Two years after treatment, 63% of the cyclophosphamide-treated group were still in remission compared with 25% of those treated with cyclosporine. The authors recommended that frequently relapsing or steroid-dependent patients be treated with cyclophosphamide first. If that fails, then cyclosporine could be used as the next agent [37]. Once again, however, it is important to emphasize that there were only 11 adults altogether in this study.

Other uncontrolled studies in adults show results similar to those in children, that is, there is a good initial response [57] but a disheartening relapse rate as the drug is tapered and discontinued [58–62].

In conclusion, the role of cyclosporine in minimal lesion disease may be (*a*) in frequently relapsing or steroid-dependent disease, in which a trial of cyclophosphamide has failed, (*b*) where cyclophosphamide is contraindicated or there are concerns about gonadal toxicity, (*c*) in steroid-dependent disease to allow a "steroid holiday" for catch-up growth and puberty, or (*d*) in steroid-resistant disease.

Cyclosporine can produce long-term nephrotoxicity, especially in adults whose underlying vascular disease is more prevalent than in children. Patients with tubulointerstitial lesions may progress to end-stage renal disease more rapidly when given this agent [61]. Without further controlled studies, however, this interaction will be hard

to tease out because the kind of nephrosis in which cyclosporine is often tried, such as steroid-resistant minimal lesion disease or focal sclerosis, is in itself associated with progression to renal failure.

Long-term outcome of adults with minimal lesion disease

The long-term outcome of patients older than 15 has been examined retrospectively [1, 4]. Adults with minimal lesion disease, in contrast to children, have equal sex distribution. In addition, more of these adults had hypertension, and there was more microscopic hematuria. Furthermore, adults show an increased prevalence of diminished glomerular filtration rate, and there was a significant mortality associated with this condition. In the Guy's Hospital series of idiopathic nephrotic syndrome in adults, 25% had minimal lesion disease, showing that this is a significant cause of idiopathic nephrotic syndrome in adults. Five of the 49 patients presented with acute renal failure, and four of these needed dialysis (acute renal failure in minimal lesion disease is discussed later in this article) [4]. Three of the 49 patients had a spontaneous remission before therapy was given, supporting the previous observation of Black, Rose, and Brewer [3]. Seventy percent of patients relapsed, most them two or more times. This may have been related to a shorter course of prednisone that they received compared with other studies. Complications of minimal lesion disease were similar to those seen in children, with the exception of acute renal failure. Three patients had pulmonary emboli, and two patients developed cellulitis. A follow-up study was published 12 years later of 89 patients with a mean follow-up of 7.5 years [1]. Again, the prevalence of hypertension and microscopic hematuria was confirmed. Glomerular filtration rate was diminished in 60% of patients. Patients who went into remission earlier also seemed to relapse earlier. In total, only 56% of patients were still protein free at nine months and only 34% at two years. There was a much lower relapse rate in these adults when they were given a course of cyclophosphamide. Sixty-three percent of the cyclophosphamide-treated patients were still in remission after 10 years of follow-up. These authors concluded that adults had a lower and slower response to corticosteroids (but were given proportionately less prednisone per body weight compared with children). They sustained fewer relapses compared with children, and they seemed to have a more stable and sustained remission after a course of cyclophosphamide. Finally, hypertension, diminished glomerular filtration rate, and acute renal failure were all more prevalent in the adult population.

Acute renal failure as a complication of minimal lesion disease

A small subset of patients develop frank acute renal failure as a complication of minimal lesion disease. In retrospective analyses, patients who develop acute renal failure are older, tend to be male, and are hypertensive with evidence of vascular disease [63, 64]. A recent review of all reports in the English medical literature found that the average age of patients with this complication was 58 years. The mean urine protein excretion was 11.6 g/day, and the patients had a mean serum albumin of just 19 g/liter [65]. Acute renal failure occurred, on average, less than a month after onset of the nephrotic syndrome and lasted an average of seven weeks [65]. Despite the prolonged course of renal failure, recovery almost always occurred. There is one report of five patients who did not recover renal function [66], but at least two of these patients probably had focal sclerosis. Many had dye studies, and one patient refused dialysis and died (perhaps before renal function would have returned).

On renal biopsy, patients with acute renal failure have more arteriosclerosis than those with preserved function [64]. Acute tubular necrosis is the most prevalent finding but is not universally seen [64, 67]. Marked edema of the tubulointerstitium has been described in some cases [63] but is conspicuously absent in others [64].

In the original descriptions of acute renal failure, it was postulated that reduced plasma oncotic pressure led to a contracted plasma volume. With the added insults of vigorous diuresis or paracentesis, for example, the kidneys became critically underperfused, and ischemic acute tubular necrosis supervened [67].

This hypothesis has several weaknesses. As discussed, in patients with acute renal failure, acute tubular necrosis is found on renal biopsy no more than 60 to 70% of the time [64]. The duration of renal failure is atypically long for acute tubular necrosis, suggesting that other factors are contributing to the renal compromise.

There is little compelling clinical evidence for marked plasma volume depletion in patients who develop renal failure [65]. Indeed, the patients who develop renal failure have the highest blood pressures, compatible with the presence of vascular disease [64]. Plasma volume repletion does not reliably reverse the renal failure [65, 68].

Improvement in techniques to measure plasma volume has led to the re-evaluation of the concept of plasma volume contraction in the nephrotic syndrome. Plasma volume in patients with minimal lesion disease appears to be normal or even increased [69, 70]. The increased rather than decreased plasma volume may be, in part, a result of a parallel fall in oncotic pressure in the interstitial compartment of body water, which would decrease flux of water out of the plasma compartment [71]. Furthermore, renal excretion of salt and water is decreased in minimal lesion disease, which serves to keep the plasma compartment expanded [72, 73].

Lowenstein, Schacht, and Baldwin noted the lack of tubular necrosis in a retrospective review of 15 patients with minimal lesion disease complicated by acute renal

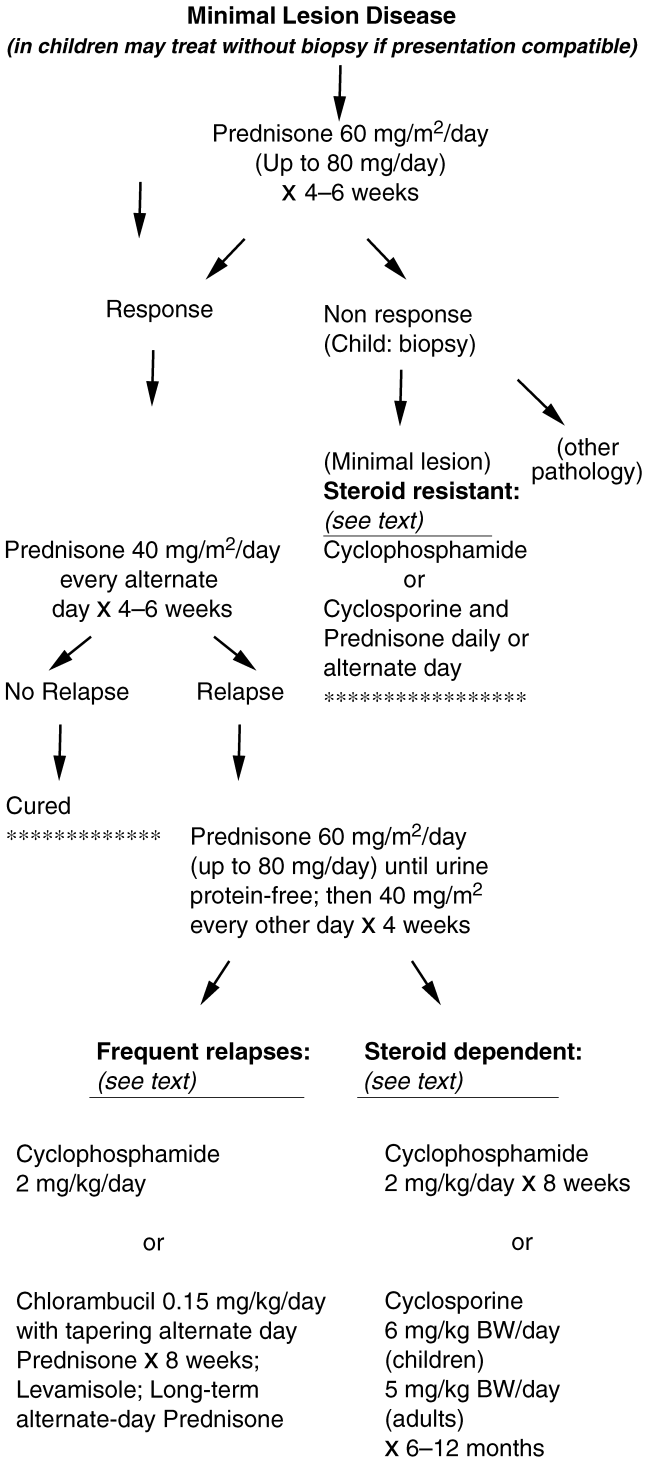

Fig. 1. Algorithm for treatment of minimal lesion disease.

failure. Instead, they noted interstitial edema in many of the biopsy specimens. Furthermore, there was improvement in renal function with induction of diuresis. They postulated that renal interstitial edema produced an increase in hydrostatic pressure in the proximal tubules and Bowman's space, leading to a decreased glomerular filtration rate [63].

If there is convincing clinical evidence of plasma volume depletion in a given patient (decreased jugular venous pressure, hypotension), it may be reasonable to try to normalize plasma volume with colloid, although this may occur only transiently [74, 75]. Advocates of the renal interstitial edema theory suggest diuretic treatment sufficient to effect a vigorous diuresis [63]. However, it is possible that the response to diuretics is simply a marker of a functioning kidney, rather than a treatment that restores function to an acutely failed kidney.

Recovery of renal function occurs in the majority of patients. The duration of renal failure is typically prolonged, and the endogenous renal function should be monitored while the patient is on dialysis.

SUMMARY

Among all of the glomerulonephritides in children, minimal lesion disease is one of the most common. This has made possible a large number of clinical trials, providing sufficient evidence for very clear treatment recommendations (Fig. 1). Corticosteroid treatment is proven effective in this group, although relapses occur. In adults, however, a paucity of large randomized trials means that recommendations cannot easily be made.

ACKNOWLEDGMENTS

The author thanks V. Brown for secretarial help.

Reprint requests to Joanne M. Bargman, M.D., The Toronto Hospital, 200 Elizabeth Street, 10EN-216, Toronto, Ontario M5G 2C4, Canada.

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