



## Management of Adult Minimal Change Disease

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### Introduction

Minimal change disease is responsible for idiopathic nephrotic syndrome in >75% of children and up to 30% of adults (1–5). Although secondary causes of minimal change disease (*i.e.*, nonsteroidal anti-inflammatory drugs, lithium, and lymphoproliferative disorders) are uncommon in children, they account for up to 15% of minimal change disease in adults (1,3). Thus, it is important to assess adults with minimal change disease for secondary causes as the prognosis, and therapeutic approach is determined by the underlying etiology.

### Patient Presentation

A 60-year-old white man presented with sudden onset of nephrotic syndrome. His serum creatinine was 1.3 mg/dl, serum albumin was 1.9 g/dl, total cholesterol was 462 mg/dl, and the 24-hour urine protein was 9 g. His BP was 140/90 mm Hg, and he had 2+ edema to the knees. He had recently been diagnosed with prostate cancer and was treated with radiation implants. A serologic evaluation was negative, there was no evidence of a lymphoproliferative disorder, and he was not taking nonsteroidal anti-inflammatory drugs. The kidney biopsy demonstrated minimal change disease.

### Clinical Presentation in Adult Minimal Change Disease

In adults as in children, minimal change disease presents abruptly with sudden onset of edema and massive proteinuria. However, unlike in children, hypertension (25%–50%), hematuria (20%–30%), and AKI (20%–25%) are more common in adults (1–6). The etiology of AKI is thought to be hemodynamic in nature, with evidence of acute tubular necrosis reported in up to 60% of patients. Features associated with a higher risk of AKI include older age, hypertension, and arteriosclerosis on the kidney biopsy (1,2,6). Occasionally, AKI in minimal change disease may be irreversible, and it is most often seen in older patients with high-grade proteinuria. Because the presenting features in nephrotic adults with minimal change disease can be indistinguishable from other causes of idiopathic nephrotic syndrome, a kidney biopsy is critical in diagnosis and management.

### Initial Treatment and Course in Adult Minimal Change Disease

Minimal change disease in adults is highly steroid sensitive, but steroid resistance is seen in 5%–20% of adult patients (1–6). When steroid resistance is observed, the patient often has FSGS on re-examination of the initial biopsy or on rebiopsy (1,3,6). Although 95% of children attain a remission with steroid therapy by 8 weeks, only 50%–75% of adults do so (1–6). It is not until after 16 weeks of treatment that most adults (75%–95%) enter a remission, with the majority attaining a complete remission (proteinuria of  $\leq 300$  mg/d) and a minority attaining a partial remission (proteinuria of  $>300$  mg but  $<3.5$  g/d). As a result, steroid resistance in adults is defined by the lack of response after a 16-week course (1,2,5,7).

In adults, an initial course of steroid therapy with prednisone at a dose of 1 mg/kg (up to 80 mg) given once daily in the morning or 2 mg/kg (up to 120 mg) given on alternate days has been equally effective. Because alternate day steroid therapy has not been associated with fewer adverse events, our initial approach is to begin with prednisone daily and treat for up to 16 weeks (1,6,7). Should a remission be attained within 4–12 weeks, we continue high-dose prednisone for an additional 2–4 weeks, after which a slow prednisone taper is initiated to complete a course of therapy of 4–6 months.

In patients with a relative contraindication for steroids (*i.e.*, obese patients or those with diabetes mellitus), a steroid-sparing approach with alkylating agents (cyclophosphamide), antimetabolites (mycophenolate mofetil), or calcineurin inhibitors (cyclosporin or tacrolimus) can be used (1,6,7).

Although initial treatment of the nephrotic syndrome includes a low sodium diet and loop diuretics, the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for their antiproteinuric effects or lipid-lowering agents, such as statins, is generally not advocated (7). In patients with persistent nephrotic syndrome despite treatment, the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and statins as well as prophylactic anticoagulation (when the serum albumin is  $<2.0$ – $2.5$  g/dl) are recommended (7).

### Patient's Initial Course

Prednisone at 60 mg daily was started, and after 9 weeks, he was in a complete remission. Prednisone

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(60 mg daily) was continued for 4 more weeks, after which a slow steroid taper was initiated. He was off prednisone after receiving a total of 6 months of treatment.

### Relapse in Adult Minimal Change Disease

Relapses occur in 65%–80% of adults with minimal change disease, with the majority of relapses being seen within the first 3–6 months after a remission (3,4,6). However, younger adults (<45 years of age) tend to relapse more frequently (88% versus 57%) (4). Most adults with minimal change disease have only an occasional relapse (*i.e.*, less than or equal to one per year). In this situation, a second course of treatment with steroids is often used, typically resulting in another remission. Patients who relapse two or more times within 6 months or four or more times within 12 months are “frequent relapsers,” and those patients having two relapses with steroid taper or within 1 month of ending therapy are “steroid dependent” (7).

In adults, 10%–30% are frequent relapsers, and 15%–30% are steroid dependent (1–6). Because the repeated use of steroids in frequently relapsing or steroid-dependent adults increases the risk of severe adverse events, the use of extremely “low-dose” prednisone or steroid-sparing immunosuppressive agents, such as cyclophosphamide, mycophenolate mofetil, and cyclosporin, has been shown to be beneficial (1,2,4–7). Recently, encouraging results have also been seen with the anti-CD20 mAb rituximab (8,9).

The greatest experience in the treatment of frequently relapsing/steroid-dependent minimal change disease in adults and children has been with the use of cyclophosphamide, and this is the approach that we prefer. After reattaining a remission with prednisone, treatment with oral cyclophosphamide is initiated at 1–2 mg/kg per day, and treatment is given for 8–12 weeks. White blood counts need to be monitored weekly, and the dose needs to be adjusted to prevent leukopenia (*i.e.*, white blood count <3000/mm<sup>3</sup> or neutrophil count <1500/mm<sup>3</sup>). The cumulative dose of cyclophosphamide given for 8–12 weeks is generally well under that associated with infertility (>200–300 mg/kg) or malignancy (cumulative dose of >36 g) (7). Once on cyclophosphamide, the prednisone is tapered over 4 weeks. Using this approach, a remission rate of up to 80% with a relapse rate at 1 year of <10% has been observed (1,4,6).

Cyclosporin has also been effective in the treatment of frequently relapsing/steroid-dependent adults, with complete remission rates of up to 80%. Relapse of nephrotic syndrome is frequent during cyclosporin tapering, often leading to the need for long-term treatment. Ponticelli *et al.* (10) evaluated the efficacy of a 9-month course of cyclosporin with a 2-month course of oral cyclophosphamide, and at the end of 9 months, a complete remission was attained in 74% versus 64% of patients, respectively. However, at 2 years, a remission was observed in 25% versus 63% of patients, respectively. Thus, the use of cyclosporin results in a tradeoff of steroid dependency for cyclosporin dependency and the potential for associated nephrotoxicity. To minimize the potential for cyclosporin nephrotoxicity, the dose should slowly tapered to the lowest dose that maintains a remission.

The use of mycophenolate mofetil has also been shown to be effective in the treatment of frequently relapsing/steroid-dependent patients with minimal change disease. However, not unlike with cyclosporin, patients treated with mycophenolate mofetil tend to relapse when the mycophenolate mofetil is discontinued, resulting in mycophenolate mofetil dependence.

Recent studies with rituximab in adults with frequently relapsing/steroid-dependent minimal change disease who failed treatment with other agents have shown encouraging results (8,9). Ruggenenti *et al.* (9), in a multicenter, off-on trial, evaluated the use of rituximab in 30 frequently relapsing/steroid-dependent patients (20 adults and 22 patients with minimal change disease). A single dose of rituximab (375 mg/m<sup>2</sup>) was given to 28 patients; two patients with increased circulating B cell counts at 1 week received a second dose. At 1 year, all patients were in remission, 60% of patients were off of all immunosuppressive agents, and 50% never relapsed (9). The median per patient number of relapses per year decreased from 2.5 before rituximab to 0.5 during the year after treatment, and the maintenance daily dose of steroid decreased from 0.27 mg/kg (interquartile range, 0.19–0.60) to 0 mg/kg (interquartile range, 0–0.23).

### Patient's Follow-Up Course

Our patient remained in remission off prednisone for 16 months but then, relapsed. Another course of prednisone resulted in a remission within 4 weeks. Over the next 5 years, he had four more relapses and ultimately, became steroid dependent. We considered using cyclophosphamide but chose not to due to his history of prostate cancer. He refused treatment with cyclosporin and mycophenolate mofetil, and rituximab was not covered by his insurance. We reinduced a remission with 30 mg daily of prednisone and tapered to 2.5 mg/daily without relapse. He has remained in remission on “low-dose” prednisone for 3 years with no untoward effects.

### Long-Term Outcome in Adult Minimal Change Disease

The long-term prognosis for adults with minimal change disease is excellent, because 75%–90% of treated patients remain in remission (1,3,4,6). Progression to ESKD occurs in <5% of adults and is often due to an alternative diagnosis of FSGS.

### Disclosures

Dr. Korbet and Dr. Whittier have nothing to disclose.

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