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Improved outcomes in nephrotic syndrome

■ ABSTRACT

Nephrotic syndrome can now be treated effectively in most cases. All patients should be treated with a low-salt diet, diuretics to reduce edema, and statins to normalize serum lipid concentrations. Patients with nephrotic syndrome are prone to deep vein thrombophlebitis, renal vein thrombosis, and pulmonary emboli. Depending on the condition, additional treatment may include corticosteroids, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), cyclosporine, cytotoxic agents, or mycophenolate.

■ KEY POINTS

Minimal-change disease usually starts with the sudden onset of edema, heavy proteinuria, and hypoalbuminemia. It usually responds to a course of corticosteroids; the course required is often longer for adults than for children.

Idiopathic focal segmental glomerulosclerosis occurs disproportionately in blacks. Patients should take corticosteroids for 6 months, then cyclosporine or other agents if remission has not been achieved.

Membranous nephropathy often presents with severe proteinuria. In men over age 50 with severe or persistent proteinuria, the condition is most likely to progress to renal failure. The optimal treatment is not known. It may include corticosteroids, cytotoxic agents, cyclosporine, or other experimental agents.

Diabetes is the most common cause of nephrotic syndrome in adults. Patients should be treated with an ARB, an ACE inhibitor, or a combination of both, with antihypertensive drugs and diuretics as needed.

NEPHROTIC SYNDROME HAS a dramatically different prognosis than it did 10 years ago. We can now effectively treat all types and achieve remission in many cases. This article discusses the manifestations and treatment of nephrotic syndrome.

■ DEFINING NEPHROTIC SYNDROME

Nephrotic syndrome is always caused by glomerular disease with heavy albuminuria (> 3–3.5 g/day). Most patients eventually develop the entire nephrotic syndrome, ie:

- Hypoalbuminemia
- Edema
- Hyperlipidemia
- A tendency for thrombosis.

Every form of nephrotic syndrome originates in the glomeruli (capillary loops). There, albumin passes from the capillary lumen into the glomerular space, an abnormal phenomenon that can be caused by problems in the charge barrier, by biochemical changes in the basement membrane, or by immune deposits.

■ KEY DIAGNOSTIC FEATURES

Foamy urine

Although urine normally forms bubbles in the toilet, protein acts as a stabilizer, giving urine a beer-like “head.” A patient with the new onset of disease may not notice this quality, but some patients actually monitor their relapses and remissions using this as a gauge.

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Edema

Edema is the most common manifestation of nephrotic syndrome, and it has a pattern distinctive from that seen in other edema-causing conditions. In the morning, edema tends to be periorbital and in the hands, moving to the legs and feet by the end of the day. In contrast, patients who have heart failure or liver disease with ascites cannot lie flat at night due to shortness of breath.

There are two major theories of how nephrotic edema develops, and both are supported by animal models and clinical evidence. The classic theory is that glomerular disease causes proteinuria, leading to hypoalbuminemia and low plasma oncotic pressure. This causes capillary filtration by gravity and produces edema at the lowest point in the body. The reduced plasma volume stimulates salt-retaining mechanisms in the renin-angiotensin-aldosterone axis, which leads to more hypoalbuminemia and edema.

An alternative theory holds that glomerular disease with significant proteinuria causes primary renal sodium retention even before hypoalbuminemia occurs. This leads to plasma volume expansion, causing increased capillary filtration and edema. Animal studies show that kidneys retain salt as soon as they start losing protein. Kidneys infused with the nephrotoxin puromycin, which induces proteinuria, cannot respond normally to atrial natriuretic peptide by excreting salt in the urine. This research shows that receptor levels for atrial natriuretic peptide are normal, but a postreceptor defect exists in the kidney, leading to a lack of responsiveness to the hormone.

■ TREATMENT ISSUES AND RECOMMENDATIONS

Resolve edema gradually

Patients with nephrotic syndrome should eat a low-salt diet, ie, less than 2 g of sodium (<1 level teaspoon) per day.

Patients should also be treated with diuretic drugs to get rid of edema fluid. Patients should weigh themselves daily throughout treatment, and the dosages should be adjusted so that they lose 1 to 2 pounds per day, even if they have massive edema: diuretics mobilize

fluids from the circulation, resulting in hypotension if fluid is lost too rapidly.

I recommend starting with a low dose of a loop diuretic such as furosemide 40 mg. If there is no response, I raise the dose by 40 mg every 12 hours until 160 mg is reached. If there is still no response, I add another diuretic, such as metolazone, which potentiates the effect of the loop diuretic.

Almost all adult patients respond to oral treatment, although some may require furosemide 160 mg plus metolazone 10 mg twice a day to get the process started.

Rarely are intravenous diuretics or albumin infusions needed to resolve edema, except in children, who usually have minimal-change nephrotic syndrome and tend to become severely hypoalbuminemic.

Hyperlipidemia

Nephrotic syndrome causes lipiduria: urine sediment in polarized light reveals “Maltese crosses,” which are cholesterol esters bound to protein. It also causes hyperlipidemia, which can be severe.

In a series of 100 consecutive new patients with idiopathic nephrotic syndrome at Columbia Presbyterian Medical Center, 87% had serum cholesterol concentrations above 200 mg/dL, 53% had over 300 mg/dL, and 25% had over 400 mg/dL.¹ It is not uncommon to see patients with levels of 600 or 700 mg/dL.

Invariably, the low-density lipoprotein (LDL) fraction was elevated: 77% of the patients had an LDL concentration above 130 mg/dL and 65% had a concentration above 160 mg/dL.¹

The mechanism for hyperlipidemia is uncertain. Low albumin or low oncotic pressure may stimulate the liver to enhance the synthesis of lipoproteins that bind cholesterol. Another theory is that the loss in the urine of an unidentified regulatory protein feeds back and increases the liver's production of lipid-elevating lipoproteins.

Although the liver in nephrotic syndrome may produce more lipoproteins, high-density lipoproteins (HDL) are not elevated. Levels of HDL-2, the protective factor for atherosclerosis, are actually often low. One reason may be that because HDL is a small molecule, it may

The urine has a beer-like 'head,' which some patients use to monitor for relapses, remissions

be more easily lost in the urine.

Another protein up-regulated by the liver in nephrotic syndrome is cholesterol ester transfer protein, which may also play a role in hyperlipidemia. It transfers cholesterol esters from HDL to very-low-density lipoproteins, which are then transferred to LDL.

Patients with untreated nephrotic syndrome have very high levels of cholesterol ester transfer protein compared with controls without hyperlipidemia or patients with primary hypertriglyceridemia.² New drugs such as torcetrapib are being developed that specifically block cholesterol ester transfer protein and thereby dramatically increase HDL levels.

Statins improve lipid profiles

As in the general population, the most important benefit of correcting hyperlipidemia is reducing the risk of atherosclerosis. Patients with nephrotic syndrome who are unlikely to enter prompt remission or who require long-term therapy, such as those with membranous nephropathy, focal sclerosis, or diabetes, derive the most benefit from lipid-lowering therapy. When patients go into remission and proteinuria is resolved, hyperlipidemia tends to correct itself.

Early studies of statins to treat patients with nephrotic syndrome found that lovastatin reduced total cholesterol, LDL, and triglycerides, but only moderately. More potent statins now make larger reductions possible. For any patient with elevated creatinine or proteinuria, the goal should be to reduce cholesterol to less than 200 mg/dL and LDL to less than 100 mg/dL.³

Statins improve endothelial function

Endothelial dysfunction is an early phase of atherogenesis that manifests as impaired flow-mediated dilatation of the peripheral circulation. It is measured at the brachial artery using ultrasonography and computerized flow-detection software.

Dogra et al⁴ found that patients with nephrotic syndrome had significantly better flow-mediated dilatation after 12 weeks of treatment with statins, and the improvement could not wholly be explained by the degree of lipid-lowering.

Statins preserve kidney function

There is also evidence that lowering lipids slows the progression of renal disease. Fried et al⁵ found in a meta-analysis that in most cases, albuminuria was reduced in patients with nephrotic syndrome treated with statins, and progression to renal failure was slowed significantly.

Bianchi et al⁶ randomized 56 patients with chronic glomerular disease who had already been treated for 1 year with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) to additional treatment with either atorvastatin or placebo. After 1 year, protein excretion had decreased in the statin group, but not in the placebo group. In addition, kidney function remained stable in the statin group but declined in the placebo group.

Thrombotic tendency

Patients with nephrotic syndrome have a higher risk of thromboses for a number of reasons, including increased coagulation tendency, increased platelet aggregation, and high fibrinogen and fibrinogen-fibrin transformation. Concentrations of fibrinolytic substances, ant clotting factors, and protective factors such as antithrombin III tend to be low in patients with nephrotic syndrome because they are small molecules that are easily lost in the urine.

Patients tend to develop deep vein thrombophlebitis, renal vein thrombosis, and pulmonary emboli. Patients at highest risk are those with membranous nephropathy with very heavy albuminuria and proteinuria and low serum albumin.

Estimates of the incidence of renal vein thrombosis in patients with nephrotic syndrome vary according to how it is detected. Most cases are asymptomatic, but patients may present with flank pain, microscopic or gross hematuria, and a low glomerular filtration rate. In extreme cases, one may see dilated collaterals on physical examination because of renal vein occlusion.

Most cases of renal vein thrombosis are currently detected by ultrasonography, computed tomography, or magnetic resonance venography.

Patients tend to have thromboses, the result of a loss of antithrombotic factors in the urine

ACE inhibitors and ARBs

The Combination Treatment of Angiotensin II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Nondiabetic Renal Disease (COOPERATE) trial²⁵ randomly assigned 263 patients with nondiabetic renal disease to treatment with an ARB (losartan 100 mg/day) or an ACE inhibitor (trandolapril 3 mg/day), or a combination of the two. The primary end point, doubling of the creatinine level or renal failure, was reached by significantly fewer patients undergoing the combination treatment than those on single-drug therapy. Blood pressure control was identical in all three groups. The study was designed to continue for 5 years but was stopped at 3 years because the effectiveness of combination therapy was already clear.

Treatment with an ARB, an ACE inhibitor, or both blocks the renin-angiotensin system and is likely to decrease proteinuria, raise serum albumin, raise the oncotic pressure, lower lipid levels, and lower thrombotic tendency in a patient with nephrotic syndrome from any cause.

■ PRIMARY NEPHROTIC SYNDROME

Although diabetes is overwhelmingly the most common cause of nephrotic syndrome in developed countries, primary (or idiopathic) nephrotic syndrome is still important to recognize. The major forms are minimal-change disease, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy.

Minimal-change disease

Minimal-change disease is so named because under light microscopy the glomeruli look normal. However, with electron microscopy one can see swollen visceral epithelial cells with their normally discrete foot processes effaced, associated with albumin crossing the membrane.

Minimal-change nephropathy accounts for only 5% to 10% of cases of nephrotic syndrome in adults but more than 85% of cases in children, who are presumptively treated for it if they present with nephrotic syndrome.

Minimal-change disease usually starts with the sudden onset of edema, heavy proteinuria, and hypoalbuminemia. However,

adults may also have hypertension, microscopic hematuria, and a decreased glomerular filtration rate.

Treatment consists of prednisone daily or every other day. Therapy should continue for 4 months before it can be considered unsuccessful.⁷ For relapses, another course of corticosteroids or another agent can be used (see discussion in following section). Minimal-change disease is unlikely to progress to renal failure if proteinuria is controlled.

Focal segmental glomerulosclerosis

The incidence of FSGS has increased dramatically over the past few decades⁸ and is four times more likely to develop in blacks than in whites.⁹

A histologic pattern, not a disease itself.

Under the light microscope, FSGS appears focal, ie, normal areas are mixed with segments of scarring sclerosis. However, under electron microscopy, even the “normal” areas have visceral epithelial cells with fused or effaced foot processes. This is associated with massive albuminuria in every capillary loop. Glomeruli that look normal develop sclerosis over time.

Focal sclerosis is a histologic pattern, not a disease itself. The differential diagnosis consists of a number of secondary conditions, including nephropathy related to a hereditary condition, obesity, human immunodeficiency virus infection, and heroin addiction. If secondary causes have been ruled out, the patient should be treated as having idiopathic disease.

Hereditary FSGS is important to identify because patients do not respond to immunosuppressive agents, and they are particularly good candidates for transplantation because the defect will not reappear. Some families have genetic abnormalities in the structural proteins of the glomerular visceral epithelial podocytes: defects have been identified in the alpha-actinin and podocin proteins. Another recently identified defect involves a transport channel in the visceral epithelial cells.

Some believe that the FSGS predilection for blacks is due to a genetic defect that manifests only after a second insult, such as a viral infection.

Obesity-related FSGS is more common in whites. These patients are much less likely

FSGS is four times more likely to develop in blacks than in whites



to present initially with nephrotic syndrome. Instead, they usually present with isolated proteinuria, have higher serum albumin concentrations vs patients with idiopathic disease, and tend to have only slow progression to nephrotic syndrome.¹⁰

Under the microscope, glomeruli appear very large with focal segmental scars. These eventually become sclerotic.

Therapy consists of ACE inhibitors or ARBs, or a combination of these drugs. Immunosuppressive drugs are not used.

Idiopathic FSGS. Only 20 years ago, idiopathic FSGS was regarded as untreatable. The small percentage of patients who had a response to corticosteroid treatment almost invariably had a relapse. Now, however, we can achieve complete remission in around 45% and partial remission in 10% with corticosteroids alone.^{11–15} Previously, patients were treated with corticosteroids for only 2 months; we now treat for at least 6 months before determining treatment failure.

Factors that predict a worse prognosis include more severe proteinuria and nephrotic syndrome, higher serum creatinine concentration, black race, and interstitial fibrosis and a collapsing pattern on histopathologic study.

Patients who experience even a partial remission with relapse have a better prognosis than those who have never had a remission. Korb et al¹⁵ reviewed patients for 5 years after treatment for FSGS and found that 52% of those who had no remission had developed end-stage renal disease vs only 2% of those who had a remission and 17% of those who had a partial remission.

For patients who do not respond to corticosteroid therapy, cyclophosphamide was once the standard alternative. However, studies show that complete remission was achieved using cyclophosphamide in only 17% of adult patients, and partial remission in only 7%.¹⁶

Cyclosporine leads to better results. The North America Nephrotic Syndrome Study Group,¹⁷ in a multicenter trial of patients with corticosteroid-resistant FSGS, found that treatment with cyclosporine plus low-dose prednisone for 26 weeks produced complete remission in 12% and partial remission in 57%, vs only 4% of the control group

TABLE 1

Risk factors for progression in membranous nephropathy

- Male gender
- Age > 50 years
- Nephrotic syndrome (especially proteinuria > 10 g/day)
- Elevated plasma creatinine at presentation
- Glomerular scarring
- Persistent proteinuria of at least:
 - 4 g/day for 18 months
 - 6 g/day for 9 months
 - 8 g/day for 6 months

*Based on data from Pei Y, Cattran D, Greenwood C. Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis. *Kidney Int* 1992; 42:960–966.

achieving either. After treatment ended, 40% of treated patients in remission stayed in remission through the end of the prolonged observation period. Progression to renal failure, as measured by decline in creatinine clearance, was also significantly slower in the treatment group.

Mycophenolate mofetil (CellCept) is an immunosuppressive agent used for patients receiving an organ transplant. In an open-label trial of 18 patients with corticosteroid-resistant FSGS,¹⁸ nearly 50% of patients treated with mycophenolate for 6 months had improved proteinuria. A similar study of patients with FSGS found that 3 months of treatment with mycophenolate led to an improved median 24-hour urine protein-to-creatinine ratio.¹⁹

Membranous nephropathy

Membranous nephropathy is the most common pattern of idiopathic nephrotic syndrome in whites.

Histologic features. Histologically, every glomerulus has thickened capillary loops, and visceral epithelial cells have fused foot processes, which are evidence of albuminuria. One can also see electron-dense subepithelial deposits, indicating the nature of the disease process.

Presenting features. Patients with membranous nephropathy usually present with

Membranous nephropathy is the most common pattern of nephrotic syndrome in whites

severe proteinuria. As in FSGS and minimal-change disease, patients may have hypertension and microscopic hematuria, and they are at increased risk of thrombosis. Biopsy is required to determine the diagnosis.

Disease course. Membranous nephropathy usually progresses only slowly to renal failure, and about 25% of patients spontaneously enter remission in 5 to 10 years. For several years, Schieppati et al²⁰ followed 100 patients who had idiopathic membranous nephropathy and were treated only symptomatically. Most patients maintained renal function, and many underwent spontaneous remission. However, some patient groups with membranous nephropathy are much more likely to develop renal failure if untreated; these include men, people over age 55, and patients with persistent, very large amounts of proteinuria.

Treatment. This indolent progression makes it difficult to study therapeutic agents, and in fact, the optimal treatment is still uncertain. Therapies that have been tried include corticosteroids; corticosteroids alternating with cytotoxic agents; cyclosporine; mycophenolate; anti-C5 antibodies; and rituximab.

High-risk patients. Risk factors have been identified that predict a poor prognosis and progression to renal failure (TABLE 1). These risk differences can probably be attributed to a difference in the etiology and the nature of the specific immune deposits that are likely to develop in older men. Pei et al²¹ found that one can use the level and duration of proteinuria to further define who is at higher risk and would likely benefit from therapy.

Studies of treatment. Ponticelli et al²² randomized 81 patients with idiopathic membranous nephropathy to 6 months of treatment with alternating corticosteroids and cytotoxic agents or with supportive therapy alone. In the treatment group, protein levels in the urine dropped dramatically within 6 months and remained low through the 2 years of follow-up. Patients followed for 5 years had

evidence of stable renal function by plasma creatinine levels, whereas the control group had a progressive decline.

Cattran et al²³ randomized 51 patients who had corticosteroid-resistant idiopathic membranous nephropathy to treatment with cyclosporine plus low-dose prednisone or to a control group treated only with prednisone. After 26 weeks of treatment, 75% of the experimental group achieved remission vs 22% of the control group. Relapses were common (40%–43%) in both groups in the 6 months after therapy was stopped. Most experts would thus recommend continuing treatment with cyclosporine therapy for 1 year.

Miller et al²⁴ studied 16 patients who had membranous nephropathy and for whom other therapies had failed. Patients were treated with mycophenolate mofetil 500 to 2,000 mg daily for a mean of 8 months. Proteinuria levels were cut in half in 6 patients and disease remission was achieved in 2 patients. Choi et al¹⁹ also treated patients with membranous nephropathy with mycophenolate and had even better results, probably because the patients were newly diagnosed and had not experienced treatment failure previously.

■ SECONDARY NEPHROTIC SYNDROME

Diabetes is the most common cause of nephrotic syndrome. In these patients, it is important to reduce proteinuria and reverse some of the syndrome's manifestations. ACE inhibitors or ARBs should be part of their care unless specifically contraindicated (eg, due to pregnancy or hyperkalemia).

Not long ago, membranoproliferative glomerulonephropathy was believed to fall mainly under the umbrella of primary nephrotic syndrome, but it is now known to most frequently be secondary to systemic lupus erythematosus or hepatitis C infection. 

**Diabetes
is the most
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