Nephrotic Syndrome in Adults: Diagnosis and Management

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Nephrotic syndrome may be caused by primary (idiopathic) renal disease or by a variety of secondary causes. Patients present with marked edema, proteinuria, hypoalbuminemia, and often hyperlipidemia. In adults, diabetes mellitus is the most common secondary cause, and focal segmental glomerulosclerosis and membranous nephropathy are the most common primary causes. Venous thromboembolism is a possible complication; acute renal failure and serious bacterial infection are also possible, but much less common. There are no established guidelines on the diagnostic workup or management of nephrotic syndrome. Imaging studies are generally not needed, and blood tests should be used selectively to diagnose specific disorders rather than for a broad or unguided workup. Renal biopsy may be useful in some cases to confirm an underlying disease or to identify idiopathic disease that is more likely to respond to corticosteroids. Treatment of most patients should include fluid and sodium restriction, oral or intravenous diuretics, and angiotensin-converting enzyme inhibitors. Some adults with nephrotic syndrome may benefit from corticosteroid treatment, although research data are limited. Intravenous albumin, prophylactic antibiotics, and prophylactic anticoagulation are not currently recommended. (Am Fam Physician. 2009;80(10):1129-1134, 1136. Copyright © 2009 American Academy of Family Physicians.)

▼ Patient information: A handout on nephrotic syndrome, written by the author of this article, is provided on page 1136.

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In nephrotic syndrome, a variety of disorders cause proteinuria, often resulting in marked edema and hypoalbuminemia. Hyperlipidemia is a common associated finding. Family physicians may encounter persons with nephrotic syndrome from primary (idiopathic) renal disease or a number of secondary causes, and should initiate appropriate diagnostic workup and medical management pending specialist consultation.

Causes

Most cases of nephrotic syndrome appear to be caused by primary kidney disease. Table 1 summarizes the recognized histologic patterns and features of primary nephrotic syndrome.1 Membranous nephropathy and focal segmental glomerulosclerosis (FSGS) each account for about one third of cases of primary nephrotic syndrome; however, FSGS is the most common cause of idiopathic nephrotic syndrome in adults.2 Minimal change disease and (less commonly) immunoglobulin A (IgA) nephropathy cause approximately 25 percent of cases of idiopathic nephrotic syndrome.2 Other conditions, such as membranoproliferative glomerulonephritis, are less common. FSGS accounts for approximately 3.3 percent of new cases of end-stage renal disease.2 A large number of secondary causes of nephrotic syndrome have been identified (Table 2),7 with diabetes mellitus being the most common.

Pathophysiology

The underlying pathophysiology of nephrotic syndrome is not completely clear.4 Although the more intuitive “underfill” mechanism of edema from reduced oncotic pressure caused by marked proteinuria may be the primary mechanism in children with acute nephrotic syndrome, edema in adults may be caused by a more complex mechanism. Massive proteinuria causes renal tubulointerstitial inflammation, with resulting increased sodium retention that overwhelms the physiologic mechanisms for removing edema.5 Patients may have an “overfilled” or expanded plasma volume in addition to expanded interstitial fluid volume. This may be clinically
important if over-rapid diuresis leads to acute renal failure from reduced glomerular blood flow, despite persistent edema.

**Clinical Features**

Progressive lower extremity edema, weight gain, and fatigue are typical presenting symptoms of nephrotic syndrome. In advanced disease, patients may develop periorbital or genital edema, ascites, or pleural or pericardial effusion. Persons who present with new edema or ascites, without typical dyspnea of congestive heart failure or stigmata of cirrhosis, should be assessed for nephrotic syndrome.

Nephrotic-range proteinuria is typically defined as greater than 3 to 3.5 g of protein in a 24-hour urine collection; however, not all persons with this range of proteinuria have nephrotic syndrome. Although a urine dipstick proteinuria value of 3+ is a useful semiquantitative means of identifying nephrotic-range proteinuria, given the logistic difficulties of collecting a 24-hour urine sample, the random urine protein/creatinine ratio is a more convenient quantitative measure. The numeric spot urine protein/creatinine ratio, in mg/mg, accurately estimates protein excretion in g per day per 1.73 m² of body surface area, so a ratio of 3 to 3.5 represents nephrotic-range proteinuria. Low serum albumin levels (less than 2.5 g per dL [25 g per L]) and severe hyperlipidemia are also typical features of nephrotic syndrome. In one study of persons with nephrotic syndrome, 53 percent had a total cholesterol level greater than

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**Table 1. Histologic Patterns and Features of Primary Nephrotic Syndrome**

<table>
<thead>
<tr>
<th>Histologic pattern</th>
<th>Key pathologic features</th>
<th>Key clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Sclerosis and hyalinosis of segments of less than 50 percent of all glomeruli on electron microscopy</td>
<td>May be associated with hypertension, renal insufficiency, and hematuria</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>Thickening of the glomerular basement membrane on electron microscopy; immunoglobulin G and C3 deposits with immunofluorescent staining</td>
<td>Peak incidence at 30 to 50 years of age; may have microscopic hematuria; approximately 25 percent of patients have underlying systemic disease, such as systemic lupus erythematosus, hepatitis B, or malignancy, or drug-induced nephrotic syndrome</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>Normal-appearing glomeruli on renal biopsy microscopy; effacement of foot processes on electron microscopy</td>
<td>Relatively mild or benign cases of nephrotic syndrome; may occur following upper respiratory infection or immunization</td>
</tr>
</tbody>
</table>

Information from reference 1.
300 mg per dL (7.77 mmol per L) and 25 percent had a total cholesterol level greater than 400 mg per dL (10.36 mmol per L).7

Possible complications of nephrotic syndrome include venous thromboembolism caused by loss of clotting factors in the urine, infection caused by urinary loss of immunoglobulins, and acute renal failure. Thromboembolism has long been recognized as a complication of nephrotic syndrome.8 In a large retrospective review, the relative risk of deep venous thrombosis (DVT) in patients with nephrotic syndrome was 1.7 compared with those without nephrotic syndrome, with an annual incidence of DVT of 1.5 percent; the risk seems highest in the first six months after diagnosis.9 The relative risk of pulmonary embolism was 1.4 and was especially high in persons 18 to 39 years of age (relative risk = 6.8). Renal venous thrombosis is a possible complication of nephrotic syndrome, but was uncommon in this case series. Membranous nephropathy and serum albumin levels less than 2.0 to 2.5 g per dL (20 to 25 g per L) seem to confer an increased risk of DVT. Arterial thrombotic complications can occur, but are rare.9

Infection is also a possible complication of nephrotic syndrome; however, this risk appears primarily in children and in persons who have relapses of nephrotic syndrome or who require longer-term corticosteroid therapy.1 Invasive bacterial infections, especially cellulitis, peritonitis, and sepsis, are the most common infections attributable to nephrotic syndrome. The mechanisms of infection are unclear, but may relate to the degree of edema, loss of serum IgG with overall proteinuria, effects of corticosteroid therapy, reduced complement or T cell function, or impaired phagocytic function.10 The risk of serious bacterial infection attributable to nephrotic syndrome in adults in the United States is unclear, but seems low.

Acute renal failure is a rare, spontaneous complication of nephrotic syndrome. Although older persons, children, and those with more profound edema and proteinuria are at highest risk, there are many possible causes or contributing factors to acute renal failure in this setting. Excessive diuresis, therapeutic drug complications, sepsis, renal venous thrombosis, renal interstitial edema, and marked hypotension may cause or contribute to acute renal failure.12

**Diagnostic Evaluation**

Typical clinical and laboratory features of nephrotic syndrome are sufficient to establish the diagnosis of nephrotic syndrome. The diagnostic evaluation focuses on identification of an underlying cause and on the role of renal biopsy. However, there are no published practice guidelines available about the diagnostic evaluation of persons with nephrotic syndrome.1

Initial investigation should include history, physical examination, and a serum chemistry panel. Given the large number of potential causes of nephrotic syndrome and the relatively nonspecific aspect of therapy, the diagnostic evaluation should be guided by clinical suspicion for specific disorders, rather than a broad or unguided approach to ruling out multiple illnesses. **Table 3** lists selected diagnostic studies for some common secondary conditions.2

### Table 2. Common Secondary Causes of Nephrotic Syndrome

<table>
<thead>
<tr>
<th>Cause</th>
<th>Key features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Glucosuria, hyperglycemia, polyuria</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Anemia, arthralgias, autoantibodies, photosensitivity, pericardial or pleural effusion, rash</td>
</tr>
<tr>
<td>Hepatitis B or C</td>
<td>Elevated transaminases; high-risk sexual activity, history of transfusion, intravenous drug use, or other risk factors for disease transmission</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Causes minimal change disease</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Cardiomyopathy, hepatomegaly, peripheral neuropathy</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Abnormal urine protein electrophoresis, back pain, renal insufficiency</td>
</tr>
<tr>
<td>HIV</td>
<td>Pathologically similar to focal segmental glomerulosclerosis; risk factors for HIV transmission, possible reduced CD4 cell count</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Edema and proteinuria during pregnancy; elevated blood pressure</td>
</tr>
</tbody>
</table>

**NOTE:** Causes are in approximate order of most to least common. HIV = human immunodeficiency virus. Information from reference 3.
causes of nephrotic syndrome, as well as baseline evaluations that should be obtained in all persons with nephrotic syndrome.

Imaging studies are generally not helpful in assessing persons with nephrotic syndrome. Renal ultrasonography may identify renal venous thrombosis if suggestive features, such as flank pain, hematuria, or acute renal failure, are present.

Renal biopsy is often recommended in persons with nephrotic syndrome to establish the pathologic subtype of the disease, to assess disease activity, or to confirm the diagnosis of diseases, such as amyloidosis or systemic lupus erythematosus. There are, however, no clear guidelines on when renal biopsy is indicated or whether it is needed in all persons with nephrotic syndrome. For example, in diabetic nephropathy, the leading cause of secondary nephrotic syndrome, renal biopsy may not be necessary if the patient has enlarged kidneys, a bland urinary sediment without cellular casts, or other evidence of microvascular disease, such as proliferative retinopathy or peripheral neuropathy. Although renal biopsy is often recommended to assess the likelihood that nephrotic syndrome will respond to corticosteroid treatment, there are no biopsy findings that accurately predict corticosteroid responsiveness. No recent studies have elucidated the true benefit of renal biopsy in guiding management; the best available evidence is from a prospective study in which the results of renal biopsy changed management in 24 of 28 persons with nephrotic syndrome, primarily through the addition of corticosteroid treatment, although the actual patient benefit is unknown. In most cases, family physicians should consult specialists in renal medicine about the need for renal biopsy in individual patients.

Management

There are no clinical guidelines and few high-quality studies on the management of nephrotic syndrome in adults. Recommendations are based primarily on early case series, other observational studies, and expert opinion.

FLUID AND NUTRITION

Creating a negative sodium balance will help reduce edema, presumably as the underlying illness is treated or as renal inflammation slowly resolves. Patients should limit their sodium intake to 3 g per day, and may need to restrict fluid intake (to less than approximately 1.5 L per day).

DIURETICS

Diuretics are the mainstay of medical management; however, there is no evidence to guide drug selection or dosage. Based on expert opinion, diuresis should aim for a target weight loss of 1 to 2 lb (0.5 to 1 kg) per day to avoid acute renal failure or electrolyte disorders. Loop diuretics, such as furosemide (Lasix) or bumetanide, are most commonly used. Large doses (e.g., 80 to 120 mg of furosemide) are often required, and these drugs typically must be given intravenously because of the poor absorption of oral drugs caused by intestinal edema. Low serum albumin levels also limit diuretic effectiveness and necessitate higher doses. Thiazide diuretics, potassium-sparing diuretics, or

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**Table 3. Diagnostic Evaluation in Persons with Nephrotic Syndrome**

<table>
<thead>
<tr>
<th>Diagnostic studies</th>
<th>Disorder suggested</th>
</tr>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
</tr>
<tr>
<td>Patient history</td>
<td>Identify medication or toxin exposure;</td>
</tr>
<tr>
<td></td>
<td>risk factors for HIV or viral hepatitis; and</td>
</tr>
<tr>
<td></td>
<td>symptoms suggesting other causes of edema</td>
</tr>
<tr>
<td>Urine dipstick</td>
<td>Confirm proteinuria</td>
</tr>
<tr>
<td>Random urine protein/creatinine ratio</td>
<td>Quantify degree of proteinuria (ratio greater</td>
</tr>
<tr>
<td></td>
<td>than 3 to 3.5)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Rule out acute renal failure, assess glomerular</td>
</tr>
<tr>
<td></td>
<td>filtration rate</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Assess degree of hypoalbuminemia</td>
</tr>
<tr>
<td>Lipid panel</td>
<td>Assess degree of hyperlipidemia</td>
</tr>
<tr>
<td><strong>Additional studies suggested by patient factors</strong></td>
<td></td>
</tr>
<tr>
<td>HIV screening test</td>
<td>Identify HIV</td>
</tr>
<tr>
<td>Hepatitis serology panel</td>
<td>Identify hepatitis B or C</td>
</tr>
<tr>
<td>Serum or urine protein electrophoresis</td>
<td>Suggests amyloidosis or multiple myeloma</td>
</tr>
<tr>
<td>Rapid plasma reagin</td>
<td>Identify syphilis</td>
</tr>
<tr>
<td>Antinuclear antibodies or complement (C3 and C4) levels</td>
<td>Identify systemic lupus erythematosus; complement levels may also be reduced in membranoproliferative disease</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus.
metolazone (Zaroxolyn) may be useful as adjunctive or synergistic diuretics.14

ACE INHIBITORS
Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce proteinuria and reduce the risk of progression to renal disease in persons with nephrotic syndrome.15,16 One study found no improvement in response when corticosteroid treatment was added to treatment with ACE inhibitors.17 The recommended dosage is unclear, and enalapril (Vasotec) dosages from 2.5 to 20 mg per day were used. Most persons with nephrotic syndrome should be started on ACE inhibitor treatment to reduce proteinuria, regardless of blood pressure.

ALBUMIN
Intravenous albumin has been proposed to aid diuresis, because edema may be caused by hypoalbuminemia and resulting oncotic pressures. However, there is no evidence to indicate benefit from treatment with albumin,18 and adverse effects, such as hypertension or pulmonary edema, as well as high cost, limit its use.

CORTICOSTEROIDS
Treatment with corticosteroids remains controversial in the management of nephrotic syndrome in adults. It has no proven benefit, but is recommended in some persons who do not respond to conservative treatment.19,20 Treatment of children with nephrotic syndrome is different, and it is more clearly established that children respond well to corticosteroid treatment.21 Classically, minimal change disease responds better to corticosteroids than FSGS; however, this difference is found primarily in children with nephrotic syndrome. One older study found that corticosteroid treatment improved proteinuria and renal function in persons with minimal change disease, but not membranous nephropathy or proliferative glomerulonephritis.22 Another small older study found that persons with less severe glomerular changes responded well to corticosteroids.23 One case series in black persons with FSGS found no benefit from corticosteroid treatment.19 Two Cochrane reviews on the treatment of nephrotic syndrome in adults found no benefit for mortality or need for dialysis with corticosteroid therapy for membranous nephropathy or minimal change disease, but found a weak benefit for disease remission and proteinuria in persons with membranous nephropathy.20,24 However, the findings for minimal change disease were based on only one randomized trial, and the role of corticosteroid treatment remains unclear. Many experts recommend the use of corticosteroids, particularly for persons with minimal change disease; however, adverse effects from corticosteroids often lead to discontinuation.

Family physicians should discuss with patients and consulting nephrologists whether treatment with corticosteroids is advisable, weighing the uncertain benefits and possibility of adverse effects. Alkylating agents (e.g., cyclophosphamide [Cytoxan]) also have weak evidence for improving disease remission and reducing proteinuria, but may be considered for persons with severe or resistant disease who do not respond to corticosteroids.

LIPID-LOWERING TREATMENT
A Cochrane review is underway to investigate the benefits and harms of lipid-lowering agents in nephrotic syndrome.25 Some evidence suggests an increased risk of atherogenesis or myocardial infarction in persons with nephrotic syndrome, possibly related to increased lipid levels.25 However, the role of treatment for increased lipids is unknown and, at present, the decision to start lipid-lowering therapy in persons with nephrotic syndrome should be made on the same basis as in other patients.

ANTIBIOTICS
There are no data from prospective clinical trials about treatment and prevention of infection in adults with nephrotic syndrome. Given the uncertain risks of infection in adults with nephrotic syndrome in the United States, there are currently no indications for antibiotics or other interventions to prevent infection in this population. Persons who are appropriate candidates should receive pneumococcal vaccination.
Nephrotic Syndrome

ANTICOAGULATION THERAPY

There are currently no recommendations for prophylactic anticoagulation to prevent thromboembolic events in persons with nephrotic syndrome who have not had previous thrombotic events and, if it is diagnosed, these events should be treated as in other patients. Persons who are otherwise at high risk of thromboembolism (e.g., based on previous events, known coagulopathy) should be considered for prophylactic anticoagulation while they have active nephrotic syndrome.

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REFERENCES