Nephrotic Syndrome

Background

Nephrotic-range proteinuria is the loss of 3 grams or more per day of protein into the urine or on a single spot urine collection, the presence of 2 g of protein per gram of urine creatinine. Nephrotic syndrome is the combination of nephrotic-range proteinuria with a low serum albumin level and edema.

Nephrotic syndrome has many causes, including primary kidney diseases such as minimal-change nephropathy, focal glomerulosclerosis, and membranous nephropathy. Nephrotic syndrome can also result from systemic diseases that affect other organs in addition to the kidneys, such as diabetes, amyloidosis, and lupus erythematosus.

Nephrotic syndrome may affect adults and children of both sexes and of any race. It may occur in typical form, or in association with nephritic syndrome. The latter connotes glomerular inflammation, with hematuria and impaired kidney function.

Classification

Nephrotic syndrome can be primary, being a disease specific to the kidneys, or it can be secondary, being a renal manifestation of a systemic general illness. In all cases, injury to glomeruli is an essential feature. Kidney diseases that affect tubules and interstitium, such as interstitial nephritis, will not cause nephrotic syndrome.

Primary causes of nephrotic syndrome include the following, in approximate order of frequency:

- Minimal-change nephropathy
- Focal glomerulosclerosis
- Membranous nephropathy
- Hereditary nephropathies

Secondary causes include the following, again in order of approximate frequency:

- Diabetes mellitus
- Lupus erythematosus
- Viral infections (e.g., hepatitis B, hepatitis C, human immunodeficiency virus [HIV])
- Amyloidosis and paraproteinemias
- Preeclampsia
- Allo-antibodies from enzyme replacement therapy

Nephrotic-range proteinuria may occur in other kidney diseases, such as IgA nephropathy. In that common glomerular disease, one third of patients may have nephrotic-range proteinuria.[1]

Nephrotic syndrome may occur in persons with sickle cell disease and evolve to renal failure. Membranous nephropathy may complicate bone marrow transplantation, in association with graft versus host disease.

From a therapeutic perspective, nephrotic syndrome may be classified as steroid sensitive, steroid resistant, steroid dependent, or frequently relapsing.

The above causes of nephrotic syndrome are largely those for adults, and this article will concentrate primarily on adult nephrotic syndrome. However, nephrotic syndrome in infancy and childhood is an important entity. For discussion of this topic, see Pediatric Nephrotic Syndrome.

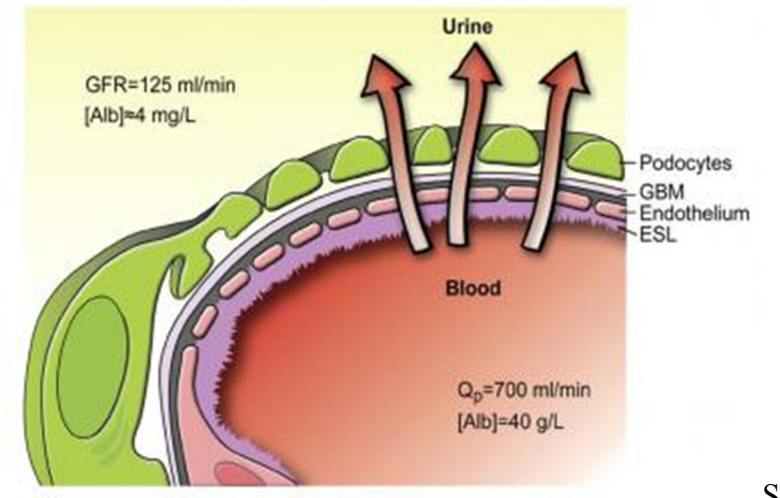
Pathophysiology

In a healthy individual, less than 0.1% of plasma albumin may traverse the glomerular filtration barrier.[2] Controversy exists regarding the sieving of albumin across the glomerular permeability barrier. On the basis of studies in experimental animals, it has been proposed that ongoing albumin passage into the urine occurs in many grams per day, with equivalent substantial tubular uptake of albumin, the result being that the urine contains 80 mg or less of albumin per day.[3]

However, studies of humans with tubular transport defects suggest that the glomerular urinary space albumin concentration is 3.5 mg/L.[4] At this concentration, and a normal daily glomerular filtration rate (GFR) of 150 liters, one would expect at most 525 mg per day of albumin in the final urine. In health, urine albumin is

less than 50 mg/day, because most of the filtered albumin is re-absorbed by the tubules. Amounts above 500 mg/day point to glomerular disease.

The glomerular capillaries are lined by a fenestrated endothelium that sits on the glomerular basement membrane, which in turn is covered by glomerular epithelium, or podocytes, which envelops the capillaries with cellular extensions called foot processes. In between the foot processes are the filtration slits. These three structures—the fenestrated endothelium, glomerular basement membrane, and glomerular epithelium—are the glomerular filtration barrier. A schematic drawing of the glomerular barrier is provided in the image below.



Schematic drawing of the glomerular barrier. Podo = podocytes; GBM = glomerular basement membrane; Endo = fenestrated endothelial cells; ESL = endothelial cell surface layer (often referred to as the glycocalyx).

Primary urine is formed through the filtration of plasma fluid across the glomerular barrier (arrows); in humans, the glomerular filtration rate (GFR) is 125 mL/min. The plasma flow rate (Qp) is close to 700 mL/min, with the filtration fraction being 20%. The concentration of albumin in serum is 40 g/L, while the estimated concentration of albumin in primary urine is 4 mg/L, or 0.1% of its concentration in plasma. Reproduced from Haraldsson et al, Physiol Rev 88: 451-487, 2008, and by permission of the American Physiological Society (www.the-aps.org).

Filtration of plasma water and solutes is extracellular and occurs through the endothelial fenestrae and filtration slits. The importance of the podocytes and the filtration slits is shown by genetic diseases. In congenital nephrotic syndrome of the Finnish type, the gene for nephrin, a protein of the filtration slit, is mutated, leading to nephrotic syndrome in infancy. Similarly, podocin, a protein of the podocytes, may be abnormal in a number of children with steroid-resistant focal glomerulosclerosis.

The glomerular structural changes that may cause proteinuria are damage to the endothelial surface, the glomerular basement membrane, or the podocytes. One or more of these mechanisms may be seen in any one type of nephrotic syndrome. Albuminuria alone may occur or, with greater injury, leakage of all plasma proteins (ie, proteinuria) may take place.

Proteinuria that is more than 85% albumin is selective proteinuria. Albumin has a net negative charge, and it is proposed that loss of glomerular membrane negative charges could be important in causing albuminuria. Nonselective proteinuria, being a glomerular leakage of all plasma proteins, would not involve changes in glomerular net charge but rather a generalized defect in permeability. This construct does not permit clear-cut separation of causes of proteinuria, except in minimal-change nephropathy, in which proteinuria is selective.

Pathogenesis of edema

There are two current hypotheses for the formation of edema in nephrotic syndrome. The *underfill* hypothesis holds that the loss of albumin leading to lower plasma colloid pressure is the cause. The *overfill* hypothesis states that the edema is due to primary renal sodium retention.

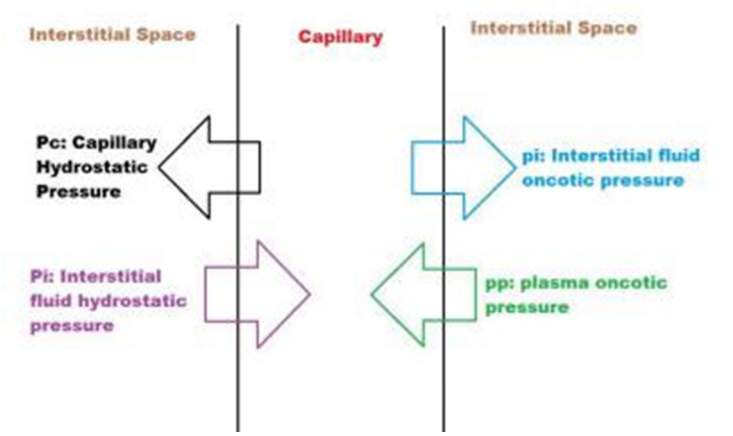
Underfill hypothesis

An increase in glomerular permeability leads to albuminuria and eventually to hypoalbuminemia. In turn, hypoalbuminemia lowers the plasma colloid osmotic pressure, causing greater transcapillary filtration of water throughout the body and thus the development of edema.

Capillary hydrostatic pressure and the gradient of plasma to interstitial fluid oncotic pressure determine the movement of fluid from the vascular compartment to the interstitium. The oncotic pressure is mainly determined by the protein content. The flux of water across the capillary wall can be expressed by the following formula:

$Qw = K ([P_c - pp] - [P_i - pi]$

In this formula, Q_w is net flux of water, K is the capillary filtration coefficient, P_c is capillary hydrostatic pressure, and pp is the plasma oncotic pressure, while P_i is the interstitial fluid hydrostatic pressure and pi is the interstitial fluid oncotic pressure, shown schematically below.



Forces determining capillary filtration

With a high enough capillary hydrostatic pressure or a low enough intravascular oncotic pressure, the amount of fluid filtered exceeds the maximal lymphatic flow, and edema occurs. In patients with nephrotic syndrome, this causes a reduction in plasma volume, with a secondary increase of sodium and water retention by the kidneys.

Overfill Hypothesis

An alternative hypothesis is an intrinsic defect in the renal tubules which cause a decrease in sodium excretion. This could occur if the filtered intraluminal protein directly stimulated renal epithelial sodium reabsorption.[5] Two facts support this hypothesis: (1) sodium retention is observed even before the serum albumin level starts falling, and (2) intravascular volume is normal or even increased in most patients with nephrotic syndrome.

A third possible mechanism is an enhanced peripheral capillary permeability to albumin, as shown by radioisotopic technique in human studies of 60 patients with nephrotic syndrome.[6] This would then lead to increased tissue oncotic pressure and fluid retention in the peripheral tissues.

Metabolic consequences of proteinuria

Metabolic consequences of the nephrotic syndrome include the following:

- Infection
- Hyperlipidemia and atherosclerosis
- Hypocalcemia and bone abnormalities
- Hypercoagulability
- Hypovolemia

Acute kidney injury may indicate an underlying glomerulonephritis but is more often precipitated by hypovolemia or sepsis. Edema of the kidneys that causes a pressure-mediated reduction in the GFR has also been proposed.

Additional consequences include the following:

- Hypertension related to fluid retention and reduced kidney function may occur
- Edema of the gut may cause defective absorption, leading to malnutrition
- Ascites and pleural effusions may develop

Infection

Infection is a major concern in nephrotic syndrome. Both gram positive and gram negative bacterial infect. Varicella infection is also common. The most common infectious complications are bacterial sepsis, cellulitis, pneumonia, and peritonitis.

Proposed explanations for the increased infection risk include the following:

- Urinary immunoglobulin losses
- Edema fluid acting as a culture medium
- Protein deficiency
- Decreased bactericidal activity of the leukocytes
- Immunosuppressive therapy
- Decreased perfusion of the spleen caused by hypovolemia
- Urinary loss of a complement factor (properdin factor B) that opsonizes certain bacteria

Hyperlipidemia and atherosclerosis

Hyperlipidemia is a classic feature of the nephrotic syndrome, rather than a mere complication. It is related to the hypoproteinemia and low serum oncotic pressure of nephrotic syndrome, which then leads to reactive hepatic protein synthesis, including of lipoproteins.[7] In addition, reduced plasma levels of lipoprotein lipase results in diminution of lipid catabolism. Some of the elevated serum lipoproteins are filtered at the glomeruli, leading to lipiduria and the classic findings of oval fat bodies and fatty casts in the urine sediment.

Atherosclerotic vascular disease appears to occur in greater frequency in persons with nephrotic syndrome than in healthy persons of the same age. Curry and Roberts showed that the frequency and extent of coronary artery stenoses were greater in patients with nephrotic syndrome than in non-nephrotic control subjects.[8]

When their study was published, in 1977, lipid-lowering treatments were less widely used than they are today. Accordingly, the average highest serum total cholesterol in this series was over 400 mg/dL. That is in the range of serum cholesterol seen in familial hypercholesterolemia, a disease that predisposes individuals to myocardial infarction.

Hypocalcemia

Hypocalcemia is common in the nephrotic syndrome, but rather than being a true hypocalcemia, it is usually caused by a low serum albumin level. Nonetheless, low bone density and abnormal bone histology are reported in association with nephrotic syndrome. This could be caused by urinary losses of vitamin D–binding proteins, with consequent hypovitaminosis D and, as a result, reduced intestinal calcium absorption.[9]

Tessitore et al reported that when the GFR was normal, persons with the nephrotic syndrome had no consistent calcium or bony abnormalities.[10] Yet in that same study, when the GFR was reduced, bone mineralization defects were found by biopsy. A later study found osteomalacia on bone biopsy in over half of adults who had longstanding nephrotic syndrome but whose GFR was preserved.[9]

Low bone mass may be found in relation to cumulative steroid dose.[11] However, intermittent corticosteroid treatment of childhood steroid-sensitive nephrotic syndrome was not associated with bone mineral deficits in one study.[12] It is possible that long duration of either the nephrotic syndrome or treatments for it are the important risk factors for bone disease in these patients.

Hypercoagulability

Venous thrombosis and pulmonary embolism are well-known complications of the nephrotic syndrome. Hypercoagulability in these cases appears to derive from urinary loss of anticoagulant proteins, such as antithrombin III and plasminogen, along with the simultaneous increase in clotting factors, especially factors I, VII, VIII, and X.

A study by Mahmoodi et al of almost 300 patients with nephrotic syndrome confirmed that the annual incidence of venous thromboembolism (VTE) was almost 10 times higher in these persons than in the normal population (1% vs 0.1 to 0.2%).[13] Moreover, that risk appeared especially elevated during the first 6 months of nephrotic syndrome, being at almost 10%. This high incidence may justify the routine use of preventive anticoagulation treatment during the first 6 months of a persistent nephrotic syndrome.

Mahmoodi et al's study also showed an increased risk of arterial thrombotic events in subjects with nephrotic syndrome, including coronary and cerebrovascular ones. Unlike the risk of VTE, which was related to proteinuria, this arterial risk was related to usual risk factors for arterial disease, such as hypertension, diabetes, smoking, and reduced GFR.

Hypovolemia

Hypovolemia occurs when hypoalbuminemia decreases the plasma oncotic pressure, resulting in a loss of plasma water into the interstitium and causing a decrease in circulating blood volume. Hypovolemia is generally observed only when the patient's serum albumin level is less than 1.5 g/dL. Symptoms include vomiting, abdominal pain, and diarrhea. The signs include cold hands and feet, delayed capillary filling, oliguria, and tachycardia. Hypotension is a late feature.

Etiology

Common primary causes of nephrotic syndrome include kidney diseases such as minimal-change nephropathy, membranous nephropathy, and focal glomerulosclerosis. Secondary causes include systemic diseases such as diabetes mellitus, lupus erythematosus, and amyloidosis. Congenital and hereditary focal glomerulosclerosis may result from mutations of genes that code for podocyte proteins, including nephrin, podocin, or the cation channel 6 protein. Nephrotic syndrome can result from drugs of abuse, such as heroin.

The proposed mechanisms of membranous nephropathy are as follows:

1. Immune complex deposition from the circulation
2. In-situ formation of immune complexes through the reaction of circulating autoantibodies to a native antigen
3. In-situ formation of immune complexes with a non-native (extrinsic) antigen that is bound to the podocytes or glomerular basement membrane

The first mechanism could explain the secondary membranous nephropathy of systemic lupus erythematosus.

The second mechanism appears to explain 70% of idiopathic membranous nephropathy. M-type phospholipase A2 receptor (PLA2R) antibodies are found in about 70% of patients who have idiopathic membranous glomerular nephropathy.[14] These IgG antibodies are found both circulating in the plasma and deposited on the glomerular basement membranes.

The third mechanism may explain the rare occurrence of nephrotic syndrome in subjects treated with enzyme replacement therapy for genetic enzyme deficiency diseases such as Pompe or Fabry disease[15, 16] This may result from allo-antibodies to the infused enzyme that are deposited on the glomerular basement membrane, with ensuing secondary membranous nephropathy.

Nephrotic-range proteinuria occurring in the third trimester of pregnancy is the classical finding of preeclampsia. It may occur de novo or it may be superimposed on another chronic kidney disease. In the latter case, the patient will have had preexisting proteinuria that worsened during pregnancy.

Medication can cause nephrotic syndrome. This includes the very infrequent occurrence of minimal-change nephropathy with use of nonsteroidal anti-inflammatory drugs (NSAIDs), and the occurrence of membranous nephropathy with use of gold and penicillamine, which are older drugs used for rheumatic diseases. Focal glomerulosclerosis can occur in association with intravenous bisphosphonates. Lithium and interferon therapy have been associated with focal glomerulosclerosis of the collapsing type.

Nephrotic-range proteinuria could occur with the use of anticancer agents, such as bevacizumab, that inhibit vascular endothelial growth factor (VEGF).[17] However, the clinical picture of this complication is of a thrombotic microangiopathy rather than of nephrotic syndrome per se.

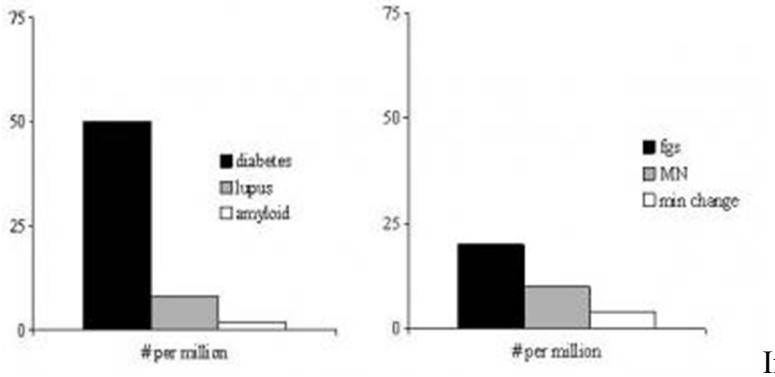
The association of membranous nephropathy with cancer is a clinical dilemma. This association presumably results from immune complex injury to the glomeruli caused by cancer antigens. While about 6000 new cases of membranous nephropathy occur each year in the United States, 1.5 million new cases of non-skin cancer are diagnosed. Therefore, from the oncologist’s standpoint, the problem of paraneoplastic membranous nephropathy is trivial. However, a carefully performed analysis from France suggested that the cancer rate is

approximately 10-fold higher in persons with membranous nephropathy than in the general population, especially in individuals over age 65 years.[18] In that study, 50% of membranous nephropathy cases were diagnosed before the diagnosis of cancer. Thus, in some patients with membranous nephropathy one should consider the possibility of an undiagnosed cancer.

Epidemiology

United States statistics

The figure below shows the incidence per million population of important causes of nephrotic syndrome. Diabetic nephropathy with nephrotic syndrome is most common, at an estimated rate of at least 50 cases per million population. In children, nephrotic syndrome may occur at a rate of 20 cases per million children.[19]



Incidence of important causes of nephrotic syndrome, in number per million population. The left panel shows systemic causes, and the right panel lists primary renal diseases that can cause nephrotic syndrome. fgs = focal glomerulosclerosis, MN = membranous nephropathy, min change = minimal-change nephropathy. Data are in part from Swaminathan et al and Bergesio et al.

International statistics

Biopsy studies in children with nephrotic syndrome have shown similar types of histology in India and Turkey, compared with what one would expect in Western countries.[20, 21] In Pakistani adults with nephrotic syndrome, the spectrum of histologies of kidney biopsies is similar to that seen in western countries.[22]

In parts of Africa and the Middle East (eg, Egypt), glomerular disease may be associated with urogenital schistosomal infection.[23] However, so-called tropical nephrotic syndrome from parasitic diseases such as schistosomiasis or malaria may not be a true entity.

Doe et al reviewed causes of nephrotic syndrome in African children; kidney biopsy most often showed typical histologic findings (focal and segmental glomerulosclerosis and minimal change disease).[24]

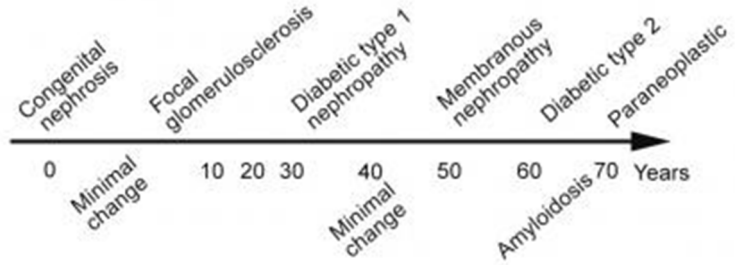
The connection of nephrotic syndrome to quartan malaria is not well-established. Indeed, Pakasa and Sumaili call attention to the apparent decline of parasite-associated nephrotic syndrome in the Congo.[25, 26] It is possible that the perceived association between nephrotic syndrome and parasitic infections was coincidental, as supported by the ongoing and probably increasing occurrence of chronic kidney disease in the Congo.[26]

Race-, sex-, and age-related demographics

Because diabetes is major cause of nephrotic syndrome, American Indians, Hispanics, and African Americans have a higher incidence of nephrotic syndrome than do white persons. HIV nephropathy is a complication of HIV infection that is unusual in whites; it is seen with greater frequency in African Americans, because of their much greater prevalence of the ApoL1 risk alleles.[27] Focal glomerulosclerosis appears to be overrepresented as a cause of nephrotic syndrome in African-American as compared with white children.[28]

There is a male predominance in the occurrence of nephrotic syndrome, as for chronic kidney disease in general. This male overrepresentation is also seen in paraneoplastic membranous nephropathy.[18] But lupus nephritis affects mostly women.

The image below shows typical ages at which a given cause of nephrotic syndrome may occur. It does not show every possible cause of nephrotic syndrome, such as lupus nephritis, which typically affects young black women. The ages shown are averages.



A schema of the average patient age at presentation in various common forms of nephrotic syndrome. (Timeline not to scale.)

Prognosis

In the pre-antibiotic era, infection was a major factor in the mortality rate among patients with nephrotic syndrome.[29] Treatments for nephrotic syndrome and its complications have reduced the morbidity and mortality once associated with the syndrome. Currently, the prognosis for patients with primary nephrotic syndrome depends on its cause.

Infants with congenital nephrotic syndrome have a dismal prognosis: survival beyond several months is possible only with dialysis and kidney transplantation.

Only approximately 20% of patients with focal glomerulosclerosis undergo remission of proteinuria; an additional 10% improve but remain proteinuric. Many patients experience frequent relapses, become steroid-dependent, or become steroid-resistant. End-stage renal disease (ESRD) develops in 25-30% of patients with focal segmental glomerulosclerosis by 5 years and in 30-40% of these patients by 10 years.

The prognosis for patients with minimal-change nephropathy is very good. Most children respond to steroid therapy; still, about 50% of children have one or two relapses within 5 years and approximately 20% of them continue to relapse 10 years after diagnosis. Only 30% of children never have a relapse after the initial episode. Approximately 3% of patients who initially respond to steroids become steroid-resistant.

Adults with minimal-change nephropathy have a burden of relapse similar to that of children. However, the long-term prognosis for kidney function in patients with this disease is excellent, with little risk of renal failure.

Analysis of 441 adult and pediatric patients by the Nephrotic Syndrome Study Network (NEPTUNE) found that complete remission of proteinuria occurred in 45% of cases, while 5% progressed to ESRD. The following were inversely associated with complete remission of proteinuria[30]:

- Higher pre-biopsy proteinuria level.
- Pathology diagnosis of focal segmental glomerulosclerosis [FSGS] versus minimal-change disease

Poor patient response to steroid therapy may predict a poor outcome. Children who present with hematuria and hypertension are more likely to be steroid-resistant and have a poorer prognosis than those without hematuria or hypertension. In a retrospective study of pediatric patients with steroid-resistant nephrotic syndrome, 13 of 16 patients achieved remission with calcineurin inhibitor therapy. However, three of the 13 experienced recurrences and progressed to ESRD.[31]

Donadio et al reported 140 patients with idiopathic membranous nephropathy, 89 of whom received no treatment with corticosteroids or immunosuppressive drugs and 51 of whom were treated primarily with short-term courses of prednisone alone, and found that survival rates in these patients were the same as those expected for the general population.[32]

The prognosis may worsen because of (1) an increased incidence of renal failure and the complications secondary to nephrotic syndrome, including thrombotic episodes and infection, or (2) treatment-related conditions, such as infectious complications of immunosuppressive drug therapy.

In secondary nephrotic syndromes, morbidity and mortality are related to the primary disease process (eg, diabetes, lupus, amyloidosis). In diabetic nephropathy, however, the magnitude of proteinuria itself relates directly to mortality.[33]

In diabetic nephropathy with nephrotic syndrome, patients usually have a good response to angiotensin blockade, with reduction of proteinuria and some slowing of the loss of renal function. True remission is uncommon, however. Cardiovascular morbidity and mortality increase as kidney function declines, and some patients will eventually need dialysis or a kidney transplant.

In primary amyloidosis, prognosis is not good, even with intensive chemotherapy. In secondary amyloidosis, remission of the underlying cause, such as rheumatoid arthritis, is followed by remission of the amyloidosis and its associated nephrotic syndrome.

Patient Education

Pediatric nephrotic syndrome is a chronic illness characterized by relapses and remissions, which can extend throughout childhood. There will be illness from the disease and from its treatment. Parents may monitor their child's urine and record the results in a diary. The diary can also be used to write down an agreed-upon plan for the management of relapses. Information booklets should be given to the family. Peer support and psychological counseling may be helpful.

Nephrotic syndrome in adults can also wax and wane, with the complications as reviewed above.

Progression to renal failure will require preparation for dialysis and/or kidney transplantation.

History

The first sign of nephrotic syndrome in children is usually swelling of the face; this is followed by swelling of the entire body. Adults can present with dependent edema. Foamy urine may be a presenting feature. A thrombotic complication, such as deep venous thrombosis of the calf veins or even a pulmonary embolus, may be the first clue to nephrotic syndrome.

Additional historical features can be related to the cause of nephrotic syndrome. Thus, the recent start of a nonsteroidal anti-inflammatory drug (NSAID) suggests such drugs as the cause and a more than 10-year history of diabetes with symptomatic neuropathy indicates diabetic nephropathy.

Physical Examination

Edema is the salient feature of nephrotic syndrome and initially develops around the eyes and legs. With time, the edema becomes generalized and may be associated with an increase in weight, the development of ascites, or pleural effusions.

Hematuria and hypertension manifest in a minority of patients.

Additional features on exam will vary according to cause and as a result of whether or not renal function impairment exists. Thus, in the case of longstanding diabetes, the patient may have diabetic retinopathy, which correlates closely with diabetic nephropathy. If the kidney function is reduced, the patient may have hypertension, anemia, or both.

Approach Considerations

Diagnostic studies for nephrotic syndrome may include the following:

- Urinalysis
- Urine sediment examination
- Urinary protein measurement
- Serum albumin
- Serologic studies for infection and immune abnormalities
- Renal ultrasonography
- Renal biopsy

In infants with nephrotic syndrome, genetic testing for the *NPHS1* and *NPHS2*mutations may be useful. These are mutations of nephrin and podocin, respectively. In children with steroid-resistant nephrotic syndrome, testing for the*NPHS2* mutation may be indicated.

In the future, novel urinary biomarkers may become available that can identify the cause and severity of nephrotic syndrome.[34] See Novel Biomarkers of Renal Function.

Urine Studies

Urinalysis

Urinalysis is the first test used in the diagnosis of nephrotic syndrome. Nephrotic-range proteinuria will be apparent by 3+ or 4+ readings on the dipstick, or by semiquantitative testing by sulfosalicylic acid. A 3+ reading represents 300 mg/dL of urinary protein or more, which correlates with a daily loss of 3 g or more and thus is in the nephrotic range. The chemistry of the dipsticks is such that albumin is the major protein that is tested.

Glucosuria points to diabetes.

Urine sediment examination

The urine sediment exam may show cells and/or casts.

Waxy casts mark proteinuric renal disease. By use of a polarizing microscope, one can see oval fat bodies and also fatty casts. These point to the nephrotic syndrome. They occur because of glomerular filtration of lipoproteins; the tubular cells that endocytose these lipoproteins then fall off into the urine. Viewed by polarizer, the oval fat bodies and fatty casts cause a "Maltese cross" appearance.

The presence of more than 2 red blood cells (RBCs) per high power field is indicative of microhematuria. Microhematuria may occur in membranous nephropathy but not in minimal-change nephropathy.

Glomerular disease may allow RBCs to traverse the damaged glomerular basement membrane, and the RBCs in the sediment may then be deformed, or dysmorphic. This points to glomerular disease with inflammation and destruction of the normal structures (ie, a nephritis, and thus a nephritic picture, with hematuria, oliguria, azotemia, and hypertension). This could occur in, for example, nephrotic syndromes associated with IgA nephropathy or proliferative glomerulonephritis.

More than 2 granular casts in the entire sediment is a biomarker for renal parenchymal disease. Variable-caliber and broad granular casts point to reduced renal function.

Urinary protein measurement

Urinary protein is measured by a timed collection or a single spot collection.[35] A timed collection is typically done over a 24-hour period, starting at 7 am and finishing the next day at the same time. In healthy individuals, less than 150 mg of total protein is present in a 24-hour urine collection.

A single spot urine collection is much easier to obtain. When the ratio of urine protein to urine creatinine is greater than 2 g/g, this corresponds to 3 g of urinary protein per day or more.

The exact type of urine protein is of potential interest. This can be tested by urine protein electrophoresis. Proteinuria that does not include albumin may point to overflow proteinuria that occurs in paraproteinemias, such as multiple myeloma.

There has been intermittent interest in establishing whether proteinuria is "selective" for albumin (ie, >85% albumin), as opposed to nonselective. In the case of selective proteinuria, a charge-selective leak of albumin across the glomerular barrier may be occurring, perhaps due to reduced negative charges on that barrier, whereas nonselective proteinurias point to more substantial glomerular injury and perhaps also predict lesser response to prednisone treatment.

Renal Biopsy

For childhood nephrotic syndrome, a renal biopsy is indicated for the following:

- Congenital nephrotic syndrome
- Children older than 8 years at onset
- Steroid resistance
- Frequent relapses or steroid dependency
- Significant nephritic manifestations

Adult nephrotic syndrome of unknown origin may require a renal biopsy for diagnosis. Reaching a pathological diagnosis is important because minimal-change disease, focal glomerulosclerosis, and

membranous nephropathy have different treatment options and prognoses. It is important to differentiate minimal-change disease presenting in adults from focal glomerulosclerosis, as the former has an excellent response to steroids. Another entity called immunoglobulin M (IgM) nephropathy falls in between the two and has an intermediate response to steroids.

A renal biopsy is not indicated in adults with nephrotic syndrome from an obvious cause. For example, in a patient with longstanding diabetes and diabetic retinopathy, the nephrotic syndrome is likely to be secondary to diabetic nephropathy, so kidney biopsy may be unnecessary. However, it is important to not assume diabetic nephropathy as the causative factor for nephrotic syndrome in all diabetic persons. A duration of diabetes of less than 5 years and the absence of retinopathy and neuropathy are clues to non-diabetic kidney disease.

It is worth noting that in clinical experience with kidney biopsies, the cause of nephrotic-range proteinuria is glomerular disease, not tubular disease. This contradicts the proposal that tubular function determines proteinuria.[3]

Laboratory Studies

Kidney function

Serum tests for kidney function are essential. Serum creatinine will be in the normal range in uncomplicated nephrotic syndrome, such as that occurring in minimal-change nephropathy. In children, the serum creatinine level will be lower than it is in adults. The normal adult serum creatinine level is approximately 1 mg/dL, whereas that of a child aged 5 years will be about 0.5 mg/dL. Values higher than this in children indicate reduced kidney function.

Serum albumin

The serum albumin level is classically low in nephrotic syndrome, being below its normal range of 3.5-4.5 g/dL. In a single-center study of patients who underwent kidney biopsy for idiopathic proteinuria, Gupta et al found that the frequency of focal and segmental glomerulosclerosis increased to three-quarters of the cases when patients had near-normal serum albumin levels.[36]

Serologic studies

In adults with nephrotic syndrome, tests for hepatitis B and C, HIV, and even syphilis may be useful. Tests for lupus, including antinuclear antibody (ANA), anti–double stranded DNA (anti-dsDNA) antibodies, and complement, may be useful. Testing for antineutrophil cytoplasmic antibodies (ANCA) is not indicated in typical nephrotic syndrome, because that test is associated with rapidly progressive glomerulonephritis, which presents with a nephritic picture rather than one that is typically nephrotic.

Tests for previous streptococcal infection, such as antistreptolysin O, are not usually indicated for nephrotic syndrome, since postinfectious glomerulonephritis usually causes a nephritic rather than a nephrotic syndrome.

Phospholipase A2 receptor

Phospholipase A_2 receptor (PLA_2 R) is a cell surface transmembrane receptor expressed on the surface of podocytes. Seventy percent of patients with idiopathic membranous nephropathy have autoantibodies directed against PLA_2 R.[37] Levels of this antibody have a strong correlation with clinical disease activity and thus help in monitoring disease activity and treatment efficacy.[38] Absence of these antibodies may suggest secondary membranous nephropathy such as that associated with cancers.

During treatment, the levels of the antibodies generally decline before remission of proteinuria. After treatment, about half the patients who are PLA_2R negative remain in remission for 5 years, but those who remain PLA_2R positive relapse in just 2 years. Use of the PLA_2R antibody test has changed the diagnosis and treatment of idiopathic membranous nephropathy.

Histologic Findings

These are particular to the causes of nephrotic syndrome, such as minimal change nephropathy, membranous nephropathy, or diabetic nephropathy, and are discussed in the Medscape Reference articles on those conditions.

Ultrasonography

Ultrasonographic scanning shows whether a patient has two kidneys. Individuals with a single kidney may be prone to developing focal glomerulosclerosis. Having only one kidney is also a relative contraindication to kidney biopsy.

Ultrasonography also demonstrates renal echogenicity. Increased renal echogenicity is consistent with intrarenal fibrosis (ie, chronic disease with reduced kidney function).

Approach Considerations

Specific treatment of nephrotic syndrome depends on its cause. These are detailed in the Medscape articles specific to each of these disorders. Treatment varies between adult and pediatric patients. Kidney Disease Improving Global Outcomes (KDIGO) issued guidelines in 2012 that include recommendations on treatment of nephrotic syndrome in adults and children.[39]

A study using the Cochrane database has put into question whether prednisone treatment is beneficial in adult minimal-change nephropathy.[40] Nevertheless, treatment is needed when the nephrotic syndrome causes illness such as uncomfortable edema or associated coagulopathy.

The role of preventive anticoagulation in nephrotic syndrome has been reported, but there is no proof that it is beneficial.

Hyperlipidemia occurs in nephrotic syndrome, and it can be controlled with lipid-lowering agents. Older studies have reported a predisposition to atherosclerosis in patients with nephrotic syndrome, but there are no data to show that lipid-lowering drugs improve renal or patient outcomes.

Specific treatment

Children

In minimal-change nephropathy, glucocorticosteroids such as prednisone are used.[41] Rituximab, an antibody against B-cells, has proved an effective steroid-sparing agent in children with steroid-dependent idiopathic nephrotic syndrome. However, children dependent on both steroids and calcineurin inhibitors are less likely to achieve drug-free remission with rituximab.[42] Rituximab may also be used in children with steroid-resistant disease.

The benefits of rituximab for nephrotic syndrome were shown in a study in 10 children and 20 adults with minimal-change disease/mesangial proliferative glomerulonephritis or focal segmental glomerulosclerosis who had suffered two or more recurrences over the previous year and were in steroid-induced remission for 1 month or longer. At 1 year after receiving one or two doses of rituximab, all patients were in remission: 18 had been fully weaned from steroids and 15 had never relapsed. In addition, rituximab halted disease-associated growth deficit in the children.[43]

A pilot study by Bonanni et al tested the new fully humanized anti-CD20 monoclonal antibody ofatumumab in four children with persistent proteinuria despite a full drug approach (including rituximab). The two patients with normal renal function experienced remission of proteinuria—transient in one patient and persistent in the other—while the two with impaired renal function failed to respond. This study used a low-dose two-infusion ofatumumab regimen (300+700 mg/1.73 m^2 2 weeks apart); the authors suggest testing whether higher doses of ofatumumab may be effective in patients with renal impairment.[44]

In a retrospective study of 64 children with steroid-dependent nephrotic syndrome and 18 children with steroid-resistant nephrotic syndrome, treatment with cyclosporine A or cyclosporine A plus mycophenolate mofetil resulted in remission in 14 of the 18 steroid-resistant patients (eight with cyclosporine A and six with combination treatment). In the steroid-dependent group, 15 patients (23%) received no medication, cyclosporine A was effective in 31 of 38 patients (82%), and mycophenolate mofetil was effective in all patients in whom cyclosporine A treatment was not successful.[45]

Adults

Minimal change nephropathy in adults should respond to prednisone.

In lupus nephritis, prednisone with cyclophosphamide or mycophenolate mofetil should induce remission.

Secondary amyloidosis with nephrotic syndrome should improve with anti-inflammatory treatment of the primary disease.

In membranous nephropathy, management with angiotensin blockade but without immunosuppression can be used for the first 6 months in patients at low risk for progression (ie, those with serum creatinine level <1.5 mg/dL and less than 4 g of proteinuria per day). Patients with renal insufficiency (serum creatinine level >1.5 mg/dL) or those with higher amounts of urine protein are at risk for loss of kidney function and should receive immunosuppressive therapy.[46] This includes regimens that combine prednisone with cyclophosphamide or chlorambucil. Mycophenolate mofetil is not helpful in membranous nephropathy. Rituximab is effective in membranous nephropathy in adults, but controlled trials are lacking.[47]

Diet and activity

The diet in patients with nephrotic syndrome should provide adequate caloric intake and adequate protein (1 g/kg/d). Supplemental dietary protein is of no proven value. A diet with no added salt will help to limit fluid overload. Fluid restriction *per se* is not needed.

There are no activity restrictions for patients with nephrotic syndrome. Ongoing activity, rather than bedrest, will reduce the risk of blood clots.

Acute Nephrotic Syndrome in Childhood

With good parental and patient education and close outpatient follow-up care, hospitalization is not usually necessary. Hospitalization should be considered if any of the following are present:

- Generalized edema severe enough to cause respiratory distress
- Tense scrotal or labial edema
- Complications such as bacterial sepsis, peritonitis, pneumonia, or thromboembolism
- Failure to thrive
- Uncertainty regarding patient or family compliance with treatment

Diuretics are needed. Furosemide (1 mg/kg/d) and spironolactone (2 mg/kg/d) will help when fluid retention is severe, provided no signs of renal failure or volume contraction are evident.

Achieving a satisfactory diuresis is difficult when the patient's serum albumin level is less than 1.5 g/dL. Albumin in a dose of 1 g/kg may be given intravenously (IV), followed by IV furosemide. Use of this approach is based on the premise that raising the serum albumin level will ‘pull’ fluid from the extravascular to the intravascular space. Albumin may also increase diuretic delivery to the kidney by keeping urosemide within the vascular space , decreasing its catabolism and facilitating its secretion into the tubular lumen.

Complications of using IV albumin may occur, including pulmonary edema.

Some evidence suggests that administration of albumin may delay the response to steroids and may even induce more frequent relapses, probably by causing severe glomerular epithelial damage. Fluid removal and weight loss remain transient unless proteinuria remits.

To prevent infection, oral penicillin can be prescribed for children with gross edema. Abdominal paracentesis should be performed if the patient develops signs of peritonitis, and any bacterial infection should be treated promptly. A non-immune patient with varicella should get immunoglobulin therapy if exposed to chickenpox, and acyclovir should be given if the patient develops chickenpox.

Depending on the cause of nephrotic syndrome, a patient may need specialty consultation. For example, an individual with lupus nephritis will benefit from rheumatologic consultation.

Acute Nephrotic Syndrome in Adults

The principles for management of adults with acute nephrotic syndrome are similar to those for children. Diuretics will be needed; furosemide, spironolactone, and even metolazone may be used. Volume depletion may occur with diuretic use, which should be monitored by assessment of symptoms, weight, pulse, and blood pressure.

Anticoagulation has been advocated for use in preventing thromboembolic complications, but its use in primary prevention is unproven.

Hypolipidemic agents may be used, but if the nephrotic syndrome cannot be controlled, the patient will have persistent hyperlipidemia.

In secondary nephrotic syndrome, such as that associated with diabetic nephropathy, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers are widely used. These may reduce proteinuria by reducing the systemic blood pressure, by reducing intraglomerular pressure, and also by direct action on podocytes.

Long-Term Monitoring

Ongoing use and adjustment of diuretics and angiotensin antagonists are done according to the amount of edema and proteinuria that a patient has.

Follow-up care in patients with nephrotic syndrome also includes immunizations, and monitoring for corticosteroid toxicity.

Routine immunizations should be delayed until the patient is free of relapses and has been off immunosuppression for 3 months. Pneumococcal and influenza vaccines are recommended but are not routinely used, because their efficacy is not established. Children who have received immunosuppressive therapy in the preceding 3 months and are not immune to varicella should receive zoster immunoglobulin if they are exposed to chickenpox or shingles. These patients should also receive acyclovir if they develop chickenpox.

Monitoring for steroid toxicity every 3 months in the outpatient clinic will detect adverse effects such as slowing of growth. Supplemental calcium and vitamin D may attenuate bone loss. A yearly checkup will detect cataracts.

Diet

A low-salt diet will limit the fluid retention and edema that occurs in nephrotic syndrome. A 24-hour urine collection is useful to quantify dietary intake of sodium. More than 88 mEq/day in the 24-hour urine suggests high salt intake. The help of a dietician will be useful to bring the daily sodium intake down to 2 g (88 mEq)/day or less.

Medication Summary

Corticosteroids (prednisone), cyclophosphamide, and cyclosporine are used to induce remission in nephrotic syndrome. Diuretics are used to reduce edema. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers can reduce proteinuria.

Treatment should be dictated by the type of renal pathology causing nephrotic syndrome.

Minimal-change disease has an excellent response to corticosteroids, while in focal glomerulosclerosis, only 20% of patients respond well to corticosteroids. Renal biopsy is very helpful to differentiate minimal-change disease and its variants such as IgM nephropathy and C1q nephropathy. Very few randomized trials are available to guide treatment for minimal-change disease in adults. Prednisone in short courses from 12-20 weeks' duration remains the mainstay of treatment for patients with minimal-change disease.

Immunosuppressive medications other than steroids are usually reserved for steroid-resistant patients with persistent edema, or for steroid-dependent patients with significant steroid-related adverse effects.

Cyclophosphamide may benefit patients who have frequently relapsing steroid-sensitive nephrotic syndrome. Associated complications include bone marrow suppression, hair loss, reduced sperm counts, hemorrhagic cystitis, malignancy, and infertility.

Cyclosporine is indicated when relapses occur after cyclophosphamide treatment. Cyclosporine may be preferable in a pubertal male who is at risk of developing cyclophosphamide-induced azoospermia. Cyclosporine is a highly effective maintenance therapy for patients with steroid-sensitive nephrotic syndrome who are able to stop steroids or take lower doses, but some evidence suggests that although remission is maintained as long as cyclosporine is administered, relapses are frequent when treatment is discontinued.

Cyclosporine can be nephrotoxic and can cause hirsutism, hypertension, and gingival hypertrophy.

For focal glomerulosclerosis, prednisone, cyclosporine, and cyclophosphamide have all been used in treatment. Corticosteroids should be the first-line agent, with cyclophosphamide or cyclosporine as backup for steroid-resistant cases. Mycophenolate and rituximab have also been used in treating focal glomerulosclerosis. However, data on the use of these latter two agents are not convincing.

For idiopathic membranous nephropathy, prednisone along with chlorambucil or cyclophosphamide remains important for treatment. Other agents that have been used include cyclosporine, synthetic corticotropin, and rituximab.

A Cochrane review of immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome concluded that combination treatment with an alkylating agent and a corticosteroid has both short- and long-term benefits, and that cyclophosphamide is a safer alkylating agent than chlorambucil. A 6-month course of alternating monthly cycles of corticosteroids and cyclophosphamide is recommended in the 2012 KDIGO Clinical Practice Guideline as initial therapy for adult idiopathic membranous nephropathy with nephrotic syndrome, but the benefits of this regimen are not supported by high-quality evidence.[39] Cyclosporine or tacrolimus are recommended as alternatives.[48]

Rituximab has been effective in some cases of nephrotic syndrome that relapse after prednisone treatment or in cases resistant to prednisone treatment.[49] This drug is a chimeric murine/human antibody against the CD20 antigen of B cells. It presumably exerts its benefit by suppressing antibody production. Its adverse effect to cause immunosuppression cannot be ignored.

Natural, highly purified corticotropin gel formulation (repository corticotropin injection) is also a potential treatment option for steroid-resistant nephrotic syndrome and has shown some results in reducing proteinuria. However, reported data are based solely on retrospective and observational studies, and, hence, this therapy should be tested further in controlled trials.[50, 51] The mechanism by which this drug decreases proteinuria is unclear. It is presumed to have an anti-inflammatory action. Its adverse effect profile is similar to steroids, but the most striking disadvantage is its cost.

Corticosteroids

Class Summary

Corticosteroids have anti-inflammatory properties and modify the body's immune response to diverse stimuli.

Prednisone

Prednisone is an immunosuppressant used in treatment of autoimmune disorders. This agent may decrease inflammation by reversing increased capillary permeability and suppressing polymorphonuclear neutrophil (PMN) activity. It may be administered as a single dose in the morning or as divided doses; once-daily dosing is equally effective and greatly improves compliance.

Immunomodulators

Class Summary

These agents regulate key steps of the immune system.

Cyclophosphamide

Cyclophosphamide is a cyclic polypeptide that suppresses some humoral immune activity. It is chemically related to nitrogen mustards. In the liver, this agent is biotransformed by the cytochrome P-450 system to its active metabolite, 4-hydroxycyclophosphamide, which alkylates the target sites in susceptible cells in an all-or-none type reaction. As an alkylating agent, the mechanism of action of the active metabolites may involve cross-linking of DNA, which interferes with growth of normal and neoplastic cells.

The mechanism of action of cyclophosphamide in autoimmune diseases is thought to involve immunosuppression due to destruction of immune cells via DNA cross-linking.

In high doses, cyclophosphamide affects B cells by inhibiting clonal expansion and suppression of production of immunoglobulins. With long-term low-dose therapy, it affects T cell functions.

Cyclophosphamide has been successfully used in conditions that require immunosuppression. It is effective for frequently relapsing steroid-sensitive nephrotic syndrome.

Cyclosporine (Sandimmune, Neoral, Gengraf)

Cyclosporine is a cyclic polypeptide that suppresses cell-mediated immune reactions. Tacrolimus (Prograf) has a similar effect.[52, 53]

For children and adults, base dosing on ideal body weight

Rituximab (Rituxan)

Rituximab is a chimeric humanized murine monoclonal antibody against CD20 antigen found on the surface of lymphocytes.

Immunosuppressants

Mycophenolate (CellCept, Myfortic)

Mycophenolate inhibits inosine monophosphate dehydrogenase and suppresses de novo purine synthesis by lymphocytes, thereby inhibiting their proliferation. It inhibits antibody production.

Diuretics

Class Summary

These agents are used for symptomatic treatment of edema.

Furosemide (Lasix)

Furosemide increases urine output by inhibiting sodium transport in the ascending loop of Henle . The dose must be individualized. Depending on response, administer at increments of 20-40 mg, no sooner than 6-8 h after the previous dose, until desired diuresis occurs.

Spironolactone (Aldactone)

Spironolactone is used for management of edema resulting from excessive aldosterone excretion. It competes with aldosterone for receptor sites in the distal nephron, thus enhancing sodium excretion.

Angiotensin-converting Enzyme (ACE) Inhibitors

Class Summary

ACE inhibitors block conversion of angiotensin I to angiotensin II and prevent secretion of aldosterone from the adrenal cortex.

Captopril

Captopril inhibits angiotensin converting enzyme (ACE), which blunts the conversion of angiotensin I to angiotensin II, resulting in less vasoconstriction and lower aldosterone secretion.

Enalapril (Vasotec)

Enalapril inhibits angiotensin converting enzyme (ACE), which blunts the conversion of angiotensin I to angiotensin II, resulting in less vasoconstriction and lower aldosterone secretion.

Lisinopril (Prinivil, Zestril)

Lisinopril inhibits angiotensin converting enzyme (ACE), which blunts the conversion of angiotensin I to angiotensin II, resulting in less vasoconstriction and lower aldosterone secretion.

Angiotensin II receptor antagonists

Class Summary

ARBs antagonize the action of angiotensin II at the type 1 receptor, reducing systemic arterial blood pressure and blunting the intrarenal effect of angiotensin II. If ACE inhibitors cause cough, ARBs may be substituted.

Valsartan (Diovan)

Valsartan directly antagonizes type 1 angiotensin II receptors. It displaces angiotensin II from the AT1 receptor and may lower blood pressure by antagonizing AT1-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses. It does not affect bradykinin and is less likely to be associated with cough and angioedema. Valsartan is useful in patients who are unable to tolerate ACE inhibitors.

Losartan (Cozaar)

Losartan directly antagonizes type 1 angiotensin II receptors. It displaces angiotensin II from the AT1 receptor and may lower blood pressure by antagonizing AT1-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses. It does not affect bradykinin and is less likely to be associated with cough and angioedema. Valsartan is useful in patients who are unable to tolerate ACE inhibitors.

Adrenocorticotropic Hormone (ACTH) Analogue

Class Summary

Consider use of corticotropin to induce diuresis or a remission of proteinuria.

Corticotropin (HP Acthar Gel)

HP Acthar Gel is a synthetic corticotropin that stimulates corticotropin production. It may induce remission of proteinuria in nephrotic syndrome.