

The Diagnosis of Glomerular Diseases

Acute Glomerulonephritis and the Nephrotic Syndrome

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Rapid and efficient diagnosis of diseases presenting as acute glomerulonephritis and/or nephrotic syndrome is critical for early and appropriate therapy aimed at preservation of renal function. Although there may be overlap in clinical presentation, and some patients present with clinical features of both syndromes, this analysis serves as an initial framework to proceed with serologic testing and/or pathologic confirmation en route to final diagnosis. Efficient and timely diagnosis is essential in these situations because progression to end-stage renal disease may result if the underlying disease is not promptly treated.

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Glomerular injury leads to impairment of the selective filtering properties of the kidney and reduction in the glomerular filtration rate (GFR).¹⁻³ Consequently, blood constituents normally excluded from the urinary space pass into the urine and are excreted. The nature and severity of the defect (ie, underlying disease and pathologic lesion) determine the quantity of red blood cells (RBC), white blood cells, and proteins lost in the urine and the extent of functional impairment.⁴ These variables determine the clinical presentation. While the GFR is reduced initially in many patients, the severity, reversibility, and progression of disease are dependent on many factors, including the nature, location, and extent of the insult and the renal and systemic response to glomerular injury.^{3,4} Prompt recognition of the cause of glomerular disease results in a more rational, safer, and effective therapeutic approach. Early diagnosis is especially important in patients with fulminant disease, where delay in treatment greatly reduces the likelihood of a beneficial response.^{4,5}

In this review, we delineate our approach to the diagnosis of acute glomer-

ular injury in adults, focusing on glomerulonephritis and nephrotic syndrome. Our intent is to provide a framework that will enable efficient and timely diagnosis. A few introductory points warrant particular emphasis. We do not discuss the evaluation of asymptomatic abnormalities discovered on routine urinalysis (ie, isolated hematuria and/or non-nephrotic-range proteinuria). The clinician should be aware that these manifestations may represent less severe forms of the full-blown entities. However, there are many nonglomerular causes of isolated hematuria and proteinuria that must also be considered in these situations, and the reader is referred to recent reviews of these entities.^{2,6-12}

Although our approach distinguishes between nephritic and nephrotic states (the two classic clinical presentations of acute glomerular injury), many of the underlying diseases can produce nephritis or nephrotic syndrome. Furthermore, this distinction is not always easily made in individual patients. For example, some patients present with nephrotic-range proteinuria and active urine sediments, whereas others present with nephrotic-range proteinuria and acute renal failure. In some instances the clinical presentation represents the initial manifestation of an acute disease, whereas in others the physician initially detects a more chronic

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Table 1. Major Causes of Acute Nephritis*

Low Serum Complement Level	Normal Serum Complement Level
Systemic Diseases	
Systemic lupus erythematosus (focal, approximately 75%; diffuse, approximately 90%)	Polyarteritis nodosa
Cryoglobulinemia (approximately 85%)	Wegener granulomatosis
Subacute bacterial endocarditis (90%)	Hypersensitivity vasculitis
"Shunt" nephritis (90%)	Henoch-Schönlein purpura
	Goodpasture's syndrome
	Visceral abscess
Renal Diseases	
Acute poststreptococcal glomerulonephritis (approximately 90%)	IgG-IgA nephropathy
Membranoproliferative glomerulonephritis	Idiopathic rapidly progressive glomerulonephritis
Type 1 (approximately 50%-80%)†	Anti-GBM disease
Type 2 (approximately 80%-90%)	Pauci-immune‡ (no immune deposits)
	Immune-deposit disease

*Normal serum complement levels indicate that production of complement components is keeping up with consumption; it does not exclude participation of complement in the inflammatory process. Repeated measurements are useful (2-3 times, 1 week apart). Consistently normal serum levels are useful in narrowing the diagnostic possibilities. Percentages indicate the approximate frequencies of depressed C3 or hemolytic complement levels during the course of disease. GBM indicates glomerular basement membrane. Adapted with permission from Madaio and Harrington.¹² Copyright ©1983, Massachusetts Medical Society. All rights reserved.

†Most common pathologic findings are associated with hepatitis C infection.

‡Pauci-immune indicates lack of significant glomerular deposition of immunoglobulin by direct immunofluorescence. Many patients have circulating antineutrophil cytoplasmic antibodies.

disturbance. Simply stated, multiple variables influence the final clinical picture, including the inciting event and the host response to the immune reactants. Nevertheless, the clinical distinction between acute glomerulonephritis and nephrotic syndrome provides a reasonable starting point to form an initial differential diagnosis, en route to serologic and pathologic determination of the underlying glomerular disease. Our discussion focuses on the initial diagnostic evaluation, and not on either the pathogenesis or the subsequent management of the underlying diseases. The reader is referred to excellent recent reviews for these further considerations.¹³⁻¹⁵

ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis is defined as the sudden onset of hematuria, proteinuria, and RBC casts.¹² Although RBC casts are diagnostic of glomerular bleeding, they may be difficult to find. Visualization of dysmorphic RBC under phase-contrast microscopy by an experienced observer is a useful surrogate.¹⁶ Proteinuria in patients with acute glomerulonephritis typically ranges from 500 mg/d to 3 g/d, but ne-

phrotic-range proteinuria (>3.5 g/d) may be present.

Acute glomerulonephritis can be due to a primary renal disease or a systemic disease. A thorough history and physical examination should focus on identification of an underlying systemic disease, and serologic evaluation should be performed for a prompt diagnosis (**Table 1** and **Table 2**). Serologic evaluation is essential and, together with the clinical presentation, focuses the differential diagnosis.¹² The serum complement levels provide useful information; if any component is depressed, assessment of the levels of other components may be helpful. Initially determine the CH₅₀ level; if results are abnormal, proceed with evaluation of individual components (eg, C3 and C4 levels). If an abnormality of the alternate pathway is suspected, determine AH₅₀ activity.

For the diagnostic approach, we arbitrarily divide the causes of glomerulonephritis into those with low and normal serum complement levels. This provides for an efficient and practical tool for the initial approach to patients in clinical practice (Tables 1 and 2).

Estimation of GFR (ie, serum creatinine level) and quantitation of urine protein excretion (ie, 24-

Table 2. Diagnostic Approach in Patients With Acute Glomerulonephritis*

Serologic Evaluation
C3, C4, CH ₅₀ †
Anti-DNA antibodies‡
Antineutrophil cytoplasmic antibodies
Cryoglobulins
Hepatitis B, C serologic tests
Blood cultures§
Anti-glomerular basement membrane (type α[3]IV collagen) antibodies
Streptozyme
Kidney Biopsy
Useful for establishing/confirming diagnosis, determining degree of inflammation and fibrosis
Sometimes, absence of findings are helpful (eg, absence of immune deposits suggests vasculitis)

*If rapidly progressive glomerulonephritis is present, empiric therapy (eg, pulse steroids) is indicated before definitive diagnosis, to prevent irreversible scarring.

†Helpful in narrowing diagnostic possibilities (Table 1).

‡Serologic findings may be negative in patients with nephrotic syndrome.

§If endovascular or occult infection is suspected (eg, endocarditis, abscess).

||If poststreptococcal glomerulonephritis is suspected (Table 3).

hour urine protein excretion rate or urine protein:creatinine ratio) also should be performed. If the GFR is depressed, evaluation of renal size (eg, by ultrasound) is a useful guide to determine the extent of fibrosis. Small kidneys (<9 cm) suggest extensive scarring; reversibility is low in this setting, whatever the underlying diagnosis. The presence of nephrotic-range proteinuria is more common in certain diseases. The use of renal biopsy will be discussed.

Acute Glomerulonephritis With Low Serum Complement Levels

Low serum complement levels in patients with glomerulonephritis most often result from activation of complement within the kidney or other sites. Most often production does not keep up with consumption,¹² although patients with congenital or acquired complement deficiencies are more prone to develop glomerulonephritis.¹⁷ The systemic diseases consistently producing hypocomplementemic glomerulonephritis include systemic lupus erythematosus, subacute bacterial

endocarditis, shunt nephritis, and cryoglobulinemia. These diseases usually are apparent from the history and results of physical examination, and serologic testing is performed to confirm these diagnoses (Table 2). Some patients (approximately 10%) with heavy proteinuria may have negative serologic findings at initial presentation due to loss of antibodies in the urine, tissue deposition, or other factors.^{18,19} Blood cultures should be obtained in all febrile patients to exclude infection, since endovascular infection must be treated promptly.

Systemic Diseases. The diagnosis of lupus usually is determined by the presence of extrarenal disease (eg, arthritis or rash) and serologic findings (eg, anti-double-stranded DNA antibodies; Table 2). Nephrotic-range proteinuria and reduced GFR are indicative of a more severe proliferative lupus nephritis. Renal biopsy is, however, necessary to distinguish the disease subtype in more severe forms,¹⁸ and therefore is recommended in patients with lupus and decreased GFR and/or nephrotic syndrome. Renal biopsy elucidates the degree of inflammation (ie, assessment of disease activity and confirmation of diagnosis) and the level of fibrosis (eg, scarring or chronicity).²⁰⁻²⁴ With clinical assessment of extrarenal lupus activity, these pathologic variables are useful in guiding administration and withdrawal of immunosuppressive therapy.

Purpura, arthralgias, and other signs of vasculitis in patients with glomerulonephritis and low serum complement levels raise the suspicion of cryoglobulinemia. Patients may present with clinical features associated with glomerulonephritis or/and nephrotic syndrome, although the former is more common. Cryoglobulinemia (75%) and rheumatoid factor activity (70%) are frequently present; however, the levels fluctuate, and they may not be detectable at initial presentation.²⁵ More than 80% will have reduced serum complement levels sometime during the course of disease, and C4 and C2 complement levels may be markedly depressed.²⁵ Pathologically, membranoproliferative glomerulo-

nephritis (MPGN) usually is present. Most cases of essential mixed cryoglobulinemia and associated glomerulonephritis are associated with hepatitis C infection,²⁶⁻²⁸ and the majority of these patients have hepatitis C RNA or anti-hepatitis C antibodies in the serum.²⁵ Therefore hepatitis C assays (ie, polymerase chain reaction and antibody evaluations) should be performed in patients with undiagnosed glomerulonephritis.²⁹ Liver enzyme levels and other liver function tests may be normal at disease onset.^{25,28,29} Characteristic lesions on kidney biopsy (eg, intraluminal thrombi or "fingerprint" pattern of the electron-dense deposits) also should raise suspicion of hepatitis C-associated disease.

Primary Renal Diseases. Primary renal diseases associated with glomerulonephritis and low serum complement levels include acute post-infectious glomerulonephritis and idiopathic MPGN (IMPGN). The former has been most extensively studied after streptococcal infections, although the syndrome has been reported after other bacterial, viral, parasitic, rickettsial, and fungal infections.³⁰ Although IMPGN remains an important cause of glomerular disease in children, the incidence of primary disease in adults has declined.^{31,32} Secondary forms of the disease may be associated with autoimmune diseases, chronic infections, microangiopathies, and paraprotein deposition diseases.³³ Most patients with IMPGN have recurrent bouts of glomerulonephritis (and/or nephrotic syndrome). By contrast, with glomerulonephritis after streptococcal infections, recovery (lack of progression to end-stage renal disease) is the rule, especially in children (<2% progression to end-stage renal disease), and, thus the disease course is helpful in confirming the diagnosis. Nevertheless, persistent urinary abnormalities may last for years, and a small percentage of adults develop slowly progressive renal failure.³⁰ For diagnosis, repeated evaluation of serum complement levels, determination of autoantibodies to complement pathway components, and renal biopsy findings are especially helpful in dis-

tinguishing glomerulonephritis after streptococcal infections from IMPGN (Table 3). These serologic determinations are especially useful in situations where the distinction between glomerulonephritis after streptococcal infections and MPGN is difficult on clinical grounds alone (eg, where there is persistent or recurrent disease).

Acute Glomerulonephritis With Normal Serum Complement Levels

One should initially consider glomerulonephritis associated with systemic diseases, then evaluate the possibility of primary renal diseases (Table 1).

Systemic Diseases. Multi-organ involvement strongly suggests a systemic process, and typical symptoms of an underlying disease may be useful in narrowing the diagnostic possibilities, eg, sinusitis, pulmonary infiltrates (Wegener granulomatosis),⁴² pulmonary hemorrhage (Goodpasture's syndrome),⁴³ nausea, vomiting and abdominal pain, and purpura (Henoch-Schönlein purpura).¹² Serologic evaluation, including measurement of antineutrophil cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane (GBM) antibodies, along with hepatitis serologic evaluation, is essential, especially for prompt diagnosis in patients with rapidly progressive glomerulonephritis (RPGN).

A few caveats warrant mention. Most patients with polyarteritis associated with hepatitis B or C display normal or near-normal complement levels (>80%); however, decreased levels occur more frequently in patients with cryoglobulinemia. The liver enzyme levels and liver function tests may be normal at disease onset, although the serologic findings are typically positive.^{25,28,29} Patients with hepatitis B and glomerulonephritis typically have positive findings for hepatitis B surface antigen and antibodies to hepatitis B core, and negative findings for antibodies to hepatitis B surface antigen in serum.^{29,44} Among this group, the incidence of systemic involvement (ie, polyarteri-

Table 3. Complement Levels and Kidney Deposits to Distinguish Idiopathic Membranoproliferative Glomerulonephritis (MPGN) and Poststreptococcal Glomerulonephritis (GN)*

	MPGN			Poststreptococcal GN
	Type 1	Type 2	Type 3	
Immunofluorescence (glomeruli)	IgG, C3	C3 predominates	C3>IgG	IgG, C3
Electron dense deposits	Subendothelial mesangial	Dense BM deposits	Like type I, often thickened BM	Subendothelial mesangial subepithelial (humps)
C3	Levels fluctuate	Persists low	Levels fluctuate	Low for 2-4 wk, then normal
C4	Normal or reduced	Normal	Normal	Normal to low normal (alternate C path)
Autoantibodies	C3NeF/III C4NeF NFI	C3NeFI	C3NeFI/III	Antistreptococcal antibodies

*C3NeFI binds to C3 convertase and blocks its inactivation by factor H; this results in alternative pathway activation.³⁴ It is present in more than 75% of patients with MPGN type II but is infrequent in MPGN type I.³⁵ C3NeFI/III converts C3 and the terminal components via properdin, activating complement (found in approximately 25% of type I and >75% of type III).^{35,36} C4NeF type binds to the C3 convertase, C4b2a, and a C3bBb stabilizing factor, NFI; it was discovered in the serum of MPGN type I patients.³⁷ Patients with lipodystrophy are more prone to MPGN and some of them produce autoantibodies vs complement component (nephritic factors).³⁸ Glomerulonephritis after streptococcal infection may occur in sporadic or epidemic form and evidence of recent infection may not be obtained. In the first few weeks, C4 and C2 levels are usually normal or near normal, with profound depression of C3 reflecting alternative pathway activation.³⁹ In most patients, the levels return to normal within a month, although they may take up to 3 months to normalize.⁴⁰ Serum antibodies to streptococcal cell wall proteins (eg, streptozyme assay) are positive in more than 95% of patients with pharyngitis and 80% of patients with skin infections.⁴¹ However, since the prevalence of streptococcal infections in the general population is high, their detection is not diagnostic.

tis) varies widely by geography, from as high as 84% in cities with increased drug use, to a much lower incidence in rural areas.²⁹ Patients with glomerulonephritis associated with abscess typically have normal complement levels (unless there is endocarditis), and the site of infection is usually apparent from the history and results of physical examination.^{39,45}

Primary Renal Diseases. The clinical presentation of IgA nephropathy varies considerably (eg, asymptomatic hematuria, RPGN, nephrotic syndrome).⁴⁶ Most often it is idiopathic, although liver disease is the most frequent association.⁴⁷⁻⁵¹ Renal biopsy is required for definitive diagnosis.

Rapidly progressive glomerulonephritis may be associated with any form of glomerulonephritis, including those associated with low complement levels. Most patients, however, present without systemic symptoms and with normal levels (>95% have normal complement levels).⁵² The majority of patients with idiopathic RPGN are ANCA positive. Less commonly (10%-20%), patients have anti-GBM disease (eg, linear GBM deposits and crescentic glomerulonephritis); occasionally (5%-10%), patients will have positive findings for ANCA and anti-GBM antibodies.⁵³⁻⁵⁶ The latter group is more likely to have vasculitis in organs other than the lungs and kid-

neys. Occasionally ANCA may be found in patients with lupus nephritis, although its significance is unclear.⁵⁶

Serologic Evaluation, Use of the Kidney Biopsy in Clinical Practice, Referral to a Nephrologist

The clinical presentation provides clues, but serologic testing facilitates rapid diagnosis, especially in patients without systemic symptoms. We recommend initially obtaining C3 and C4 levels, along with determination of serum ANCA, anti-DNA, and anti-GBM antibody levels (Table 2). The perinuclear (pANCA) and cytoplasmic (cANCA) patterns of staining for ANCA should be determined. These serologic evaluations are especially important in patients with RPGN and should be determined immediately in this situation. The results may obviate the need for immediate kidney biopsy, and the serologic results should dictate initial therapy.^{52,53} Determination of hepatitis serologies and evaluation of cryoglobulin levels also should be performed.

Patients with Wegener granulomatosis typically have serum ANCA (80%-95%), and the most common pattern is cANCA, with antigenic specificity for proteinase 3. Most of the rest of the ANCA are directed at myeloperoxidase (pANCA).⁵⁷ Al-

most all patients with idiopathic, pauci-immune glomerulonephritis have ANCA; however, 75% of this group express pANCA.⁵⁸ In the clinical setting of RPGN, these assays are especially useful, with high positive and negative predictive values (>90%).⁵⁷ However, they have much lower predictive values in other clinical settings (eg, hematuria or non-nephrotic-range proteinuria with normal serum creatinine levels), and the utility of ANCA vs other intracellular antigens is less clear.

Pathologic evaluation also is useful for rapid diagnosis, for distinguishing primary renal diseases, and for determining disease severity.⁵⁸ In most cases, systemic diseases associated with glomerulonephritis are apparent from the clinical presentation, and serologic testing confirms the diagnosis. In some instances, however, the serologic findings are not diagnostic or not readily available, and histologic examination of the kidney is required. Although the pathologic findings are not always diagnostic, they help to narrow the differential diagnosis. The pathologic findings also are helpful in determining the degree of disease activity (eg, the level of inflammation or the extent of fibrosis), and this information may help guide therapy.

Renal biopsy may be especially important for patients with RPGN, where prompt diagnosis and treatment are essential.⁵² For ex-

ample, in a patient with RPGN (crescentic glomerulonephritis) for whom serologic findings are not rapidly available, the absence of immune deposits (ie, pauci-immune glomerulonephritis) on evaluation of biopsy is consistent only with vasculitis or Wegener granulomatosis; anti-GBM disease (ie, linear immune deposits) and the major immune deposit-mediated diseases are excluded by that finding. In this regard, if systemic vasculitis is suspected, angiography or biopsy of other affected organs provides a more specific diagnosis.⁵⁸ As mentioned previously, the extent of disease activity in this situation is also useful in guiding therapy.

Pathologic evaluation is also particularly helpful in diagnosing glomerulonephritis in patients with unexplained, acute renal failure, when the diagnosis is uncertain from the clinical findings. For example, in patients with progressive renal failure without significant urinary or systemic symptoms, the pathologic findings may be very helpful in confirming or excluding a diagnosis. The results derived from the biopsy are also very useful in patients with slowly progressive renal failure due to glomerular disease, where it is difficult to determine the level of disease activity (eg, the extent of fibrosis and irreversible disease) from the clinical presentation alone.⁵⁹ For example, in some instances it may be difficult to distinguish disease activity (ie, exacerbation amenable to further immunosuppression) from progressive fibrosis, unassociated with a disease flare. Treatment in the latter situation would not be specific to the underlying disease, but it would include control of systemic hypertension (preferably by use of an angiotensin-converting enzyme inhibitor) and hyperlipidemia.

Nevertheless, the clinician must be aware of limitations of the use and interpretation of the kidney biopsy results. If the kidneys are small (eg, <9 cm in length for a 70-kg patient), the risk associated with biopsy (ie, major bleeding requiring transfusion and other intervention) is increased, and the probability of obtaining clinically useful, diagnostic information is substantially reduced.⁵⁹ In this setting, severe and irreversible glomerulosclerosis and

interstitial fibrosis will be present, whatever the underlying cause of the primary renal disease, and diagnostic interpretation will be limited. Furthermore, the probability of response to subsequent therapeutic intervention is greatly reduced.⁵⁹

In situations where the patient is asymptomatic (eg, RBC and RBC casts present on urinalysis, without systemic findings) and the GFR is normal, the physician should observe the serum creatinine level closely over time, while proceeding with the evaluation. We emphasize that in cases of isolated hematuria (ie, without casts or proteinuria), the source of bleeding from other sites within the urinary tract (eg, bladder, prostate, or ureters), should be explored by means of visualization of the kidney and the collecting system (ie, cystoscopy and intravenous pyelogram and/or computed tomographic scan). Depending on the results, renal biopsy may be performed to confirm or elucidate the diagnosis of glomerulonephritis and to determine the level of disease activity. Sometimes, lack of abnormal findings on histologic evaluation is helpful in excluding a renal cause of the bleeding.

The urgency for referral to a nephrologist for further consideration and renal biopsy depends on the GFR. For example, in situations where there are isolated urinary abnormalities, history and physical examination are unrevealing, and serum creatinine level is normal and stable (ie, <88.4 $\mu\text{mol/L}$ [1.0 mg/dL] in a 70-kg man), proceed with the serologic workup while closely monitoring renal function, before consultation, consideration of biopsy, and treatment. However, if the GFR is abnormal or rapidly deteriorating, or if there are systemic symptoms, immediate consultation (ie, that day) is advisable for clinical decisions regarding treatment, biopsy, need for dialysis, etc.

NEPHROTIC SYNDROME

Nephrotic-range proteinuria in adults is defined as urinary excretion of more than 3.5 g protein per 1.73 m² in 24 hours. Although an arbitrary definition, persistent proteinuria at or above this level usu-

ally leads to hypoalbuminemia, resulting in edema. Furthermore, we have known for more than 20 years that patients with urinary protein excretion rates of less than 2 g/d have a better prognosis.⁶⁰ The clinical complex referred to as nephrotic syndrome results from heavy proteinuria and includes edema, hypoalbuminemia, hyperlipidemia, and lipiduria. Many factors influence the onset and severity of edema, including the degree and duration of proteinuria, the serum albumin level, the patient's underlying renal disease (ie, sodium retentive state and renal function), dietary sodium intake, accompanying cardiovascular and liver function, etc. The presence or severity of nephrotic syndrome does not predict the underlying pathological disturbance, and the syndrome can be due to a primary renal or a systemic disease. The incidence of diseases associated with the nephrotic syndrome varies markedly with age, thus providing important diagnostic information. In most children and adults, the initial manifestation of disease is peripheral edema. The elderly (aged >65 years) may be misdiagnosed with congestive heart failure. Many patients are asymptomatic.

Systemic Diseases

Initial diagnostic evaluation includes consideration of systemic diseases and drugs; the most common associations are listed in **Table 4**. Diabetes mellitus is the most common cause of nephrotic syndrome in adults in the United States.⁶²⁻⁶⁴ Approximately one third of patients with juvenile-onset (type 1) diabetes mellitus develop nephrotic syndrome, predictably leading to renal failure,⁶⁵ and recent evidence indicates that there is genetic susceptibility to the development of nephropathy.⁶⁶ In patients with type 1 diabetes mellitus in whom nephropathy develops, the natural history of the disease is fairly predictable and has diagnostic utility. Asymptomatic microalbuminuria, the initial manifestation, occurs 5 to 10 years into the illness; overt proteinuria (0.5-3.0 g/d) occurs 13 to 20 years after disease onset, and nephrotic-range proteinuria (>3.5 g/d) develops a few years

Table 4. Major Causes of Nephrotic Syndrome

Primary renal diseases
Membrane nephropathy (MN) (33%)
Focal glomerulosclerosis (FSGS) (33%)
IgA nephropathy (IgA) (10%)
Minimal-change disease (MCD) (15%)
Membranoproliferative glomerulonephritis (MPGN) (2%-5%)
Other (eg, proliferative glomerulonephritis) (5%-7%)
Systemic diseases*
Diabetes
Amyloidosis
Systemic lupus erythematosus
Dysproteinemias
Multiple myeloma
Immunotactoid/fibrillary glomerulonephritis
Light chain–deposition disease
Heavy chain–deposition disease
Infections
Human immunodeficiency virus disease (FSGS)
Hepatitis B (MN)
Hepatitis C (MPGN)
Syphilis (MN)
Malaria (MN)
Schistosomiasis (MN)
Tuberculosis (Amyloid)
Leprosy (MN)
Malignant neoplasms
Solid adenocarcinomas, eg, lung, breast, colon (MN)
Hodgkin lymphoma (MCD)
Other malignant neoplasms
Drugs or toxins
Nonsteroidal anti-inflammatory drugs (MCD)
Gold (MN)
Penicillamine (MN)
Probenecid (MN)
Mercury (MN)
Captopril (MN)
Heroin (intravenous, FSGS)
Heroin (“skin poppers,” amyloid)
Other
Preeclampsia
Chronic allograft rejection
Vesicoureteral reflux (FSGS)
Bee sting

*Lesions that resemble primary glomerular diseases are indicated in parentheses. Table modified with permission from Koenig and Bolton.⁶¹

thereafter. The period between onset of microalbuminuria and renal failure can be extended by rigorous control of blood glucose level and blood pressure, use of angiotensin-converting enzyme inhibitors, and, perhaps, restriction of dietary protein and reduction of hyperlipidemia.^{67,68} Nevertheless, progression to end-stage renal failure is fairly predictable within a few years after the onset of nephrotic syndrome.⁶⁹ In patients with type 2 diabetes mellitus, the prevalence and expression of diabetic nephropathy are more variable, as the nephropathy is often complicated by hypertensive and atherosclerotic disease in older patients.⁶³

Diabetic retinopathy is a useful marker of diabetic nephropathy in patients with nephrotic syndrome, especially in patients with type 1 diabetes (>90% of patients with nephropathy have retinopathy); microvascular disease in the retina is indicative of diabetic nephropathy and usually precedes it.^{63,64} Fluorescein angiography is necessary to adequately evaluate the retinal microvasculature, and it should be performed in patients with diabetes and proteinuria when the diagnosis is uncertain. Nevertheless, retinopathy is less predictable in patients with type 2 disease and proteinuria (approximately 50%-80% will have diabetic le-

sions), and those without retinopathy are more likely to have nondiabetic glomerular disease. We reserve renal biopsy for diabetic patients with nephrotic syndrome with atypical history, examination results, or clinical course for diabetic nephropathy (eg, early-onset renal failure, rapid progression of renal failure, lack of evidence of microvascular disease elsewhere, or evidence of overt glomerulonephritis).

Nephrotic syndrome in patients with lupus nephritis is most often indicative of a severe proliferative or inflammatory lesion.²⁰⁻²⁴ However, some patients develop non-inflammatory, membranous, lupus lesions and present with a normal GFR and heavy proteinuria. Acute renal failure for another reason (eg, use of nonsteroidal anti-inflammatory drugs or interstitial nephritis) in a patient with membranous lupus nephropathy may confuse the situation.¹⁹ As discussed previously, loss of autoantibodies in the urine can result in negative serologic findings and delay diagnosis. However, depressed serum complement levels or/and other clinical features of systemic lupus should raise suspicion of this disorder. Pathological evaluation of the kidney is necessary for determination of disease activity and the extent of fibrosis. Less commonly, nephrotic syndrome has been associated with other rheumatologic diseases^{5,52,59,70} (Table 4).

Amyloidosis and the dysproteinemias should be considered in patients older than 40 years, although most patients are older than 50 years. Eighty percent of patients with amyloidosis have proteinuria, and the nephrotic syndrome occurs in about one third.⁷¹ Amyloidosis may be idiopathic or associated with multiple myeloma, long-standing rheumatoid arthritis, or chronic infections, although the latter are much less common in recent decades.^{71,72} Most patients with amyloidosis in the United States have immunoglobulin light chain–associated disease.⁷³ Accompanying systemic symptoms (eg, fatigue or weight loss) and/or cardiac involvement are common, although other organs may be affected. A monoclonal spike is found in the serum or urine by electrophoresis in more than 80% of proteinuric individuals and more

than 90% of patients with nephrotic syndrome; approximately 20% of these patients will have free light chains.^{71,72} The yield of abdominal fat-pad biopsy is approximately 75% in this group, and the procedure should be performed in patients older than 40 years with unexplained proteinuria.⁷³ Skin, gingival, and rectal biopsy findings are less sensitive, unless there is overt clinical involvement.^{73,74} Results of bone marrow examination may demonstrate evidence of monoclonal restriction.⁷³

Other related disorders, including immunotactoid and/or fibrillary glomerulopathy and heavy chain-deposition disease, may present as nephrotic syndrome (with or without progressive renal failure). These entities are difficult to diagnose on clinical grounds alone, and renal biopsy is required for diagnosis.⁷³⁻⁸¹ The size, shape, and nature of the immune deposits and microfibrils distinguish these entities from amyloid deposits and each other.

Recognition of the association of nephrotic syndrome with infections has been rekindled with the epidemic of acquired immunodeficiency syndrome (AIDS).⁸²⁻⁸⁴ Patients with AIDS may present with a variety of nephrologic syndromes (**Table 5**).⁸⁵ The varied clinical presentations and pathologic entities observed in these patients likely reflect differences in pathogenesis and host response to viral infection. Renal involvement may occur at any stage of infection, although the entity occurs more commonly in patients with established AIDS. The pathologic abnormality in patients with nephrotic syndrome is typically focal and segmental glomerulosclerosis.⁸⁶ A more severe form, termed *collapsing glomerulopathy*, more common in patients who are seropositive for human immunodeficiency virus (HIV), is associated with rapid progression to end-stage renal failure within months.⁸⁷ It has been postulated that HIV infection of renal cells (eg, mesangial or epithelial) contributes to fibrosis and the more rapid progression to renal failure observed in these patients.⁸⁸ Urinary protein excretion can exceed 20 g/d in some patients (ie, supernephrotic syndrome), and therefore this level of

Table 5. Human Immunodeficiency Virus Glomerulopathies*

Renal Abnormalities	Clinical Features
FSGS (collapsing more common)	Proteinuria Nephrotic syndrome Progressive renal insufficiency
HUS/TTP/TMA	Progressive renal insufficiency Microangiopathic hemolytic anemia Thrombocytopenia Systemic involvement (eg, central nervous system)
IgA/IgG	Acute glomerulonephritis Predominantly IgA and/or IgG deposits
Membranous/MPGN	Associated with hepatitis B, hepatitis C Syphilis
APSGN	Post infectious glomerulonephritis, associated with bacterial or other infections

*FSGS indicates focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; TMA, thrombotic microangiopathy; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis; and APSGN, glomerulonephritis after streptococcal infection. Clinical presentation may be complicated by drug-induced disease (eg, elevated creatinine level secondary to trimethoprim sulfamethoxazole on other nephrotoxins) and/or the presence of tubulointerstitial disease (including acute tubular necrosis), etc.

proteinuria should raise suspicion of the diagnosis.⁸⁹ Less common forms of glomerulopathies associated with HIV include IgA deposition, microangiopathy, and acute renal failure.⁸⁵ Regarding the latter, renal biopsy may be necessary to distinguish the cause of acute renal failure in these individuals. Other infections associated with the nephrotic syndrome are given in Table 4.³⁰

A variety of neoplasms and drugs have been linked to the nephrotic syndrome; the more common pathologic associations are indicated in Table 4.^{61,90} In most cases, the neoplasm is obvious from the history and results of physical and laboratory examinations, although occasionally the nephrotic syndrome represents the initial manifestation of disease. Nonsteroidal anti-inflammatory drugs are the most common drugs associated with the nephrotic syndrome, probably the result of their widespread use. With drug-induced disease, determining causality may be difficult, as resolution of nephrosis may take weeks to months after discontinuation of use of the offending agent.

Primary Glomerular Diseases

Idiopathic nephrotic syndrome is the term used to describe nonsystemic disease or disease without another pathogenically relevant association. Patients typically present with

edema and heavy proteinuria.⁹¹ The cause of these entities is uncertain, although circumstantial evidence of an immune-mediated pathogenesis exists in most instances. The terms used to categorize these patients refer to the typical pathologic description of the light microscopy findings of kidney tissue (Table 4). Accordingly, histologic evaluation of kidney biopsy specimens is required to make a definitive diagnosis. These lesions usually are indistinguishable from those of patients with systemic diseases. In fact, kidney biopsy specimens from patients with systemic diseases frequently are categorized as having "disease like" the idiopathic varieties (ie, membranous-like or minimal change-like lesions). Nevertheless, although the causes of these entities are uncertain, identification of the abnormality using results of kidney biopsy has utility in classifying the disease and in predicting outcome and response to therapy.

Diagnosis of Nephrotic Syndrome

Because of these considerations, our recommendations for the initial workup of adults with nephrotic syndrome are outlined in **Table 6**. Unless the GFR is abnormal or rapidly deteriorating, proceed with the diagnostic evaluation and subse-

Table 6. Evaluation of Nephrotic Syndrome in Adults*

History
Family history and history of drug use or toxin exposure
Physical examination
If patient >50 y, usual recommendations for age, including stool examination (hemocult testing 3×)
If stool examination is negative, perform flexible sigmoidoscopy
If stool examination is positive, perform standard gastrointestinal tract workup
Laboratory testing
Complete blood cell count; measurement of serum creatinine, glucose, liver enzymes, lactate dehydrogenase, alkaline phosphatase, and albumin; lipid profile; and chest x-ray
Consider systemic diseases
Fluorescein angiography (for diabetes mellitus)
Antinuclear antibodies (for systemic lupus erythematosus)
Consider malignant neoplasms, eg, amyloid or light chain disease or myeloma
If either patient >50 y or initial evaluation raises suspicion, perform
Serum protein electrophoresis
Serum immunoelectrophoresis
Urine protein electrophoresis
Abdominal fat-pad biopsy
Consider infection
Perform hepatitis C, hepatitis B, human immunodeficiency virus serologic testing
Renal biopsy
To distinguish primary glomerular disease
For diagnosis of unsuspected secondary glomerular disease (eg, amyloid)
To determine disease severity

*If the initial workup is negative, stop looking for other causes; reevaluate in 6 to 12 months.

Table 7. Other Considerations in the Diagnosis of Glomerular Diseases*

Hereditary nephritis (including thin basement membrane disease) ⁹²
Typically X-linked, rarely autosomal recessive
Family history, males severely affected
Female carriers develop hematuria but not renal failure
Type $\alpha(5)$ IV collagen abnormality or impaired assembly of $\alpha(3)$, $\alpha(4)$, and $\alpha(5)$ collagen
Patients who have undergone transplantation may develop anti-glomerular basement membrane (type $\alpha(3)$ IV collagen)
Hemolytic uremic syndrome ^{93,94}
Spontaneous form
Autoantibodies to inhibitor of von Willebrand factor cleaving protease
Familial form
Deficiency of von Willebrand factor cleaving protease
Thrombotic thrombocytopenic purpura ^{93,94}
Malignant hypertension
Interstitial nephritis (eg, drug induced)
Acute tubular necrosis
Atheroembolic renal disease

*Previous history of severe hypertension or hypertensive retinopathy, systemic features (eg, rash, arthritis), or associated complications leading to disseminated intravascular coagulation (eg, sepsis) may be helpful in distinguishing from glomerulonephritis.

quently refer the patient to a nephrologist to assist with management. Further evaluation (and therapy) should be driven by the results of the initial studies. If the results of the initial workup are nor-

mal, the patient most likely has idiopathic nephrotic syndrome. The results of the kidney biopsy distinguish among primary renal diseases and occasionally uncover unsuspected systemic diseases. Kidney

biopsy findings also provide prognostic information, thereby influencing therapeutic decisions.⁵⁹ Thus, we recommend renal biopsy when the diagnosis is uncertain or knowledge of the severity of disease will influence therapy. Nevertheless, if the probability of a specific disease or group of diseases is high, the risk of complication due to biopsy is high, and the risks of therapy appear reasonable (eg, short course of high-dose oral steroids), then empirical therapy without biopsy should be strongly considered.⁶⁰ Empirical use of steroids in children with minimal-change disease is a good example of this approach.

As noted in the discussion of glomerulonephritis, pathological evaluation of the kidney also has utility in defining the disease subtype and determining the severity of disease. The results of renal biopsy are also very helpful when attempting to sort out the potential contribution of 2 or more diseases. In this regard, it is sometimes difficult to determine whether activity of the underlying disease or superimposition of another primary disease is the cause of the worsening situation. For example, nephrotic syndrome in a patient with well-controlled diabetes without retinopathy or other manifestations of microvascular disease should raise suspicion of another cause. The pathological results often are very helpful in the setting of rapidly progressive renal failure in an HIV-seropositive patient; this clinical presentation should evoke a diagnostic workup for other causes of glomerular disease.

RENAL DISORDERS THAT MASQUERADE AS ACUTE GLOMERULONEPHRITIS AND/OR NEPHROTIC SYNDROME

Patients with the diseases listed in **Table 7** may present with significant hematuria, RBC casts, and/or nephrotic-range proteinuria, thus mimicking acute glomerulonephritis or nephrotic syndrome. These conditions should be considered in patients without an obvious disease association. The clinical history, results of physical examination, and laboratory findings are useful in construct-

ing a differential diagnosis. Renal biopsy, however, often is necessary to make a precise diagnosis.

CONCLUSIONS

Early recognition and prompt diagnosis of glomerular disease are essential, because delay in therapy may result in irreversible loss of renal function. The clinical presentation (eg, nephritis vs nephrosis, normal vs abnormal GFR, or systemic symptoms or lack thereof) provides clues to the underlying cause. Serologic evaluations and repeated measurement of serum creatinine levels should be performed in all patients for diagnosis, to determine disease severity and monitor disease progression. Renal biopsy should be performed when either rapid diagnosis is essential, the presence of multiple diseases contributing to the clinical picture confounds diagnosis, and/or the level of disease activity requires pathological determination. Collectively, this diagnostic approach provides rapid evaluation en route to specific therapy.

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