



Published in final edited form as:

*Am J Nephrol.* 2013 ; 38(3): . doi:10.1159/000354390.

## Differential diagnosis of glomerular disease: a systematic and inclusive approach

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### Abstract

**Background**—Glomerular disease is a complex and evolving topic. In evaluating a specific case it is not unusual for the clinician to ask: Am I missing something? Should I biopsy? When? Should I treat first, then biopsy? This work, which is both evidence based and experience based, is intended to address each of these concerns, and many other issues relevant to the differential diagnosis of glomerular disease.

**Summary**—The central approach is the use of diagnostic algorithms that are based on quantitative measures routinely obtained early in the course of the diagnostic evaluation. The algorithms are designed to be easy to navigate, systematic, and inclusive. Also provided is a detailed and prioritized list of recommended diagnostic testing, and the rationale for each test.

**Key message**—This work is intended to facilitate accurate diagnosis in the individual patient presenting with evidence of glomerular disease.

### Keywords

glomerular disease; proteinuria; glomerulonephritis

## INTRODUCTION

A glomerular disease can be assumed to be present if the patient manifests glomerular hematuria, glomerular proteinuria, or both.

Glomerular hematuria is the result of disruption of the glomerular filtration barrier (GFB) to the extent that red cells are able to pass through the GFB. The hallmarks of glomerular hematuria are that the urine sediment shows:

- Increased numbers of red cells that are acanthocytes. These are red cells that have been distorted by passage through the GFB [1]. If 5% of urine red cells are acanthocytes, this has about a 50% sensitivity and 95% specificity for glomerular hematuria. Increased numbers of small red cells is also characteristic of glomerular hematuria [2].
- The presence of casts that contain red cells or a mixture of red cells and white cells. These “cellular casts” are formed when red cells and white cells are forced through the GFB and then become encased in a protein matrix (Tamm-Horsfall protein). Eventually these casts are extruded into the urine. In urine sediment these casts are

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Conflict of Interest Statement: All authors have no conflict of interest of any type.

diagnostic of glomerular hematuria. When seen in tubular lumens on kidney biopsy, they are diagnostic of glomerular hematuria.

In patients with glomerular hematuria, acanthocytes are far more common than cellular casts. Cellular casts usually indicate a more severe form of glomerular injury [3].

Glomerular hematuria is usually accompanied by increased albuminuria. This is consistent with the notion that the disruptions of the GFB that are sufficiently severe to cause hematuria also increases albuminuria. In this regard, it has been reported that, in those with glomerular hematuria, the proportion of urine protein that is albumin usually exceeds 40% [4].

Glomerular proteinuria is the result of disruption of the GFB to the extent that plasma proteins, which normally are largely excluded from the glomerular filtrate, are able to readily pass through the disrupted GFB. The most abundant of the plasma proteins is albumin. So, the hallmark of glomerular proteinuria is albuminuria. The threshold for abnormal albuminuria is 30 mg albumin/g urine creatinine [5]. However, albuminuria is not diagnostic of glomerular proteinuria. Albuminuria can also occur in those with tubular proteinuria. The albuminuria in tubular proteinuria reflects tubular injury that results in decreased tubular reabsorption of the albumin that normally is filtered (about 1 g/d) and normally is nearly completely reabsorbed by the renal tubules [6]. Also, marked albuminuria can occur in overflow proteinuria (increased urinary excretion of immunoglobulin light chains or heavy chains because of their overproduction). The albuminuria occurs because the free monoclonal light chains or free monoclonal heavy chains induce a glomerulopathy (light chain deposition disease, heavy chain deposition disease, AL amyloidosis or AH amyloidosis), which then cause glomerular proteinuria. Also, the filtered paraproteins can cause tubular injury, which causes albuminuria. So, the presence of substantial albuminuria does not exclude tubular proteinuria or overflow proteinuria.

Abnormally increased albuminuria can be assumed if the urinary dipstick shows a value of 2+ or greater (> 100 mg/dl). However, a false positive test for albumin by dipstick can occur in very concentrated urine (specific gravity > 1.030) or in very alkaline urine (pH > 7.0 in which the high pH is the result of bicarbonaturia) [7]. Highly alkaline urine is seen in those on a high alkaline-ash diet (strict vegetarians) or in those receiving high-dose sodium bicarbonate therapy. A false positive test for albumin due to concentrated urine or alkaline urine can be confirmed by testing the urine with 20% sulfosalicylic acid (SSA) and showing that no turbidity develops with addition of the SSA. In alkaline urine bubbles may develop as the bicarbonate in the urine is changed to CO<sub>2</sub> by the SSA [7].

Albuminuria is confirmed by immunoassay. Tubular proteinuria, and overflow proteinuria are confirmed by urine immunofixation assay, which characterizes the low molecular weight proteins in urine. The routine clinical laboratory tests for urine protein are chemical assays (e.g., pyrogallol red or Coomassie blue), which detect both albumin and non-albumin proteins (total proteinuria) [6]. In general, if glomerular disease is the cause of the proteinuria, albumin represents > 40 % of total proteinuria (i.e., the ratio: urine albumin (A)/protein (P)(APR) > 0.4) If the urine total protein/creatinine ratio (PCR) is > 0.4 usually the APR is 60–80% of total proteinuria [4,6,8,9]. So, in most of these patients, measuring total proteinuria provides about the same information as measuring albuminuria, and is much less expensive. However, in those with total proteinuria < 500 mg/d, the preferred method for monitoring glomerular proteinuria is by measuring albuminuria. The rationale is that even though these patients have glomerular proteinuria, most of the proteinuria can be non-glomerular in origin. So, total proteinuria can obscure clinically important changes in albuminuria [6].

If tubulo-interstitial disease is the cause of the proteinuria, albumin usually is less than 40% of the total urine protein (APR < 0.4) [4,8,9].

In light of the above, it is clear that determining whether a glomerular disease is present is relatively straightforward. However, determining which glomerular disease is present can be challenging because there are multiple pathways to glomerular disease, including non-glomerular kidney diseases that transform into a glomerular disease through the process of secondary focal and segmental glomerular sclerosis (secondary FSGS) as shown in Figure 1. Adding to the challenge of differential diagnosis of glomerular disease are the following paradoxes:

**1. Glomerular hematuria can be present even though glomerulonephritis (inflammatory glomerular disease) is not present.**

Examples include:

- Diabetic nephropathy. Glomerular hematuria, including red blood cell casts, is a not uncommon manifestation in patients with biopsy proven diabetic glomerulosclerosis [10,11].
- Warfarin-related nephropathy (WRN). This is a newly recognized but not uncommon syndrome in which acute kidney injury (AKI) follows shortly after an increase in INR to > 3.0. On kidney biopsy there are multiple tubules occluded by red blood cell casts but the glomeruli usually are unremarkable. So, the patient manifests severe glomerular hematuria in the absence of glomerulonephritis. WRN can occur in those with or without chronic kidney disease, although the presence of chronic kidney disease increases the risk of WRN by about twofold [12–15]. Glomerulonephritis may especially increase the risk of WRN [16].
- Constitutive abnormally thin or thick glomerular basement membrane (GBM) disease. These conditions can also cause prolonged gross hematuria thereby mimicking severe glomerulonephritis [17–19].
- Atheroembolism in which the cholesterol crystals damage the glomeruli causing glomerular hematuria [20].
- Allergic interstitial nephritis. This can mimic glomerulonephritis by causing gross hematuria, including acanthocytes, and overt proteinuria [21–23]
- Idiopathic FSGS. Glomerular hematuria is common in this disorder [24].

**2. Hematuria can be absent or minimal even though the patient has severe glomerulonephritis.** This is not rare phenomena. The published work states that the urine sediment can appear “normal or bland” [25–28]. In our experience a better description is that the urine sediment is “unremarkable” in that it contains few or no red cells. If acanthocytes are present, they are rare. Also, there are no cellular casts. This paradox can be explained if the severely affected glomeruli do not contribute importantly to urine formation, and the other glomeruli have relatively little inflammatory change. The combination of severely involved glomeruli side by side with minimally involved glomeruli is especially common in ANCA-related vasculitis [29].

**3. In diabetic glomerulosclerosis proteinuria and microalbuminuria can be absent even in Stage 3 CKD.** This is common and is seen in both Type 1 and Type 2 diabetics with nephropathy [30–33]. However, progression to end-stage kidney disease is strongly dependent upon the development of macroalbuminuria [34].

4. **Proteinuria can be nephrotic range and accompanied by microscopic and even gross hematuria suggesting a form of severe primary or secondary glomerulopathy, but the problem is malignant hypertension.** As the malignant hypertension is controlled, the kidney manifestations rapidly resolve (see UpToDate: Malignant hypertension and hypertensive encephalopathy). So, generally, malignant hypertension can be easily distinguished from severe glomerulonephritis which, generally, does not present with malignant hypertension and does not resolve rapidly.
5. **Non-glomerular kidney disease that results in substantial nephron loss can, over time, develop secondary FSGS with nephrotic-range proteinuria** (see Figure 1) [35–37].
6. **Glomerulopathies that began as a primary or secondary glomerulopathy can transform into secondary FSGS.** This occurs when the initial glomerulopathy results in substantial nephron loss (e.g., > 50% loss) [35,38]. If the surviving glomeruli heal, the patient will show an elevated serum creatinine but proteinuria will be low level because the surviving glomeruli are in good condition. However, over time the surviving glomeruli may be transformed into a new glomerulopathy, secondary FSGS (Figure 1). In such patients nephrotic-range proteinuria can develop. Hematuria usually is not conspicuous. The clinician must then decide whether the patient is experiencing recurrence of their primary or secondary glomerulopathy, or another glomerulopathy is developing, especially secondary FSGS [39].

Note that the term “secondary FSGS” can also refer to glomerulopathies in which the characteristic change is FSGS but, unlike primary FSGS, the cause of the FSGS is known (e.g., FSGS secondary to HIV infection). In these forms of secondary FSGS, the glomerular changes may be initiated by the disease process itself, not hyperperfusion injury [40].

7. **The biomarkers that are used to detect the presence of a secondary glomerulopathy may be unreliable.** As examples, the ANA, which is the hallmark of SLE and certain other autoimmune-related glomerulopathies, is very sensitive but very non-specific. Indeed, the vast majority of patients with a positive ANA do not have lupus or any other autoimmune disease [41]. Antineutrophil cytoplasmic antibodies (ANCA), the hallmark of ANCA-related vasculitis, are positive in conditions that can mimic ANCA-related vasculitis such as infection (bacterial endocarditis, atypical pneumonia, invasive amoebiasis, and HIV), cancer and other conditions such as inflammatory bowel disease and cystic fibrosis, and during therapy with propylthiouracil or hydralazine [42–48]. Low levels of complement C3 and C4 are the hallmarks of classical pathway activation by diseases caused by deposition of circulating immune complexes. However, low C3 and C4 can be present in conditions as disparate as primary antiphospholipid syndrome [49], sepsis, severe liver disease, and severe atheroembolism [50].
8. **Kidney biopsy, which is the ultimate step in the differential diagnosis of glomerular disease, often does not provide a disease-specific result.** There is only a limited number of ways that the glomerulus can respond to injury. So it is not surprising that the same glomerular pattern of injury can be the result of a wide range of pathogenetic mechanisms. For example, membranous nephropathy can be the result of a variety of disease mechanisms including idiopathic, SLE, infections with Hepatitis B, Hepatitis C, HIV, syphilis, or parasites, or can be drug induced (NSAIDs, gold injections, penicillamine) [51] Similarly, glomerulonephritis with a membranoproliferative pattern can be the result of a systemic immune complex

disease (for example, bacterial endocarditis, systemic lupus erythematosus, or hepatitis C virus), or genetic or acquired complement dysregulation, chronic thrombotic microangiopathy, monoclonal immunoglobulin deposition disease, or cryoglobulinemia [52,53]. Pauci-immune crescentic glomerulonephritis (immune complexes are absent or minimal) is characteristic of ANCA-related glomerulonephritis. However, little or no immune complex deposition can also be seen in some infection-related glomerulonephritides, including legionella, visceral abscess, and other infections [54–58]. Nodular glomerulosclerosis, the hallmark of diabetic glomerulopathy, can result from conditions as disparate as chronic thrombotic microangiopathy and cigarette smoking [59].

To summarize, in most patients with evidence of glomerular disease there is no single measure that provides a specific diagnosis, not even kidney biopsy. To achieve a specific diagnosis, and all that this implies for appropriate management, it is often necessary to test broadly (as described in the tables shown below) and use a systematic approach (as described in the algorithms shown below). However, to use these tables and algorithms optimally they need to be interpreted in light of the paradoxes described above, and the cardinal manifestations of glomerular disease, which are discussed next.

### Nephrotic syndrome

In adults, nephrotic-range proteinuria is defined as  $> 3.5$  g/d. Severe nephrotic syndrome is variously defined but usually includes the following: proteinuria exceeding 10 g/d, serum albumin  $< 2.5$  g/dl, and severe edema. Deciding whether the patient has severe nephrotic syndrome is of diagnostic value because severe nephrotic syndrome is characteristic of minimal change disease, idiopathic membranous nephropathy, primary FSGS, and AL amyloid of the kidney. By contrast, it is unusual for severe nephrotic syndrome to be a manifestation of IgA nephritis, secondary FSGS, or Alport's syndrome.

The extent to which a glomerular disease can manifest the signs and symptoms of severe nephrotic syndrome is influenced by a number of nonrenal factors including whether the patient has high-salt intake or is receiving calcium channel blocker therapy, both of which exacerbate proteinuria [37]. The edema of nephrotic syndrome can be increased by calcium channel blockers, hydralazine, or the oral hypoglycemic drugs pioglitazone or rosiglitazone. The low serum albumin of nephrotic syndrome can be worsened by low protein intake, liver disease, or nonrenal albumin losses such as protein-losing enteropathy. Other factors influencing edema formation in nephrotic syndrome are the patient's dominant posture (e.g., standing or sitting for prolonged periods) or whether lymphatic or venous insufficiency or congestive heart failure is present [60].

The conditions that cause severe nephrotic syndrome typically are noninflammatory glomerulopathies. So, typically the urine sediment is "bland", indicating that it is not "nephritic" (see below). The typical nephrotic urine sediment contains few red cells, no red cell/white cell casts, but oval fat bodies and fatty casts are present. The latter are the result of the filtration of plasma lipoproteins because of the hyperlipidemia that is characteristic of severe nephrotic syndrome.

### Nephritic syndrome

A nephritic urine can be defined by a urine sediment showing red cells  $> 5$ /high power field (hpf) and the presence of one or more of the following: acanthocytes, red cell casts or mixed red cell/white cell casts [61] (discussed above). A normal urine sediment usually contains fewer than 2 red cells/hpf and acanthocytes and small red cells are generally absent (see UpToDate: Hematuria: glomerular versus extraglomerular). The urine dipstick test for "blood" should also be negative. However, occasionally dipstick testing for blood will show

“blood-trace” in normal persons (unpublished personal observations). If glomerular hematuria is present, usually at least 1 per 20 red cells is an acanthocyte. Cellular casts are far less common than acanthocytes [3].

Pyuria can also be conspicuous in nephritic patients, particularly in inflammatory forms of glomerulonephritis such as post-streptococcal glomerulonephritis. However, pyuria is never the sole manifestation of a nephritic urine sediment. Acanthocytes are best detected by phase contrast microscopy [1]. However, acanthocytes can also be readily detected by standard transmission microscopy (unpublished personal observations).

## LABORATORY TESTING IN PATIENTS WITH SUSPECTED GLOMERULAR DISEASE

In general, the recommended laboratory diagnostic approach should include routine testing (e.g., a “metabolic panel”, CBC, and platelet count) and should be the same for all patients presenting with evidence of a major glomerular disease (see Table 1), with a few notable exceptions (see Table 2). The rationale for a single uniform diagnostic approach is that, as discussed in Introduction, there is no pattern of urine sediment, quantitative proteinuria, serum creatinine level, or biomarker testing that definitively rules in or rules out any nephritic or nephrotic glomerular disorder. So, in many instances the final diagnosis (and management plan) is deduced from a mosaic of information that includes both positive and negative outcomes of specific tests. It could be argued that, if it has already been determined that a kidney biopsy is to be done, a more economical approach would be to perform the kidney biopsy, and when the result returns, tailor the laboratory diagnostic approach to the kidney biopsy findings. Although this is reasonable, we suggest that generally it is not the most efficient or cost-effective approach for the following reasons:

- In most instances, the glomerular pattern itself does not identify a specific glomerular disease, as discussed above. So, not having in hand the results of the recommended broad testing can cause important delays in arriving at an accurate diagnosis, and deciding on appropriate management plan.
- The recommended broad testing provides information that is of general management value, regardless of the final diagnosis, as discussed in Tables 1 and 2.
- The recommended broad testing is usually a one-time expense, which often can be justified by the critical importance of quickly and accurately identifying the cause of the patient’s kidney condition.

We recognize, however, that broad pre-kidney biopsy testing (Tables 1 and 2) is not needed for every patient presenting with evidence of glomerular disease and, in whom, kidney biopsy is planned. For example, broad testing is not needed in the patient with indolent, non-severe glomerular disease. In such patients it is appropriate to do limited testing prior to the kidney biopsy. When the biopsy results return, obtain the testing needed to elucidate the cause of the kidney disease and decide on its management.

Assessing GFR from measurement of serum creatinine in the patient with glomerular disease is important for both diagnosis (does the patient have acute or chronic kidney disease) and management (e.g., does medication dose need to be adjusted because of impaired kidney function). In this regard, it is important to recognize the limitations of creatinine-based eGFR equations. These include marked overestimation of true GFR in nephrotic syndrome, especially in those with hypoalbuminemia [62] and uncertainty regarding whether CKD is present because of confounding by age, gender, race [63] and creatinine production if it deviates substantially from normal [64].

## APPROACH TO DIFFERENTIAL DIAGNOSIS OF GLOMERULAR DISEASE IN THE INDIVIDUAL PATIENT USING ALGORITHMS 1, 1A, AND 2

Algorithm 1 is a systematic and inclusive approach intended to narrow the differential diagnosis of glomerular disease to a single cluster of the most likely diagnoses, ranked in approximate incidence. Further diagnostic separation within the diagnosis cluster is achieved by using the references provided herein, and those available from standard sources. For rare or very recently described conditions, references are provided in the algorithm. Algorithm 1 is intended for those with overt proteinuria. Algorithm 1A is intended for those with minor proteinuria.

Algorithm 2 proceeds naturally from Algorithm 1 because it bridges the gap between arriving at the most likely diagnoses, and whether a kidney biopsy is needed to achieve a specific diagnosis. Kidney biopsy usually is not needed for the types of patients described in Algorithm 1A.

Algorithms 1 and 2 are intended for evaluation of the patient with overt glomerular proteinuria arbitrarily defined as  $\geq 1.0$  g/24 h, based on a complete 24-h collection documented by the creatinine content of the collection [65,66]. This level of proteinuria was chosen because it will generally exclude those with mild glomerular disease. In addition, proteinuria  $\geq 1$  g is associated with progression of kidney disease [67] and is generally regarded as a threshold for considering kidney biopsy to elucidate the cause of glomerular proteinuria.

Although Algorithms 1 and 2 are intended for those with proteinuria  $\geq 1.0$  g/d, likely they will also be informative in those with proteinuria 500–1000 mg/d. Algorithm 1A is intended for those with abnormal proteinuria but  $< 500$  mg/d.

The following steps are recommended when applying Algorithms 1 and 1A to the individual patient:

**Step 1** Exclude those for whom the algorithm is not intended, as follows:

- The cause of the proteinuria is tubular proteinuria, documented by urine immunofixation showing that the dominant protein is non-albumin small molecular weight proteins.
- The cause of the proteinuria is overflow proteinuria, documented by urine immunofixation showing increased amounts of free monoclonal light chains or heavy chains or an intact monoclonal immunoglobulin. This is an exclusion from Algorithms 1 and 2 only if a diagnosis of multiple myeloma or B-cell lymphoma can be established by the usual methods. In these instances, Algorithms 1 and 2, and kidney biopsy generally are not needed for diagnosis and management.
- Renal imaging shows evidence of a primary cystic disease of the kidney (autosomal dominant or recessive polycystic kidney disease: ADPKD, ARPKD, tuberous sclerosis, or von Hippel-Lindau disease), obstructive uropathy, or the characteristic radiographic findings of reflux nephropathy.
- The proteinuria is likely related to drug toxicity or hypersensitivity. These cause proteinuria that generally is reversible when the drug is discontinued. As examples, minimal change or membranous

nephropathy associated with NSAIDs, minimal change disease/ FSGS associated with lithium, the proteinuric renal disease associated with heavy metals (gold salts, mercury), rapamune, drug-induced allergic interstitial nephritis or chemotherapy [68] including anti-VEGF therapy. The latter may be overlooked as a cause of glomerular disease when it is used as an intraocular injection to treat macular degeneration [69].

- Relapse of minimal change disease likely is present. In these cases, a trial of steroid therapy is more appropriate than application of Algorithm 1.
- Systemic cancer is present. Here the management strategy is to treat the cancer. If the glomerular disease is the result of cancer, resolution of the glomerular disease may occur [70].
- The patient is pregnant. The manifestations of glomerular disease as induced by or modified by pregnancy is beyond the scope of this work.

**Step 2** Undertake the recommended initial testing/optional testing (see Tables 1 and 2)

**Step 3** Proceed through the algorithm to determine which diagnostic cluster best describes the patient's condition.

**Step 4** Narrow the differential diagnosis by using standard sources, and the information provided herein, including the "paradoxes" and the discussion of nephrotic and nephritic syndrome.

**Step 5** If a specific diagnosis is not achieved, proceed to Algorithm 2. Also proceed to Algorithm 2 if a specific diagnosis is achieved, but the management plan is dependent on whether a specific histologic pattern is present (for example, the WHO/RPS Class II-V of SLE GN).

Algorithm 2 first turns on whether there is evidence of an infection-related glomerulonephritis. Next it turns on whether rapid progression is developing, and it is not explained by hemodynamic factors or drug nephrotoxicity. In such patients the recommendation is to begin high-dose steroid therapy, and then proceed to the kidney biopsy as soon as feasible. The rationale is that, if the patient has an acute immune-mediated glomerulonephritis, TTP, or an anti-phospholipid syndrome, the steroid therapy will move things in the right direction. On the other hand, if the patient has a covert infection, short-term high-dose steroid therapy (e.g., 3 days) is unlikely to cause important difficulties [54,55,71,72]. Similarly, if the patient has HUS, or aHUS a few days of high-dose steroid until that diagnosis can be established, should not cause harm.

If antiphospholipid syndrome is the prime suspect, systemic anticoagulation with heparin should be given until that diagnosis is excluded.

If TTP or aHUS are the prime suspects, plasma exchange with fresh frozen plasma should be given until these diagnoses are excluded. Generally TTP and aHUS do not require a kidney biopsy for diagnosis [73].

Algorithm 2 also turns on whether the serum creatinine is abnormally elevated. In general, a kidney biopsy is not recommended if secondary FSGS or obesity-related glomerulopathy is the likely cause of the proteinuria and elevated serum creatinine. In these circumstances, a more prudent approach is conservative management with kidney protective/antiproteinuric



therapies. In the obese patient, weight loss [38] and ACE inhibitor therapy[74] have been shown to favorably influence their nephropathy. If the patient progresses despite these measures, a kidney biopsy might then be indicated.

Another key example of conditions in which kidney biopsy generally is not part of the initial evaluation is the hypertensive nephrosclerosis that is seen in those of African ancestry [75]. This disorder begins as a low-proteinuria disease, even though the serum creatinine can be substantially elevated (Stage 3 CKD) [76]. Over time, these patients may develop progressive proteinuria, usually related to secondary FSGS. In such patients, aggressive kidney protective/antiproteinuria therapy is recommended, including weight loss, if obese. If these measures fail to control progression, kidney biopsy might then be indicated.

## Acknowledgments

This work is supported in part by NIH grant DK55546, NIH grant R01 DK074661, NIH grant U01 DK085673, NIH CTSA grant UL1RR025755-01, and the James E. Casto Fund

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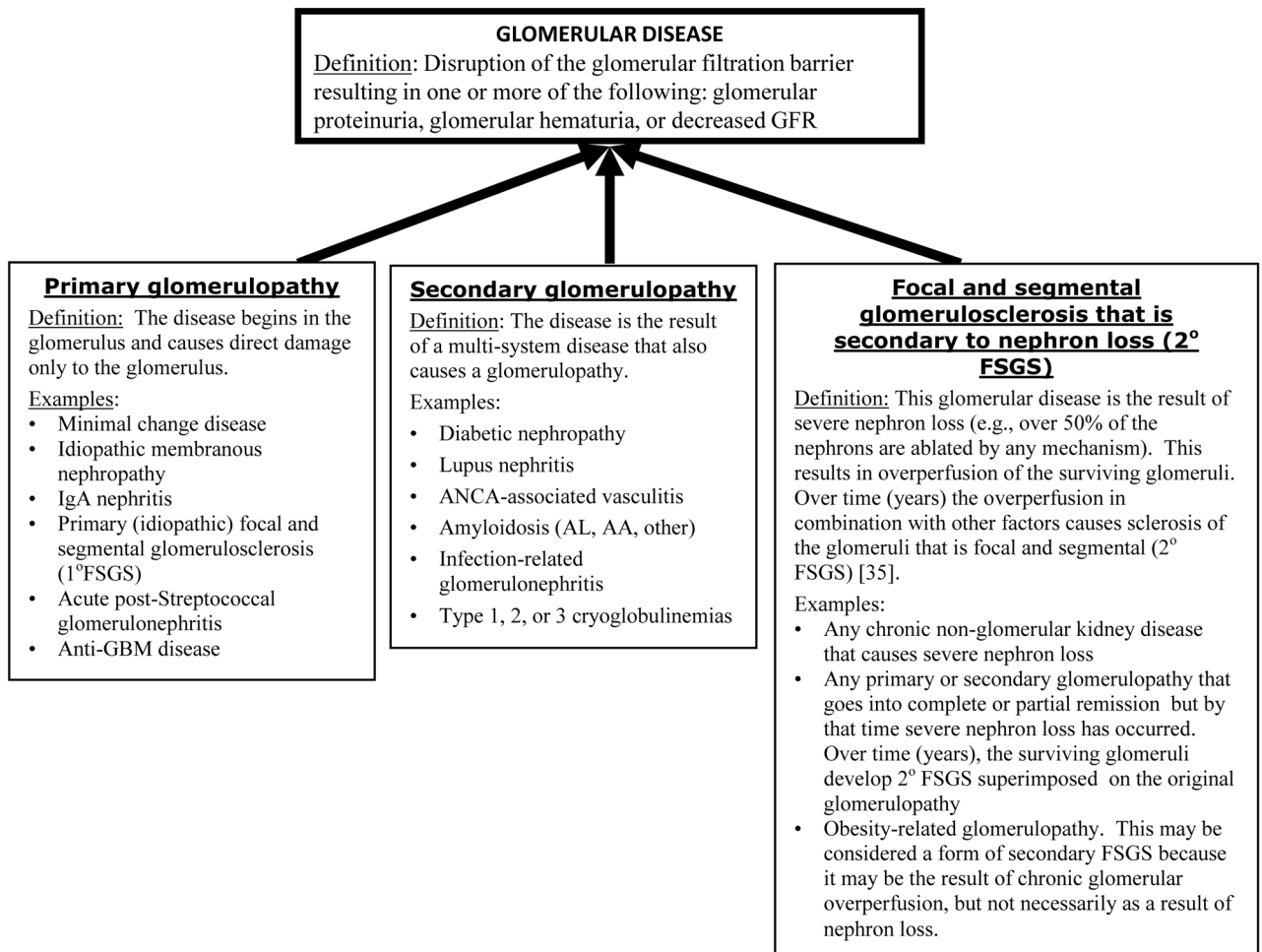
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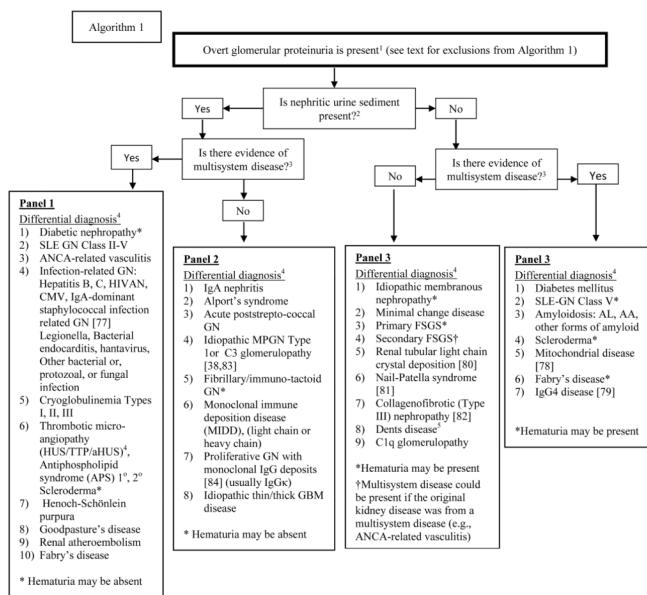
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**Figure 1.**  
 Pathways to glomerular disease.



<sup>1</sup>Overt glomerular proteinuria is arbitrarily defined as urine protein > 1.0 g/d in a collection that is documented to be a complete 24-h collection based on its creatinine content [85].

<sup>2</sup>>5 rbc/hpf + acanthocytes or red cell/white cell casts (see text).

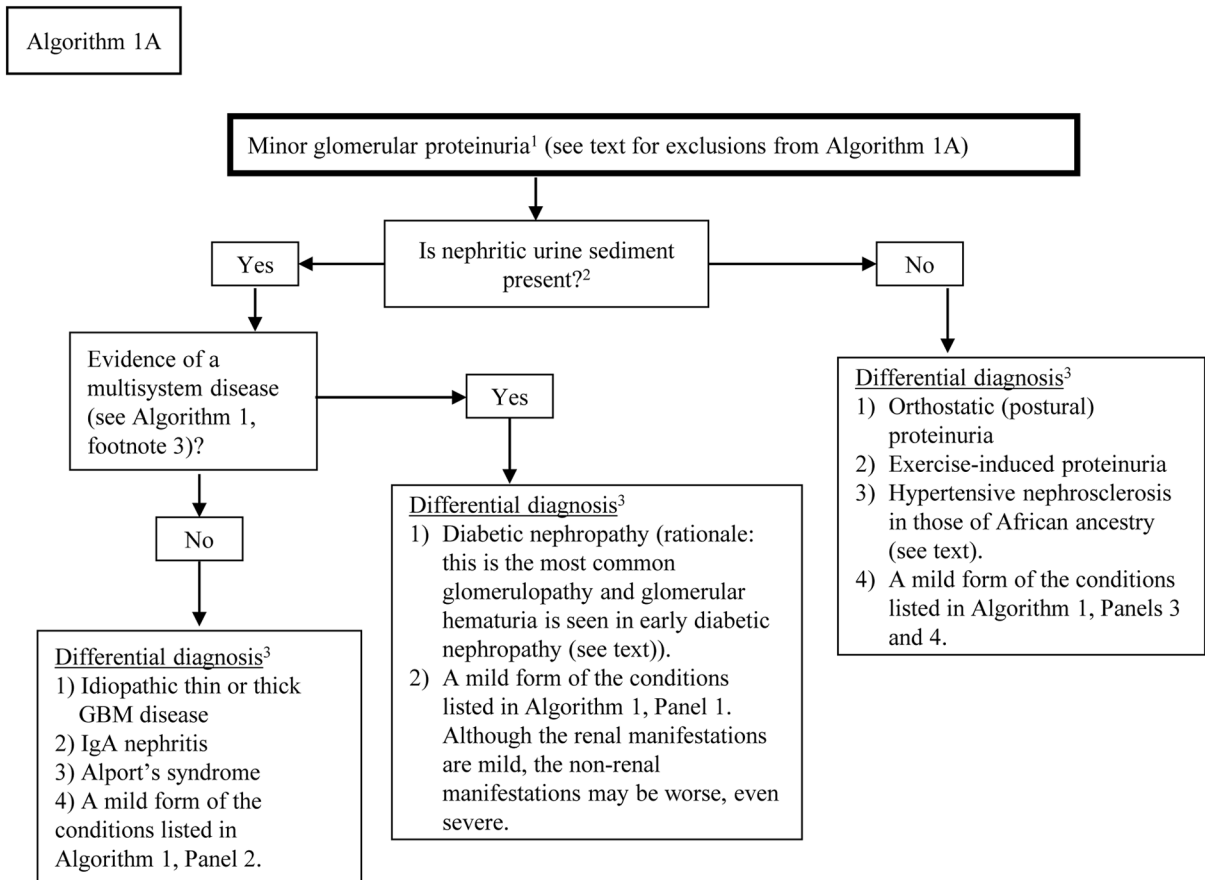
<sup>3</sup>One or more of the following are involved: abdomen (enteritis, colitis, pancreatitis), joints (arthritis), central nervous system (stroke, seizure, cognitive impairment), heart disease, ear (unexplained effusions), extremities (ischemia, infarction), eye (inflammation of the retina, uveae, plexus, or sclera), lungs (hemoptysis, infiltrates, lymphadenopathy, pleuritic pain, pleural effusion), mouth (ulcers), nose (epistaxis), skin (alopecia, purpura, palpable purpura, maculopapular rash, vesicular rash, sclerosis).

<sup>4</sup>In each diagnosis cluster the diseases are listed in order of approximate incidence. Diabetic nephropathy and scleroderma are listed in 2 diagnosis clusters because a nephritic urine sediment may or may not be present.

<sup>5</sup>Nephrocalcinosis causes nephron loss, causing secondary FSGS. Hematuria may be present (see UpToDate: Dents disease).

**Algorithm 1.**  
 Approach to the differential diagnosis of the patient presenting with overt glomerular proteinuria.





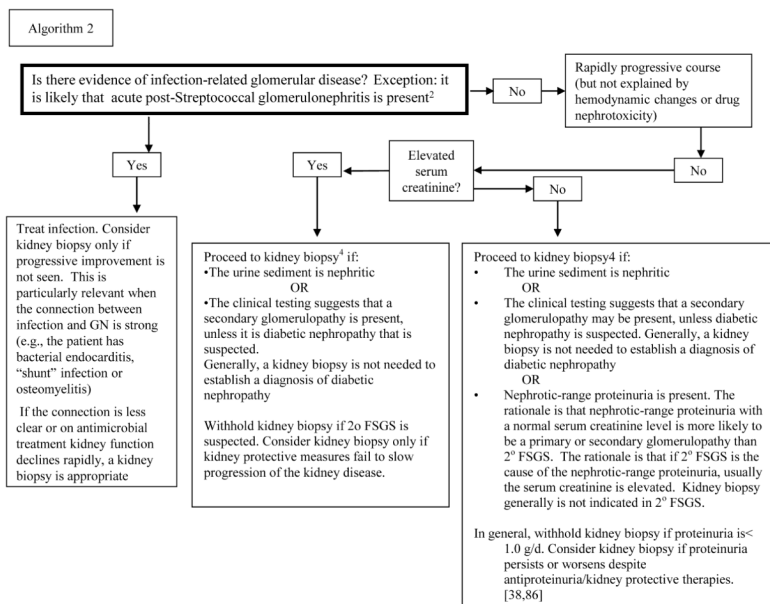
<sup>1</sup>Minor proteinuria is arbitrarily defined as urine protein above normal but  $\leq 500$  mg/d based on a collection that is documented to be a complete 24-h collection based on its creatinine content [85].

<sup>2</sup> $>5$  rbc/hpf + acanthocytes or red cell/white cell casts (see text).

<sup>3</sup>In each diagnosis cluster, the diagnoses are listed in the order of approximate incidence.

**Algorithm 1A.**

Approach to the differential diagnosis of the patient presenting with minor proteinuria.



<sup>1</sup>See discussion of Algorithm 1 for exclusions from Algorithm 2.

<sup>2</sup>Recent streptococcal Group A infection, low C3, normal C4, nephritis sediment, streptozyme test positive. In this instance, kidney biopsy usually is not indicated.

<sup>3</sup>See text for rationale for empiric steroid therapy.

<sup>4</sup>If there are no contraindications to kidney biopsy (see UpToDate: Indications for kidney biopsy).

**Algorithm 2.**  
 Approach to deciding whether the kidney biopsy is needed to manage the patient presenting with overt glomerular proteinuria<sup>1</sup>.

Table 1

Recommended initial testing in the patient being evaluated for glomerular disease<sup>1</sup>

Test	Specific Purpose	Comments
1. 24-h urine collection	Quantify proteinuria. Spot PC (protein/creatinine ratio) is not recommended for this purpose because it is unreliable in individual patients [66,85,87–89]. Measuring albuminuria is useful in monitoring low-level glomerular proteinuria. However, once the total proteinuria exceeds 500 mg/d, albuminuria is about 60–80% of total proteinuria. So, proteinuria provides the same information as albuminuria, and is less expensive [6].	Also recommended is the measurement of sodium, potassium, and urea content of the collection. If the collection is a complete or nearly 24-h collection, these are reliable estimates of 24-h intake of salt, potassium, and protein, which are important for nutrient management the CKD patient [38].
2. Serum albumin	Assess severity of the disruption of the GFB, and whether protein nutrition, and hepatic albumin synthesis is adequate.	At any given level of proteinuria, the lower the serum albumin, the greater is the glomerular permeability to albumin. The serum albumin also assesses nutritional/liver status. For example, if proteinuria is modest (e.g., 3.0 g/d) and serum albumin is low (e.g., 1.5 g/dl), this suggests that a low rate of albumin synthesis is partly to blame for the low albumin level. This may be nutritional or related to liver disease.
3. LDH	Assess for hemolysis, or damage to muscles or viscera.	In the absence of muscle injury or visceral organ necrosis, elevated LDH is evidence for hemolysis (e.g., a thrombotic microangiopathy).
4. Reticulocyte count Platelet count	Assess for increased or decreased red cell production. Assess for thrombotic microangiopathy.	If elevated reticulocyte count or decreased platelet count, do blood smear to search for schistocytes and haptoglobin to assess for intravascular hemolysis. These will assess for thrombotic microangiopathy, which can cause glomerular disease (e.g., vasculitis, antiphospholipid syndrome, TTP, HUS, aHUS, scleroderma, malignant hypertension, blood stream infection, and the cryoglobulinemias).
5. C3, C4	Test for disorders that activate the classical or alternative complement pathways.	Low C3 and C4 are characteristic of the glomerulonephritis caused by deposition of circulating immune complexes (e.g., SLE, infective endocarditis). Normal or nearly normal C3 with very low C4 is characteristic of Type 2 and Type 3 cryoglobulinemia. Very low C3 and normal C4 is characteristic of post-streptococcal glomerulonephritis. Low C3 and normal C4 is seen in HUS, aHUS, C3 glomerulopathy, and idiopathic MPGN Type 1 [50].
6. Serum protein electrophoresis (SPEP) + free light chains	Screen for monoclonal gammopathy (SPEP + free light chains), or hypogammaglobulinemia, hypergammaglobulinemia (SPEP). Serum or urine for immunofixation is not recommended for routine screening because it is much more expensive than SPEP + free light chains, which are sensitive and specific for detection of monoclonal gammopathy [90].	If monoclonal protein is present on SPEP, and/or there is an abnormal ratio of kappa/lambda light chains, serum immunofixation is indicated to characterize the monoclonal proteins [90] (see Algorithm 1). If hypogammaglobulinemia is present, measure serum IgG, IgA, IgM levels to assess for immunodeficiency. If hypergammaglobulinemia is present, measure serum IgG, IgA, IgM levels. If IgG is increased, measure IgG isotypes (IgG1,2,3,4) to test for IgG4 disease.
7. Hepatitis B surface antigen, Hepatitis C antibody, and HIV (if risk factors for HIV are present)	These infections are common causes of glomerular disease.	Even if the patient's glomerular diseases is not the result of one of these infections, it is important to know whether these infections are present, especially if immunosuppressive therapy is planned.
8. ANA	Screen for autoimmune disorders	See text for Limitations of ANA testing to identify SLE and (other autoimmune disorders)
9. ANCA	Screen for ANCA-related vasculitis	See text for Limitations of ANCA testing. If ANCA is present, test for anti-myeloperoxidase (if pANCA positive) or proteinase 3 (if c-ANCA positive).
10. Rheumatoid factor	Screen for cryoglobulinemias (Types 2 and 3), and certain autoimmune disorders.	In cryoglobulinemic glomerulonephritis, plasma cryoglobulins are often undetectable. So, the rheumatoid factor serves as a surrogate marker for Type 2 and Type 3 cryoglobulinemia. This is especially helpful in cryoglobulinemic glomerulonephritis because

Test	Specific Purpose	Comments
		often the deposits are cleared rapidly and are not present in the kidney biopsy.

<sup>1</sup>Not included in this list is testing that is routinely indicated in the CKD patient, such as intact PTH, serum creatinine, BUN, electrolytes, blood glucose, lipid panel, calcium, phosphorus, bilirubin, ALT, AST, CBC and urinalysis (as discussed above).

**Table 2**

Recommended optional initial testing for the patient being evaluated for glomerular diseases.

Test	Specific Purpose	Comment
1. Blood cultures	Test for the blood stream infection, particularly bacterial, fungal, or viral. A low threshold for doing blood culture is recommended. Usually infection-related GN, particularly bacterial infection, manifests with fever and leukocytosis. Remarkably, some times manifestations are absent in infection-related GN.	Most infection-related glomerulonephritides are due to bacterial infections. However, CMV, EBV, and parvovirus may also cause glomerulonephritis. Legionella infection can cause glomerulonephritis but it is more quickly identified by the presence of Legionella antigen in the urine. Bacteria and fungi are detected by the same culture technique. Virus culturing and detection requires separate material. Testing for parasite infections require separate testing methods.
2. Anti-GBM assay	Test for Goodpasture's syndrome.	The renal biopsy findings for Goodpasture's syndrome are diagnostic and generally are available more quickly than anti-GBM assay. So, in general, there is little point in ordering the anti-GBM assay if the kidney biopsy is imminent, unless the patient presents with a pulmonary-renal syndrome.
3. Streptozyme assay	Screen for recent streptococcal group A infection.	Usually the diagnosis of acute post-streptococcal glomerulonephritis can be made by its clinical presentation (recent infection, nephritic urine, low C3 and normal C4, and a positive streptozyme test).
4. D-dimer	To search for evidence of the hypercoagulable state. To search for evidence that a clinically important clotting event has occurred.	Elevated D-dimer (e.g., > 2.0 ng/ml) identifies those who have formed a clot or are at increased risk of clotting [91,92]. In the patient with severe nephrotic syndrome, an elevated D-dimer warrants a search for venous clot (extremities, renal vein) and a search for a thrombotic microangiopathy (see Table 1). Even if clot is not found, the elevated D-dimer may warrant preemptive systemic anticoagulation in the severely nephrotic patient (see UpToDate: Severe nephrotic syndrome). Also, in those with antiphospholipid antibodies, a D-dimer > 2.0 µg/l may be a better predictor of a future major clotting event than the presence of antiphospholipid antibodies [91].
5. Quantitative immunoglobulins (IgG, IgA, IgM)	Characterize the polyclonal abnormalities identified by SPEP (also see Table 1, SPEP)	Low IgG levels are occasionally seen in untreated SLE with or without GN, and in severe nephrotic syndrome [93]. This increases the risk of infection. So careful monitoring for signs of infection in these patients is warranted. Also, if immunosuppressive therapy is needed, IgG levels should be monitored to avoid over-immunosuppression.
6. ADAMTS-13 activity	Assess for TTP.	This test is indicated in any patient with glomerular disease who presents with evidence of a thrombotic microangiopathy [73]
7. Chest X-ray	Assess for a pulmonary-renal syndrome or a pulmonary complication of the glomerular disease (e.g., pleural effusion, cardiomegaly), that would influence management.	A routine chest X-ray is warranted in any patient presenting with glomerular disease to search for a pulmonary-renal syndrome, and especially if the patient has pulmonary symptoms, abnormal lung findings on physical exam, or has a low oxygen saturation by pulse oximeter.