1. How do patients with kidney disease typically present?

Patients with kidney disease typically present in several ways:

- Abnormal blood laboratory studies (e.g., elevated blood urea nitrogen [BUN] and serum creatinine, decreased estimated glomerular filtration rate, or abnormal serum electrolyte values)
- Asymptomatic urinary abnormalities (e.g., microscopic hematuria, proteinuria, microalbuminuria)
- Changes in urinary frequency or problems with urination (e.g., polyuria, hematuria, nocturia, urgency)
- New-onset hypertension
- Worsening edema in dependent areas
- Nonspecific symptomatologies (e.g., nausea, vomiting, malaise)
- At times, symptoms can be specific (e.g., ipsilateral flank pain in those with obstructing nephrolithiasis)
- Incidental discovery of anatomic kidney abnormalities on routine imaging studies (e.g., horseshoe kidney, congenitally absent or ptotic kidney, asymmetric kidneys, angiomyolipoma, kidney mass, polycystic kidneys)
- Symptoms related to underlying systemic disease (e.g., skin changes and/or rash with scleroderma, vasculitis, systemic lupus erythematosus [SLE], arthritis due to gout, SLE, etc.)

2. What important features need to be elicited in the history of patients referred for kidney disease evaluation?

- Previous diagnosis of kidney disease (e.g., previous documentation of BUN and serum creatinine values)
- History of asymptomatic urinary abnormalities (e.g., hematuria, proteinuria)
- History of alterations in urinary frequency or urgency, etc.
- Change in the urinary character or appearance (e.g., smell, color, frothy appearance)
- History of diabetes (duration, severity, end-organ damage)
- History of hypertension (including cardiac history)
- Previous exposure to nephrotoxic medications (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], antibiotics such as aminoglycosides)
- Previous adverse reactions to renin-angiotensin-aldosterone system blocking agents (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists)
- Recent gastrointestinal endoscopic procedures requiring bowel cleansing (risk of acute phosphate nephropathy in those who use phosphate-containing enema)
- Recent exposure to contrast-requiring procedures (risk of contrast-induced acute kidney injury)
- Recent systemic infections or intercurrent illnesses
- Family history of kidney disease or any relative requiring some form of renal replacement therapy (e.g., polycystic kidney disease [PKD], Alport syndrome)
- History of autoimmune diseases
- Recent changes in dose of a medication, or any new medication recently started
- Any over-the-counter medications used (e.g., NSAIDs) and/or herbal, natural supplements

3. Why is smoking history important in patients with kidney disease?

Chronic kidney disease has been shown to be closely related to cardiovascular disease and smoking. The concept of smoking as an “independent” progression factor in kidney disease has been a subject of interest in numerous investigations. Since 2003 several publications of clinical and experimental data concerning the adverse kidney effects of smoking have drawn interest, including large, prospective, population-based, observational studies. These studies clearly demonstrate that smoking is a relevant risk factor, and it does confer a significant increase in the risk for progression of kidney dysfunction (i.e., elevation of serum creatinine) regardless of the underlying cause of the kidney disease.
It has been suggested that urinary cotinine, a metabolite of nicotine, can potentially be used as an objective measure of smoking exposure. Its use has not been studied in the population with chronic kidney disease.

4. What familial diseases are characterized by kidney involvement?
- Autosomal dominant PKD (ADPKD) (chromosomes 4 and 16)
- Autosomal recessive PKD (linked to chromosome 6)
- Autosomal dominant tubulointerstitial kidney disease (previously known as familial juvenile hyperuricemic nephropathy type 1, medullary cystic kidney disease type 2, and or uromodulin-associated kidney disease, linked to chromosomes 1, 16, 17)
- Focal segmental glomerulosclerosis (linked to chromosomes 1, 9, 10, 11, 19)
- Hypertension
- Diabetes mellitus
- Fabry disease
- Alport syndrome
- Sickle cell nephropathy
- Familial hypercalcemic hypocalciuria
- Cystinuria
- HDR syndrome (syndrome of hypoparathyroidism, sensorineural hearing loss, and kidney disease; also called Barakat syndrome; mapped to chromosome 10p)
- Liddle syndromes of apparent mineralocorticoid excess and other monogenic hypertension
- Bartter and Gitelman syndromes
- Congenital nephrotic syndrome (Finish and other variants, mapped to chromosomes 1, 3, 11, 19)

5. What are the common symptoms and signs that are seen in patients with advanced kidney disease?
Chronic kidney disease is usually characterized by nonspecific signs and symptoms in the earlier stages and can be detected only by an increase in serum creatinine.

**Symptoms**
- Loss or decreased appetite (protein aversion)
- Easy fatigability
- Generalized weakness
- Involuntary weight loss (resulting from cachexia) or gain (resulting from fluid retention)
- Alterations in mentation (e.g., lethargy, coma, difficulty concentrating)
- Nausea and vomiting; dyspepsia
- Metallic taste
- Generalized itching or pruritus
- Seizures
- Difficulty breathing
- Edema

**Signs**
- Intractable hiccups
- Frothy appearance of urine (usually results from proteinuria)
- Decreased sexual interest (e.g., erectile dysfunction)
- Restless legs

6. What is a bedside diagnostic test that will suggest the presence of underlying diabetic nephropathy?
Funduscopy. It is believed that the similarities in the vascularization between the retina and the kidneys account for the correlation of the typical microvascular complications commonly seen in patients with diabetes mellitus.

Patients with type 2 diabetes with proliferative retinopathy often present with kidney involvement, manifested by either microalbuminuria (in the earlier stages) or overt proteinuria. Therefore it is recommended that all patients with diabetes and proliferative retinopathy undergo an evaluation of kidney function including testing for microalbuminuria.

It must be remembered that although the presence of retinopathy does support a diabetic source of proteinuria, the lack of diabetic retinopathy does not rule out diabetic nephropathy.

7. What are the common extrarenal manifestations associated with kidney diseases?
- Dermatologic
  - See Question 8
- Arthritis and/or Musculoskeletal Symptoms
  - Lupus nephritis
  - Rheumatoid arthritis
  - Henoch-Schönlein purpura
  - Cryoglobulinemia
  - Sarcoidosis
8. What is importance of itching in kidney diseases, and how do you treat it?

Pruritus or itching is among the most common symptom of ESKD. In severe cases, it can be unrelenting. Although mostly benign in etiology (see xerosis, previous), it can lead to secondary complications, such as excoriations and lichen simplex chronicus, which may be disfiguring in extreme cases.

The use of emollients, moisturizing lotions, keratolytic agents, and hydration have been commonly recommended as conservative treatment.

In some cases, phototherapy (ultraviolet B radiation [UVB] administered as total body irradiation 3 times a week for a total of 8 to 10 sessions) has been shown to be helpful. It has been suggested that UVB (wavelength 280 to 315 nm) inactivates certain pruritogenic chemicals and induces the formation of metabolites with antipruritic effects. The risk of malignancy is fairly significant, especially in fair-skinned individuals.

Topical capsaicin (0.025%), by reducing the levels of substance P in cutaneous type C sensory nerve endings, has been useful for localized pruritus.

Topical tacrolimus (0.03% for 3 weeks, followed by 0.01% for another 3 weeks) may be beneficial but can predispose to dermatologic malignancies, so it is not recommended as a first line therapy or for prolonged use.

Gabapentin (100 to 300 mg after each dialysis treatment) also has antipruritic effects. Prominent side effects include depression of the central nervous system.

\( \mu \)-opioid receptor antagonists, such as per os (PO) naltrexone, has antipruritic properties. In the same family, intranasal butorphanol (a F06BF06B-opioid receptor agonist and \( \mu \)-opioid receptor antagonist) is another option.

Other treatment options include PO-activated charcoal, selective serotonin antagonists (ondansetron and granisetron), oral cromolyn, cholestyramine, thalidomide, erythropoietin, and intravenous lidocaine.

9. What is calciphylaxis?

Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is characterized by painful, subcutaneous purpuric plaques and nodules. These nodules may necrose in advanced disease. Although the skin manifestations are dramatic, it is useful to think of it as a systemic disease, and treat aggressively, given its high fatality rate. When the extremities are involved, the lesions tend to be bilateral and symmetric in distribution and often are described as a mottled or violaceous discoloration with a reticular pattern, similar to livedo reticularis (seen in atheroembolic kidney disease, antiphospholipid syndrome, and cryoglobulinemia). Of note, those with proximal lesions (trunk, buttocks, and thighs) tend to have a worse prognosis compared with those with more distal lesions (forearms and fingers; calves and toes).
Several known risk factors predispose to CUA—namely, poorly controlled secondary hyperparathyroidism, uncontrolled diabetes mellitus, obesity, female sex, duration of renal replacement therapy, history of skin trauma, and use of warfarin.

The increased expression of osteopontin and bone morphogenic protein 4 suggests the pivotal role that inducers of vascular calcification play in its pathogenesis.

Suspicion is the key to early diagnosis. When identified in its earlier stages (nonulcerative), initiation of therapeutic measures has been shown to improve prognosis.

Prevention is the key to management of CUA. Aggressive control of secondary hyperparathyroidism (see Chapter 21) is pivotal.

Sodium thiosulfate is one of the therapies for established CUA. It is believed to work by two mechanisms of action:
1. Chelates calcium from soft tissues
2. Antioxidant, inducing endothelial nitric oxide synthesis, thereby improving local blood flow and soft tissue oxygenation.

A commonly used regimen is 5 to 25 g of intravenous (IV) Na thiosulfate administered toward the end of dialysis for several weeks to months.

Bisphosphonates (IV pamidronate and ibandronate and PO etidronate) may be effective in altering ectopic deposition of calcium phosphate and directly inhibiting calcification via the nuclear factor 

Hyperbaric oxygen therapy improves oxygen delivery to damaged tissues by increasing the partial pressure of oxygen; it also promotes wound healing by supporting phagocytosis and angiogenesis while decreasing tissue edema.

10. What is nephrogenic systemic fibrosis (NSF)?
NSF, previously known as nephrogenic fibrosing dermopathy, is characterized by progressive fibrosis and thickening of the skin (similar to scleroderma), which is particularly painful, and also fibrosis in other organs (e.g., pleura, diaphragm). The skin lesions appear as plaques, papules, or nodules distributed in an asymmetric fashion over the distal extremities. The pathogenesis is deposition of gadolinium (contrast material used in magnetic resonance imaging), which does not get cleared in the presence of severe chronic kidney disease or acute kidney injury. The interval between exposure to gadolinium and the early manifestations of NSF can range from 2 days to 18 months. This variability is attributed to mobilization of gadolinium from bone over time. The risk of NSF appears to be higher with the linear molecules (e.g., gadodiamide) compared with macro cyclic gadolinium molecules.

NSF has no effective treatment and a high fatality rate, so the primary focus is on prevention. Gadolinium-enhanced scans should be avoided in patients with severe chronic kidney disease or acute kidney injury. When gadolinium-enhanced scans are necessary, prophylactic measures that have been described include the use of hemodialysis (HD; eliminates 92% of gadolinium after two HD sessions; 99% after three HD sessions) in patients with advanced chronic kidney disease. Similarly, an intensified regimen of peritoneal dialysis (PD) can remove gadolinium (90% of the gadolinium in 2 days with a regimen of 10 to 15 exchanges per day of PD). The effectiveness of these measures is not clear.

11. What are the other common dermatologic manifestations of kidney disease?
Xerosis or dryness of the skin, especially on the extensor surfaces of the extremities, is common among patients receiving dialysis. It can lead to generalized pruritus and can be uncomfortable.

Changes in pigmentation—in particular, hyperpigmentation—have been attributed to the increased levels of melanocyte-stimulating hormone and the subsequent deposition of melanin in the basal layer of the epidermis.

Some patients may have a “sallow” discoloration of the skin believed to be caused by deposition of lipochrome pigment and carotenoids in the dermis and subcutaneous tissues.

Pallor is commonly associated with varying degrees of anemia as a result of chronic kidney disease.

Uremic frost refers to the deposition of crystalized urea that is excreted from sweat in the epidermis, seen in cases of untreated and advanced kidney disease.

Ecchymoses are commonly associated with uremic platelet dysfunction.

Lindsay nails, also known as “half and half nails,” refer to the whitish discoloration of the proximal half of fingernails, believed to be a result of edema of the nail bed and underlying capillary network.

Acquired perforating dermatosis (Kyrle disease) is predominantly seen in African Americans with diabetes mellitus. It is usually characterized by a linear confluence of papules with a central, oyster shell–like keratotic plug, distributed on the trunk, proximal extremities, scalp, and face, and
the lesions are pruritic. Possible etiologies include an inflammatory skin reaction secondary to the presence of uremic toxins, uric-acid deposits, or scratching-induced trauma.

**Porphyria cutanea tarda (PCT)** commonly presents as a vesiculobullous disease commonly involving the dorsum of both hands and feet but can affect any sun-exposed areas. It is commonly accompanied by solerodermoid plaques (facial hyperpigmentation) and hypertrichosis. It is usually secondary to increased levels of uroporphyrins.

Avoidance of sun exposure is the cornerstone of management. Other measures to decrease uroporphyrin levels include the use of high-flux dialysis membranes (to improve dialysis efficacy) and small-volume weekly phlebotomies in extreme, rare cases.

Common precipitating factors are alcohol intake, use of estrogen and iron supplementations, and chronic infections (e.g., hepatitis B or C virus, human immunodeficiency virus).

One common differential diagnosis is pseudoporphyria, which is clinically similar to PCT with the exception of normal uroporphyrin levels.

12. **What are the causes of palpable kidneys?**
   Palpation for the kidneys is best performed bimanually, with one hand behind the patient in the costovertebral angle and the other anteriorly just below the costal margin. They may be normally palpable in very thin individuals. Pathologic causes include:
   - ADPKD (both kidneys will be palpable)
   - Large kidney tumors
   - Obstruction of the urinary tract with severe hydronephrosis
   - Very large kidney cyst(s)

13. **What are the causes and significance of an abdominal bruit?**
   - Normal: Approximately 5%–25% of normal individuals may have a midsystolic bruit audible, with the prevalence being higher in younger individuals.
   - Renovascular disease: The characteristic bruit seen in renovascular hypertension, due to renal artery stenosis, is an epigastric systo-diastolic bruit. Although it has a low sensitivity, it has a high specificity in the patient in whom one is suspecting renovascular hypertension. Renovascular hypertension can be due to either atherosclerotic disease or fibromuscular dysplasia (typically seen in young or middle-aged women). In fibromuscular dysplasia, extrarenal disease is common, with cervicocranial and other abdominal arteries being involved in particular.
   - Nonrenal causes of abdominal bruit include portal hypertension (periumbilical venous hum), pancreatic neoplasia (epigastric bruit), splenic arteriovenous malformation (left upper quadrant), hepatic carcinoma (right upper quadrant), and abdominal aortic aneurysms.

14. **What are the other important aspects of physical examination in kidney disease?**
   - BP measurement is a keystone of assessment of kidney disease. High BP can be a cause or a consequence of kidney disease. Proper measurement, with adequate resting, measurement of both arms, and assessment of change with posture should be a part of BP measurement.
   - Assessment of volume: This is important for any case of acute kidney injury to make decisions about volume resuscitation, as well for advanced kidney disease to assess for volume overload. Typical components include jugular venous pressure, orthostatic BP measurements, skin turgor, and mucus membranes.
   - Chest examination: Signs of volume overload (pulmonary edema); pericardial friction rub (in uremic pericarditis)
   - Musculoskeletal system: See “Arthritis” section earlier.
   - Skin: Many diseases, especially autoimmune diseases, can be accompanied by a skin rash, such as SLE and Henoch-Schönlein purpura. Kidney disease can also have skin manifestations (see Question 11 for more details).

**KEY POINTS**

1. The similarities in the vascularization between the retina and the kidneys account for the correlation of the typical microvascular complications commonly seen in patients with diabetes mellitus.
2. Tobacco abuse confers a significant increase in the risk for progression of kidney dysfunction, regardless of the underlying cause of the kidney disease.
3. In patients with calciphylaxis, those with proximal lesions (trunk, buttocks, and thighs) tend to have worse prognosis compared with those with more distal lesions (forearms and fingers; calves and toes).
### Commonly Used Terms for Signs and Symptoms of Kidney Disease and their Meaning and Significance

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>Oliguria</td>
<td>Decreased urine output (&lt;0.5 mL/kg·hour in children, &lt;400 mL/day in adults)</td>
<td>Volume depletion; kidney failure</td>
</tr>
<tr>
<td>Anuria</td>
<td>Severely decreased urine output (&lt;100 mL/day)</td>
<td>Kidney failure</td>
</tr>
<tr>
<td>Absolute anuria</td>
<td>No (0 mL) urine output</td>
<td>Blocked/kinked catheter, urinary obstruction</td>
</tr>
<tr>
<td>Dysuria</td>
<td>Pain or burning while passing urine</td>
<td>Urinary tract infections, stones, sexually transmitted infections, interstitial cystitis</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Presence of blood in urine; Gross: visible with naked eye Microscopic: only seen with dipstick/urinanalysis</td>
<td>Source of blood can be urinary tract or glomerulus</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Presence of protein in urine, by dipstick (trace or more) or quantitation</td>
<td>Usually suggests intrinsic kidney disease</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Very small amounts of albumin in urine, usually missed by urine dipstick</td>
<td>Sign of early diabetic kidney damage; in nondiabetic conditions suggests endothelial dysfunction</td>
</tr>
<tr>
<td>Polyuria</td>
<td>Increased amount of urine (opposite of oliguria)</td>
<td>Increased water intake; diabetes</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Increased frequency of urine at night</td>
<td>Usually accompanies polyuria; also with chronic kidney disease (decreased urinary concentrating ability)</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>Frequent urination in the daytime</td>
<td>Benign condition in children; accompanies polyuria; neurogenic bladder; drugs (e.g., tolvaptan)</td>
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### Bibliography