

21.3 Clinical presentation of renal disease 4764 R

21.3 Clinical presentation of renal disease 4764 Richard E. Fielding and Ken Farrington

ESSENTIALS Renal disease may present in many ways, including (1) the screening of asymptomatic individuals; (2) with symptoms and signs resulting from renal dysfunction; and (3) with symptoms and signs of an underlying disease, often systemic, which has resulted in renal dysfunction. History and clinical signs—in many cases these are nonspecific or not apparent, and detection of renal disease relies on a combination of clinical suspicion and simple investigations, including urinalysis (by dipstick for proteinuria and haematuria, with quantification of proteinuria most conveniently performed by estimation of the albumin:creatinine ratio, ACR, or protein:creatinine ratio, PCR) and estimation of renal function (by measurement of serum creatinine, expressed as estimated glomerular filtration rate, eGFR). Asymptomatic renal disease—this is common and most often detected as chronic depression of eGFR (known as chronic kidney disease, CKD), proteinuria, or haematuria, either as isolated features or in combination. Symptomatic renal disease—may present in many ways, including (1) with features of severe chronic depression of GFR—‘uraemia’, manifesting with some or all of anorexia, nausea, vomiting, fatigue, weakness, pruritus, breathlessness, bleeding tendency, apathy and loss of mental concentration, and muscle twitching and cramps; (2) acute kidney injury (AKI); (3) with urinary symptoms—frequency, polyuria, nocturia, oliguria, anuria, and visible (macroscopic) haematuria; and (4) loin pain. Specific renal syndromes—these include (1) nephrotic syndrome—comprising oedema, proteinuria, and hypoalbuminaemia—caused by primary or secondary glomerular disease; and (2) rapidly progressive glomerulonephritis with AKI. Other conditions—renal disease may be associated with and present in the context of many underlying conditions, including (1) diabetes mellitus; (2) renovascular disease; (3) myeloma and other malignancies; (4) infectious diseases, either as a

nonspecific manifestation of the sepsis syndrome or as a specific complication of the particular infection (e.g. haemolytic uraemic syndrome, poststreptococcal glomerulonephritis, hantavirus infection, leptospirosis, and HIV nephropathy); (5) systemic inflammatory diseases (e.g. systemic vasculitides, rheumatological disorders, sarcoidosis, and amyloidosis); (6) drug-induced renal disease; and (7) pregnancy.

Introduction Renal disease may present in a multitude of ways. In practice, it is usually detected as a result of:

- screening of asymptomatic individuals
- symptoms and signs resulting from renal dysfunction
- symptoms and signs of an underlying disease, often systemic, which has resulted in renal dysfunction

Symptoms and signs of renal pathology are often absent or subtle, even in the presence of significant disease, hence the detection of renal problems requires careful evaluation of the history and clinical findings to assess the potential risk of underlying renal disease. This evaluation should focus on features of systemic and inflammatory disease as well as those relating directly to the renal tract, and similarly a drug and obstetric history may help elucidate the cause of renal disease. However, in many cases the history and clinical signs are nonspecific or not apparent, with detection of renal disease relying on a combination of clinical suspicion and simple investigations, including urinalysis and estimation of renal function.

Presentation of asymptomatic renal disease Asymptomatic renal disease is common and may often remain stable and undetected. However, some patients with asymptomatic disease are at increased risk of developing renal failure with the passage of time or in the event of intercurrent illnesses. Active screening for subclinical disease is thus carried out in certain subpopulations with the result that patients may be identified with abnormal renal function or with abnormalities on urinalysis that may indicate significant renal pathology. Examples of such screening include:

- screening patients in primary care—general population screening via eGFR reporting (see ‘Asymptomatic renal dysfunction and 21.3 Clinical presentation of renal disease

Richard E. Fielding and Ken Farrington

21.3 Clinical presentation of renal disease 4765 screening for chronic kidney disease’); monitoring of patients at ‘high risk’ of developing renal disease (e.g. hypertension, diabetes, or multisystem disease); and occupational and insurance medicals

- screening patients admitted to hospital with acute illnesses—as an incidental finding, and as part of renal and electrolyte surveillance in patients at risk (e.g. in the presence of sepsis, hypovolaemia, and usage of nephrotoxic drugs)
- incidental finding on abdominal imaging—stones, cysts and tumours, or reduced renal size
- screening of the family members of patients with inherited renal disease

Asymptomatic renal dysfunction and screening for chronic kidney disease Traditionally, the main means of assessing renal function has been estimation of serum creatinine, and this can be used—with or without estimation of urinary creatinine excretion—to estimate the GFR, as described in Chapter 21.4. The Cockcroft–Gault equation, which estimates creatinine clearance from serum creatinine, weight, age, and sex, has largely given way as a screening tool to the Modification of Diet in Renal Disease (MDRD) formula, which in its simplest form generates an eGFR normalized to body surface area from serum creatinine, age, sex, and race. Using this method, population studies have estimated the global prevalence CKD as around 15%, with that of moderate to severe kidney failure (eGFR <60 ml/min per 1.73 m² body surface area—stage 3 to 5 CKD) as around 8% (Fig. 21.3.1). Over 90% of these subjects have CKD stage 3 (eGFR 30–59 ml/min/1.73m²), most of whom are elderly, and it is notable that very few progress to require treatment for endstage kidney disease (ESKD). Over a five-year period, only around 1 to 3% of people with CKD stage 3 progress, compared with about 20% of those with CKD stage 4, but it is increasingly recognized that CKD is an important risk factor for cardiovascular mortality. People with CKD are around 10 times more likely to die

than to progress to ESKD, with cardiovascular disease being the commonest cause of death.

Population and 'risk group' screening for renal dysfunction

Population data suggest that most renal disease identified by screening is not progressive, but there are subpopulations in which progressive renal disease is more likely and in whom early intervention and optimal management may delay or prevent the need for dialysis. Hence in the United States of America and the United Kingdom, guidelines have been drafted in which 'risk groups' are screened for renal dysfunction/CKD (Box 21.3.1). It is not yet known whether screening for renal dysfunction has any effect on outcome, but in the United Kingdom, data on the prevalence of CKD and associated information such as blood pressure measurement, its control, and the use of angiotensin-converting enzyme (ACE) inhibitors in the CKD population, were incorporated into the Primary Care Quality and Outcomes Framework, which linked funding to the achievement of targets. As a consequence, there has been a substantial rise in the number of patients identified with asymptomatic renal dysfunction, and an increased rate of referral to secondary care, especially of elderly patients. There is still considerable doubt about the validity and value of labelling many very elderly people as having moderate to severe renal failure, especially since in many patients an eGFR in this range seems to confer a very much higher risk of cardiovascular demise than of ESKD.

Stage 3 (7.6%) Stage 2 (3.9%) Stage 1 (3.5%) Stage 4 (0.4%) Stage 5 (0.1%)

Fig. 21.3.1 Global prevalence of chronic kidney disease (CKD stages 1–5) in the general population. Overall global prevalence of CKD (stages 1–5) has been reported as over 15%.

Box 21.3.1 Summary of United Kingdom guidelines for serum creatinine measurement and estimation of GFR

Serum creatinine concentration should be measured at initial assessment and then at least annually in all adult patients with the following conditions:

- Persistent proteinuria
- Unexplained haematuria
- Identified renal pathology
- Conditions associated with a high risk of developing obstructive kidney disease:
 - Bladder voiding dysfunction (outflow obstruction, neurogenic bladder)
 - Urinary diversion surgery
 - Urinary stones
- Conditions associated with a high risk of silent development of parenchymal kidney disease:
 - Diabetes
 - Hypertension
 - Cardiovascular disease—ischæmic heart disease, chronic heart failure, peripheral vascular disease, and cerebrovascular disease
 - Conditions requiring long-term treatment with potentially nephrotoxic drugs:
 - ACE inhibitors, angiotensin receptor blockers, NSAIDs, lithium, mesalazine, ciclosporin, and tacrolimus
 - Multisystem diseases that may involve the kidney:

- Systemic lupus erythematosus
- Systemic vasculitides
- Myeloma
- Rheumatoid arthritis
- Individuals with a family history of stage 5 CKD or hereditary renal disease

section 21 Disorders of the kidney and urinary tract 4766 Employment or insurance health screening As well as targeted screening of 'at-risk' populations, asymptomatic renal disease may also be identified as a result of employment or insurance health screening. Common abnormalities identified are hypertension or abnormal urinalysis, such as proteinuria and nonvisible (microscopic) haematuria. Patients identified in this way will often be referred for subsequent investigation. Screening for renal dysfunction in secondary care In the secondary care setting, patients in specialist clinics who are at risk of renal disease, such as patients with diabetes, are periodically screened for the development of hypertension, proteinuria, and renal dysfunction. Renal disease also often presents in acute medical and surgical patients, with up to 15% of patients admitted as emergencies to hospital suffering some acute deterioration of kidney function, mostly due to hypotension, sepsis, or the use of nephrotoxic drugs (see Chapter 21.5). Monitoring renal function in such patients may help in the acute management of their illness and may also identify those with underlying chronic renal impairment who require long-term management. Screening for drug-induced renal disease Renal disease resulting from the use of nephrotoxic drugs is often asymptomatic, and CKD may develop as a result of long-term use of agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), lithium, and calcineurin inhibitors. Often the only evidence for this is a progressive rise in serum creatinine and fall in eGFR, which may be progressive and—if not detected by routine screening—may present with advanced renal failure. Other drugs such as ACE inhibitors may cause an acute deterioration in renal function, screening for which is required, especially in high-risk groups. Other incidental findings of renal disease Subclinical renal disease may also present as an incidental finding on biochemical testing, for example, abnormalities of potassium and acid-base homeostasis identified on a 'routine' sample may indicate a renal tubular acidosis and prompt further investigation for an underlying cause. Renal disease identified incidentally with imaging Advances in imaging technology combined with their widespread use have increased the number of incidental renal abnormalities identified. Many of these are anatomical abnormalities which are of little consequence, such as duplex ureters and isolated renal cysts, but significant pathology is sometimes found incidentally, such as polycystic kidneys, renal tumours, and asymmetrical kidneys. Family screening for renal disease Patients with a family history of inherited renal disease may also be identified with early, asymptomatic renal disease as a result of screening. The most common example is autosomal dominant polycystic kidney disease, which may be reliably identified by ultrasonography from the third decade onwards. The identification of disease genes for inherited renal diseases such as autosomal dominant polycystic kidney disease, tuberous sclerosis, von Hippel-Lindau disease, Alport's syndrome, and congenital nephrotic syndrome raises the possibility of future antenatal screening and early detection of these diseases long before they become clinically manifest. Proteinuria Detection of proteinuria The availability of reliable and cheap urine dipstick reagent strips has led

to their widespread use to screen for and monitor renal disease in primary and secondary health care (Fig. 21.3.2). Most multireagent strips are sensitive to 100 to 200 mg/litre of protein, giving either a 'trace' or '+', although some designed to screen for microalbuminuria are more sensitive. Within the general population, up to 5% of apparently healthy adults and 16% of those aged over 80 years have either a 'trace' or '+' of protein, but most of these do not have significant treatable disease, making routine population screening uneconomic and unnecessary. Reagent strips do not detect low molecular weight proteins such as immunoglobulin light chains, and thus assay of light chains using urine immunoelectrophoresis is essential as part of the investigations for myeloma, primary amyloidosis, and light-chain glomerulopathy. The kidney normally excretes less than 150 mg of protein in 24 h, mainly due to failed tubular reabsorption of albumin. Urinary protein excretion also reduces overnight while recumbent, but increases during the day owing to posture and exercise. Urinary protein concentration also depends on urine flow rate. To overcome the diurnal variation, proteinuria has been traditionally evaluated from a 24-h urine collection, but these have been largely superseded by measuring the ratio of albumin or protein to creatinine in the urine (albumin:creatinine ratio, ACR; protein:creatinine ratio, PCR). This method has been validated against 24-h urinary collections and—as a rule of thumb—a urinary ACR of 70 mg/mmol or PCR of 100 mg/mmol equates approximately to a 24-h protein excretion of 1 g/24 h. Screening for proteinuria Guidelines aimed at identifying subclinical renal disease recommend screening for proteinuria only for patients with renal disease or at increased risk of renal disease. The guidelines recommend use of the urinary ACR rather than standard reagent sticks in this population. Current United Kingdom guideline recommendations (2014) for screening in this population are summarized in Box 21.3.2. Approach to patient with proteinuria Proteinuria may be an early presentation of renal disease, but transient proteinuria is not associated with significant renal disease. A finding of proteinuria should lead the physician to take a history focusing on risk factors for renal disease (e.g. diabetes, drugs, Fig. 21.3.2 Multireagent test strips used to screen patients for proteinuria and nonvisible haematuria.

21.3 Clinical presentation of renal disease 4767 multisystem disease, and family history), to measure the blood pressure, and examine for oedema (Box 21.3.3). In the absence of risk factors or signs of renal disease, transient proteinuria is not likely to indicate underlying renal disorder, hence an initial finding of proteinuria on dipstick testing should be repeated a week or so later, and any positive result confirmed and quantitated by estimation of ACR (or PCR). If postural or orthostatic proteinuria is suspected, an early-morning urine specimen should be sent for ACR (or PCR). The diagnosis is substantiated by the finding of normal urinary protein excretion in this specimen. Management of asymptomatic proteinuria Persistent proteinuria (ACR >70 mg/mmol, PCR >100 mg/mmol) on two or more occasions requires further investigation with:

- renal function (eGFR)
- serum albumin, for diagnosis of nephrotic syndrome
- serum paraprotein electrophoresis and urinary Bence Jones protein for myeloma
- immunological screen (antinuclear antibodies, complement, antineutrophil cytoplasmic antibodies (ANCA))
- renal ultrasonography
- consideration of renal biopsy

The presence of nonvisible haematuria in addition to proteinuria implies a high likelihood of intrinsic renal disease. It may be the first sign of a severe glomerulonephritis, perhaps in relation to multisystem disease. Apparently asymptomatic patients with persistent proteinuria and haematuria may describe subtle symptoms on close questioning (e.g. myalgia, arthralgia, 'sinusitis', rash, or fever) which may be clues to an underlying multisystem disorder. Nephrology referral for further investigation, including serum ANCA, antiglomerular basement membrane (anti-GBM) antibodies, antinuclear and anti-double-stranded

DNA antibodies, complement levels, and renal biopsy, is indicated. Those with abnormal renal function, haematuria, and proteinuria require urgent referral. Asymptomatic nonvisible haematuria

Nonvisible haematuria may potentially arise from anywhere in the urinary tract. As with renal dysfunction and proteinuria, isolated nonvisible haematuria, that is in the absence of other features of renal disease—hypertension, renal impairment, proteinuria, systemic disease, or a family history of renal disease—is common. Population studies indicate a prevalence between 0.2 and 16%, with a higher prevalence of up to 18% in men aged over 50 years. Studies of male army recruits screened and followed up for 12 years showed that 39% had nonvisible haematuria on one occasion, and 16% had nonvisible haematuria on two or more occasions. Although isolated nonvisible haematuria may be associated with benign glomerular disease, in practice, the main concern is the possibility of urinary tract malignancy. Urothelial and bladder carcinomas account for approximately 5% of nonvisible haematuria. This risk increases with age, particularly in men over the age of 65 years. In contrast, underlying malignancy in those younger than 40 years is very rare, particularly in the absence of risk factors such as smoking and exposure to azo dyes. Causes of nonvisible haematuria

The causes of nonvisible haematuria are summarized in Box 21.3.4. The true prevalence of intrinsic renal disease is unknown because renal biopsies are not routinely performed in the absence of proteinuria or abnormal renal function. However, small biopsy studies of patients with no other cause for haematuria identified a glomerular cause in 16 to 30%. Within this group, IgA nephropathy and thin basement membrane disease are most common.

Management strategy for nonvisible haematuria

The key to managing patients with asymptomatic nonvisible haematuria is identifying risk factors for malignancy. In routine practice, patients older than 50 years, smokers, or those with an occupational history of dye exposure should be investigated for malignancy and referred to a urologist for cystoscopy. Numerous different approaches to the management of patients with nonvisible haematuria have been published, reflecting a lack of consensus and an insufficient evidence base. There are no indications for screening for nonvisible haematuria as the positive Box 21.3.2 United Kingdom guidelines for screening for albuminuria in patients at risk of CKD

ACR estimation should be carried out in people with:

- diabetes
- hypertension
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease, or cerebral vascular disease)
- structural renal tract disease identified on imaging
- recurrent renal calculi or prostatic hypertrophy
- multisystem diseases with potential kidney involvement—for example, systemic lupus erythematosus, vasculitis, and myeloma
- family history of ESKD (glomerular filtration rate <15 mL/min per 1.73 m²) or hereditary kidney disease
- opportunistically detected haematuria
- following an episode of AKI if the GFR remains below 90 mL/min per 1.73 m²

Box 21.3.3 Approach to the patient with dipstick-positive proteinuria

Key features to establish

- Is there any evidence of urinary tract infection?
- Is there any evidence of diabetes?
- Are there any risk factors for, or signs of, renal disease?
- Is proteinuria transient or persistent?

Transient proteinuria

Causes include:

- urinary tract infection
- fever
- exercise
- orthostatic proteinuria

Persistent proteinuria

- Send urine for spot ACR (or PCR)
- Evaluate risk factors for renal disease:

— Diabetes, hypertension, systemic inflammatory disease, myeloma, and family history of renal disease

— Are there any features of nephrotic syndrome (heavy proteinuria with oedema and low serum albumin)?

section 21 Disorders of the kidney and urinary tract 4768 predictive value for malignancy is as low as 5% in an elderly population, and there is little evidence that early detection of disease improves prognosis. Following the detection, on urine dipstick, of nonvisible haematuria without proteinuria, a history of recent menstruation, exercise, or sexual activity should be elicited and the urine sent for microscopy and culture. Urinalysis should be repeated after 7 days. If still positive for blood, in the absence of urinary tract infection, further evaluation is required including measurement of blood pressure, urinary ACR or PCR, and serum creatinine/eGFR. Patients should be referred to urological services to exclude urinary tract malignancy and disease if they are over 40 years of age with: 1. persistent asymptomatic haematuria (defined as two out of three positive dipsticks), or 2. symptomatic nonvisible haematuria, or 3. visible haematuria. Patients should be referred to a nephrologist if a urological cause has been excluded, or the criteria for urological assessment are not met, and the patient has: 1. declining GFR, or 2. CKD stage 4 or 5, or 3. proteinuria with urinary PCR greater than 50 mg/mmol or ACR greater than 30 mg/mmol, or 4. age less than 40 years and hypertension. Patients not meeting criteria for referral to urological or renal services, or who have had negative urological or nephrological investigations, need long-term monitoring in primary care due to the uncertainty of the underlying diagnosis, with appropriate referral should they develop: 1. voiding lower urinary tract symptoms, or 2. visible haematuria, or 3. significant or increasing proteinuria, or 4. progressive renal impairment (falling eGFR), or 5. hypertension.

Symptomatic renal disease Many patients with renal disease remain asymptomatic, but others develop symptoms that may be nonspecific (e.g. due to the gradual onset of uraemia in patients with progressive CKD), renal specific (e.g. loin pain or polyuria), or unrelated to the kidney and manifesting as isolated 'nonrenal' symptoms or as a constellation of symptoms suggestive of a particular systemic condition. Key features to establish are the duration of symptoms, the presence of nonspecific symptoms possibly related to uraemia, the presence of specific renal symptoms, and the presence of symptoms possibly indicative of systemic disease.

Chronic kidney disease The symptoms of CKD are attributed to the gradual onset of uraemia, anaemia, and salt and water retention. Patients often develop these slowly and may not report them until renal function is severely impaired, perhaps even an eGFR as low as 10 ml/min per 1.73 m² or less. The number of symptoms and their severity tend to increase as renal function declines, forming a spectrum from asymptomatic to overtly symptomatic uraemia. Symptoms and the level of eGFR may not correlate well: some patients with an eGFR of 15 to 20 ml/min per 1.73 m² may be symptomatic, whereas a few with an eGFR around 5 ml/min per 1.73 m² may be remarkably symptom free. Most patients have some symptoms by the time that they start dialysis. Indeed, the presence of uraemic symptoms in the context of CKD stage 5 (eGFR <15 ml/min per 1.73 m²) (Box 21.3.5) is now considered the indication to start dialysis. These include anorexia, nausea, and vomiting (in 76% of patients), fatigue and weakness (72%), pruritus (40%), breathlessness and orthopnoea (26%), bleeding tendency (14%), apathy and loss of mental concentration (12%), and muscle twitching and cramps (11%). Factors contributing to the development of 'uraemia' and other symptoms include retention of small-molecular nitrogenous substances and other end products of protein metabolism, metabolic acidosis, salt and water retention, disturbances of mineral metabolism (e.g. phosphate retention), malnutrition, and anaemia. Some of these symptoms may be improved by treatment with agents such as erythropoietin, diuretics, and oral sodium bicarbonate, and dietary advice to improve malnutrition and phosphate control. Others respond to the initiation of dialysis. Some symptoms may persist in spite of all these measures. It is unfortunately not uncommon for patients to present for the first time very late in the course of progressive CKD, with profound and symptomatic uraemia. This is the initial mode of presentation

in Box 21.3.4 Causes of nonvisible haematuria without proteinuria

Glomerular disease • IgA nephropathy • Thin basement membrane disease • Hereditary nephritis (Alport's syndrome) • Other glomerulonephritides (mesangiocapillary glomerulonephritis, vasculitis, lupus, etc.)

Nonglomerular renal disorders • Nephrolithiasis • Pyelonephritis • Renal cell carcinoma • Cystic kidney disease (polycystic and medullary sponge) • Trauma • Papillary necrosis • Ureteric strictures • Hydronephrosis • Sickle cell disease • Renal infarcts and arteriovenous malformations • Renal tuberculosis

Lower urinary tract disorders • Cystitis, prostatitis • Bladder carcinoma • Benign bladder and ureteral tumours and polyps • Urethral strictures

Miscellaneous • Exercise • Over-anticoagulation • Factitious

21.3 Clinical presentation of renal disease 4769

around 20% of patients entering dialysis programmes in the United Kingdom, who tend to be older, more dependent, and with greater comorbidities than those presenting earlier. Late presentation presents major problems: it is not possible to plan dialysis initiation, and patient choice of modality is limited, with haemodialysis being the default mode. Furthermore, it is often not possible to create definitive vascular access, hence patients often need to begin dialysis with temporary or semi-permanent central venous lines. These and other features increase morbidity and mortality after late presentation. It can be difficult and sometimes impossible to distinguish patients presenting late with advanced CKD ('crash-landers') from those with severe AKI with potentially reversible causes. Failure to become dialysis independent by 90 days after dialysis initiation is often taken as proof that the acute presentation was with ESKD rather than AKI. Patients who 'crash-land' are often extremely unwell and may be obtunded with uraemic encephalopathy. Fluid overload is common, with pulmonary and peripheral oedema. Metabolic acidosis is often present and if severe may cause Kussmaul's respiration as well as cerebral and cardiac depression. Patients may also show signs of muscle twitching, which may be a sign of hyperkalaemia or hypocalcaemia. A pericardial friction rub indicates uraemic pericarditis, which if unrecognized may lead to pericardial tamponade and occasionally to fatal pericardial haemorrhage. See Chapter 21.6 for further discussion of CKD.

Acute kidney injury Acute kidney injury is discussed in detail in Chapter 21.5, but, in brief, causes can be classified as being prerenal, renal (due to intrinsic renal disease), or postrenal (obstruction). In the general hospital setting, most cases are prerenal and occur as the result of reduced renal perfusion due to volume depletion (30%), cardiac failure (12%), and sepsis (12%). Drug-induced kidney injury accounts for 30%, urinary tract obstruction 10%, and acute glomerular disease and acute interstitial nephritis cause 5 to 10%. Key features to establish sequentially when managing a patient with AKI are as follows:

1. How ill are they? The condition of patients with similar biochemical abnormalities can range from the asymptomatic to the moribund: those with cardiorespiratory compromise need critical care support.
2. Does the patient need emergency haemodialysis or haemofiltration? The major indications are severe hyperkalaemia, pulmonary oedema, profound acidosis, and severe uraemia—the latter being defined more on clinical than biochemical grounds.
3. Is there a prerenal element that may respond to volume repletion or inotropic support? Clinical examination, perhaps supplemented by central venous pressure measurement, facilitates this decision.
4. Is the patient obstructed? Clinical features can be helpful, and ultrasonography of the urinary tract is usually diagnostic.
5. Is this AKI or chronic renal failure? Sometimes this is difficult or impossible to determine on clinical grounds, but small kidneys on ultrasonography signify chronic disease.
6. Is this intrinsic renal disease? Clinical features of systemic disease and relevant immunological tests (including ANCA and anti-GBM antibody) must be pursued, and renal biopsy will usually be required to establish the diagnosis. As with

CKD, many of the symptoms and signs attributed to loss of renal function are nonspecific and occur with advanced AKI (GFR <15 ml/min per 1.73 m²). However, in contrast to CKD, the acute metabolic changes are often less well tolerated. The greatest danger is hyperkalaemia, which may develop quickly and is almost always asymptomatic until the onset of cardiac arrhythmias and potentially cardiac arrest. Other potentially life-threatening features include pulmonary oedema, metabolic acidosis, and uraemic pericarditis. The clinical context and history are of overriding importance in establishing the likely aetiology of AKI. A patient developing AKI after surgery is likely to have prerenal and acute tubular injury due to a combination of hypovolaemia, sepsis, and analgesia with an NSAID. A patient presenting acutely after a prolonged period of unconsciousness following a drug overdose is likely to have rhabdomyolysis. A patient with a past history of lupus presenting with a recent fever, myalgia, and rash is likely to have rapidly progressive lupus nephritis. A patient with a history of lower urinary tract symptoms or of urinary stones is likely to have obstruction. It is always important to consider the possibility of urinary tract obstruction as it may be readily reversible. Complete anuria is highly suggestive of total obstruction, although it may also occur in patients with rapidly progressive glomerulonephritis (RPGN) and those with acute obstruction of the renal arterial supply. However, urinary output is generally a poor guide to the presence of urinary tract obstruction, and a normal or even increased output does not exclude the diagnosis. All patients with unexplained AKI should undergo ultrasound imaging of the kidneys and urinary tract. This permits the diagnosis or exclusion of obstruction in most cases, and also allows renal size to be assessed: small kidneys indicate chronic renal failure. It is important to emphasize that, after stabilization, patients in whom the clinical features and initial investigations do not give sufficient clues to allow a diagnosis to be established will require a renal biopsy to avoid missing potentially reversible intrinsic renal disease. Details of important and common presentations of acute renal disease are discussed later in this chapter and in Chapter 21.5.

Urinary symptoms Micturition Most symptoms related to micturition relate to problems arising in the lower urinary tract. Bladder outflow obstruction is commonly

Box 21.3.5 Features of uraemia and an eGFR less than 15 ml/min per 1.73 m² body surface area

- Anorexia and malnutrition
- Nausea and vomiting
- Tiredness
- Fluid overload with oedema, breathlessness, and orthopnoea
- Anaemia
- Pruritus
- Mental apathy and depression
- Muscle twitching, restless legs, and cramps
- Bleeding tendency—haematemesis, epistaxis
- Sexual dysfunction—loss of libido and impotence
- Cardiac—pericarditis

section 21 Disorders of the kidney and urinary tract 4770 associated with symptoms such as urgency, hesitancy, poor urinary stream, nocturia, dysuria, and dribbling. Recognition of these symptoms is important as outflow obstruction may result in complete obstruction with AKI or chronic obstructive uropathy with CKD. Patients may also describe discomfort or pain on micturition. This symptom of dysuria may also be associated with burning within the urethra or suprapubic pain during or after micturition. When associated with urinary frequency or fevers in young women, dysuria is likely to be caused by a urinary tract infection. However, dysuria occurring in isolation in men of any age suggests structural lesions within the prostate or bladder and warrants further investigation. Perineal or rectal pain associated with micturition suggests prostatic inflammation, such as prostatitis or malignancy.

Frequency Patients may present with symptoms of increased frequency of micturition. In this situation, it is important to distinguish between frequent voiding of small volumes of urine and an overall increase in urinary volume with more frequent emptying of a full bladder. Charting urinary frequency and voided volumes over a number of days can allow these to be distinguished. The frequent passage of small volumes of

urine suggests bladder irritation (from inflammation, stone, or tumour) or reduced volume from extrinsic compression or contraction (e.g. following radiotherapy). Increased frequency of emptying a full bladder is suggestive of polyuria. Polyuria (defined as a urinary output >3 litres/24 h) may result from solute diuresis, water diuresis, or a combination of both. Solute diuresis occurs in conditions such as hyperglycaemia and salt-losing states (e.g. overuse of diuretics and salt-losing nephropathies). Water diuresis may result from primary polydipsia, failure to synthesize or secrete ADH normally (congenital and acquired cranial diabetes insipidus), or failure of cortical and medullary collecting ducts to respond to ADH (congenital and acquired nephrogenic diabetes insipidus). There are numerous causes of acquired nephrogenic diabetes insipidus, including CKD (especially associated with ureteric obstruction, postobstructive states, and chronic interstitial nephritis), electrolyte abnormalities (hypercalcaemia and hypokalaemia), nephrotoxic drugs (such as lithium and amphotericin), and many other miscellaneous conditions including sickle cell disease, Sjögren's syndrome, and sarcoidosis. Most patients with polyuria have associated thirst, polydipsia, and nocturia. Polyuria needs confirmation by 24-h urinary collection as most patients are unclear as to their true daily urine output. Once it is established that the patient is polyuric, common causes such as hyperglycaemia and excessive diuretic use need to be excluded, after which investigations should focus on excluding primary polydipsia and distinguishing between cranial and nephrogenic diabetes insipidus, as discussed in Chapter 21.2.1.

Nocturia Nocturia is defined as the need to get up once or more times for nocturnal voids. It may have a considerable negative impact on quality of life and in older people predisposes to falls. Three types of nocturia have been identified: low voided volume, nocturnal polyuria, and mixed origin. Nocturia due to low voided volumes occurs in patients with bladder outflow obstruction and those with hyperactive bladders from any cause. Nocturnal polyuria occurs when there is a reversal of the normal circadian pattern of voiding such that there is an increased urine output overnight. These types of nocturia are distinguishable by the use of voiding diaries. Elderly patients who void in excess of 33% of their total 24-h output between 11 p.m. and 7 a.m. are said to have nocturnal polyuria, the corresponding fraction in young adults being 20%. Factors predisposing to nocturnal polyuria include renal impairment, diabetes mellitus, congestive cardiac failure, sleep apnoea, and the mobilization of peripheral oedema due to any cause. In patients without predisposing causes, usually elderly, low nocturnal levels of ADH have been described.

Oliguria and anuria Oliguria is arbitrarily defined as a urinary output of less than 400 ml/24 h or 0.5 ml/kg of body weight per hour. Oliguria is the normal renal physiological response to reduced renal perfusion from any cause and is common in hospital inpatients, particularly those with acute illnesses associated with hypotension and reduced effective circulating volume. Monitoring of fluid balance and urinary output in such patients allows its early detection and treatment, which may help prevent progression to established AKI. The recognition of oliguria should prompt an evaluation of the patient with attention to volume status, blood pressure, and the detection/exclusion of sepsis, followed by appropriate management to optimize blood pressure and circulating volume. Oliguria may also be a feature of intrinsic renal failure due to nephrotoxic drugs, acute glomerulonephritis, or interstitial nephritis, but it is a poor marker of intrinsic renal disease as urinary output often remains normal despite significantly impaired renal function. The development of anuria, meaning the total absence of urine, is strongly suggestive of urinary tract obstruction, which may occur at any level in the urinary tract. A careful history, examination for an enlarged bladder, and digital rectal examination for a prostatic or pelvic mass, should be followed by urgent ultrasonography of the kidneys and bladder. Very occasionally, anuria may be a manifestation of severe intrinsic renal disease, such as a RPGN, cortical necrosis, or renal infarction. Urine appearance and

visible haematuria Visible haematuria is the most common abnormality of the urine noted by patients. As little as 5 ml of blood in a litre of urine will lead to a visible change in urinary colour. Haematuria may arise from anywhere within the urinary tract, but bright red haematuria (with or without clots) is suggestive of lower urinary tract bleeding, whereas dark, smoky brown-black urine is more suggestive of renal pathology. Haematuria at the beginning of micturition, which then clears, suggests urethral pathology, whereas end-stream haematuria is consistent with bladder pathology. Although the causes of haematuria are numerous (Box 21.3.6), infection, stones, and malignancy are the most common. Visible haematuria warrants investigation in all patients. Frank haematuria is uncommon in glomerular disease, with the notable exception of IgA nephropathy in which visible haematuria classically occurs immediately following mucosal inflammation, typically an upper respiratory tract infection. In patients with polycystic disease, cysts may haemorrhage to cause loin pain and haematuria. This may be associated with infection of the cysts and usually

21.3 Clinical presentation of renal disease 4771 resolves with conservative management, with antibiotics if there are signs of infection. Red-brown-black urine is occasionally caused by haemoglobinuria due to haemolysis or myoglobinuria precipitated by rhabdomyolysis. Beetroot and food colouring may turn the urine pink, whereas drugs such as rifampicin may discolour the urine orange-red. Rarely, urine is found to darken following exposure to light, suggesting a diagnosis of porphyria or alkaptonuria. Turbid white urine suggests chyluria. Loin pain The presence of pain in the renal angle (loin pain) is consistent with inflammation, obstruction, or stretching of the renal capsule by a mass lesion. Pain arising from acute obstruction is common and typically colicky in nature, with radiation into the groin and scrotum. The pain may be exacerbated by oral fluids, which increase urinary volume and pressure within the renal pelvis. Acute pyelonephritis typically causes renal angle pain on the affected side and is often associated with pyrexia and leucocytes in the urine. Similarly, a renal abscess extending into the renal capsule may present with loin pain or with isolated symptoms of diaphragmatic irritation or involvement of the psoas muscle, with pain on leg extension. Patients with polycystic kidneys may also develop loin pain as a result of infection or haemorrhage of single or multiple cysts. Renal pain is an uncommon feature of glomerulonephritis and other intrinsic renal diseases: IgA nephropathy is very occasionally associated with renal pain, but active necrotizing glomerulonephritis and acute interstitial nephritis are almost invariably pain free. Loin pain-haematuria syndrome Rarely, patients may present with recurrent intermittent loin pain, haematuria (nonvisible or visible), and normal renal function, with no relevant structural abnormality of the renal tract. The cause of this condition, termed the loin pain-haematuria syndrome, is unknown: it is a diagnosis of exclusion which is most often seen in young women. The pain—often described as ‘deep’, ‘burning’, or ‘throbbing’—is usually felt in the loin, but can radiate in a typical renal pattern to the groin, genital area, and medial thigh. Some will describe a psychologically traumatic event before the onset of pain. The pain can sometimes be induced or exacerbated by exercise and affected by posture (e.g. sitting for a prolonged length of time can be uncomfortable), and in some cases there is associated nausea and vomiting. Some patients report continuous pain that never goes away, whereas others describe episodic pain that lasts more or less continuously for days or (more typically) weeks, interspersed with periods of remission. The pain is usually unilateral at presentation, but many patients eventually develop pain bilaterally. Many patients are taking large quantities of opioids and other analgesics (e.g. amitriptyline or gabapentin) by the time they are referred to specialist services. Urological investigation is unremarkable, or shows incidental abnormalities only. If renal biopsy is performed, the appearances may be normal, but thinning or

thickening of the GBM has been reported in about 60% of cases in some series, appearances of IgA nephropathy are sometimes seen, and deposition of complement component C3 in the renal arterioles has been described, but the relationship—if any—between these findings and symptomatology remains obscure. Aside from loin pain, many patients will have other medically unexplained somatic symptoms, raising the possibility that this symptom is also a somatoform disorder. Patients may request nephrectomy and/or renal autotransplantation, which the wise physician will not accede to, preferring to help the patient by sympathetic discussion and referral to pain management services.

Specific renal syndromes

Nephrotic syndrome

Definition Nephrotic syndrome is the triad of oedema, proteinuria, and hypoalbuminaemia (see Box 21.3.7 for a case study). Proteinuria is usually greater than 3.5 g in 24 h, which equates approximately to an ACR of 250 mg/mmol or PCR of 350 mg/mmol. When patients have clinically apparent oedema, serum albumin is usually less than 25 g/litre (Fig. 21.3.3). However, in practice, the definition is somewhat arbitrary, and the correlation between the degree of proteinuria, serum albumin, and presence of oedema is poor. Some patients (particularly older people) may develop oedema with proteinuria less than 3.5 g, whereas others remain free of oedema despite having a serum albumin considerably less than 25 g/litre. Other patients may have heavy proteinuria but maintain a normal serum albumin and remain free of oedema. Nephrotic syndrome indicates the presence of glomerular disease. Causes can usefully be divided into primary glomerular diseases and those arising secondary to systemic disease (Box 21.3.8).

Box 21.3.6 Causes of visible haematuria

- Infections:

- Cystitis and pyelonephritis

- Prostatitis

- Urethritis

- Schistosomiasis • Urinary stones • Tumours:

- Renal cell

- Transitional cell

- Prostatic

- Urethral • Glomerular diseases:

- IgA nephropathy

- Alport's syndrome

- Crescentic glomerulonephritis • Interstitial and medullary renal diseases:

- Polycystic kidneys

- Interstitial nephritis

- Papillary necrosis
- Tuberculosis • Miscellaneous causes:
- Release of urinary obstruction
- Trauma
- Loin pain-haematuria syndrome
- Arteriovenous malformations
- Anticoagulation
- Factitious

section 21 Disorders of the kidney and urinary tract 4772 with the geographical context important in determining the most likely cause in any particular case. The most common cause of nephrotic syndrome in Western countries is diabetes mellitus, whereas in developing countries it is most commonly associated with infection. Nephrotic syndrome due to malaria and hepatitis are particularly common in sub-Saharan Africa, and poststreptococcal glomerulonephritis is also an important cause. Pathophysiology The traditional explanation for oedema formation—known as the ‘underfill hypothesis’—is that, via alterations in Starling forces, hypoalbuminaemia leads to intravascular volume depletion, stimulation of the renin-angiotensin-aldosterone system, and thereby to sodium retention. This is likely to be correct in children with minimal change nephrotic syndrome, but the evidence is much less convincing in adults, in whom nephrotic syndrome is more likely caused by an intrinsic renal inability to excrete salt (‘overfill hypothesis’). The cause for this inability is uncertain, but it may be due to the activation of the epithelial sodium channel in the distal nephron by serine proteases in the glomerular filtrate of nephrotic patients. Clinical features One of the earliest symptoms patients may report is that of frothy urine. This often occurs before the onset of oedema and may be a useful indicator of the onset of heavy proteinuria. As proteinuria develops and serum albumin falls, patients gradually develop oedema. This may be noticed first as periorbital swelling and ‘puffiness’ in the morning, or as ankle swelling in the evening due to the effects of gravity. Worsening leg oedema develops as salt and water retention

Box 21.3.7 Case illustration—proteinuria and oedema A 54-year-old woman presents with worsening peripheral oedema. She had been diagnosed with type 2 diabetes 6 months earlier, but remained well until 4 weeks ago, when she suddenly noted frothy urine and mild peripheral oedema. Over the following weeks the oedema had worsened and she noted some abdominal distension. Her only regular medication is gliclazide.

Examination • Pitting oedema to her lumbar spine, with bilateral small pleural effusions • Jugular venous pressure not elevated and heart sounds normal • Mild erythema over right ankle and lower leg

Investigations • Urine dipstick test: protein 4+, no haematuria • ACR: 452 mg/mmol • A 24-h urinary collection: 6.8 g proteinuria • Serum albumin: 13 g/litre • Serum creatinine: 82 µmol/litre • Autoimmune and hepatitis serology: negative • Renal ultrasonography and venous Doppler: normal • Doppler ultrasonography of right leg: normal • Renal biopsy: membranous nephropathy with subepithelial spikes on silver stain

Diagnosis • Membranous nephropathy with nephrotic syndrome

Comment Frothy urine, oedema, and hypoalbuminaemia indicate the onset of heavy proteinuria and nephrotic syndrome. The rapid

onset of symptoms suggests a primary glomerular lesion rather than long-standing diabetic nephropathy. The presence of leg erythema may be due to infection or deep venous thrombosis, hence a Doppler ultrasound scan was requested. To make the diagnosis, a renal biopsy was performed, which showed membranous nephropathy. The patient was initially managed conservatively with diuretics and low molecular weight heparin as thromboembolic prophylaxis. Fig. 21.3.3 Severe peripheral oedema of the lower legs with pitting below the right knee (arrow). Box 21.3.8 Causes of nephrotic syndrome • Primary glomerular diseases:

- Minimal change
- Focal segmental glomerulosclerosis (FSGS)
- Membranous
- Mesangiocapillary glomerulonephritis (MCGN) • Secondary glomerular diseases:
- Diabetes
- Amyloid • Drugs:
- Gold, penicillamine, NSAIDs, captopril, heroin • Systemic disease:
- Lupus • Infectious diseases:
- Poststreptococcal glomerulonephritis
- Hepatitis B and C
- HIV
- Malaria
- Schistosomiasis
- Filariasis • Malignancy:
- Minimal change
- Membranous • Pre-eclampsia • Hereditary:
- Alport's syndrome
- Nail-patella syndrome

21.3 Clinical presentation of renal disease 4773 increases, followed by abdominal distension from ascites. In men, scrotal oedema may be marked and very uncomfortable. Further fluid retention leads to pleural effusions, which are often bilateral but may be unilateral. Patients often feel lethargic, with a loss of appetite and nausea due to associated gut oedema. Clinical examination

of the patient's volume status may reveal a normal or low jugular venous pressure despite marked oedema. Although rare in untreated adult patients, it is important to identify intravascular volume depletion because the use of high-dose diuretic therapy in this setting may provoke circulatory collapse from hypovolaemia, or less dramatically may further reduce renal perfusion and exacerbate renal dysfunction. Conversely, a raised jugular venous pressure with a low blood pressure may suggest a significant pericardial effusion or underlying amyloid with cardiac involvement. Patients may also present with complications associated with nephrotic syndrome. Thromboembolism may be difficult to detect clinically. Patients with marked peripheral oedema often have swollen legs of unequal size and associated erythema due to an increased susceptibility to cellulitis. These may mask the signs of deep venous thrombosis. Similarly, subtle symptoms of breathlessness, perhaps suggesting pulmonary embolism, or headache, perhaps suggesting cerebral venous sinus thrombosis, may be overlooked. In practice, a low threshold is required for investigation and treatment of suspected thromboembolism. The combination of severe peripheral oedema and susceptibility to infection following skin breakdown often leads to cellulitis. Long-standing hypoalbuminaemia may lead to leuconychia. Severe hyperlipidaemia, which is a feature of nephrotic syndrome, may lead to cutaneous xanthomas. Establishing a clinical diagnosis of nephrotic syndrome is often straightforward. The clinical history and examination may also provide clues to an underlying cause, which may be clear, such as in a patient with long-standing diabetes and progressive diabetic nephropathy. Alternatively, the immediate cause may only become apparent after a detailed history revealing long-standing use of drugs that may precipitate the condition (e.g. ACE inhibitors, NSAIDs, gold, or penicillamine). A history of chronic infections (such as hepatitis) may suggest an underlying membranous or mesangiocapillary glomerulonephritis, whereas a rash and arthralgia may lead to a diagnosis of an autoimmune condition such as systemic lupus erythematosus or cryoglobulinaemia. The presence of other long-standing inflammatory conditions, such as rheumatoid arthritis, raises the possibility of systemic amyloidosis. In older patients, an associated malignancy remains a possibility and should be sought in the history and examination, but does not warrant further investigation apart from a chest radiograph in the absence of clinical clues (e.g. disturbance of bowel habit which would merit imaging of the colon). Very occasionally, a family history may reveal an inherited nephrotic syndrome such as familial focal segmental glomerulosclerosis.

Rapidly progressive glomerulonephritis with acute kidney injury Around 5% of cases of AKI are caused by a RPGN. Recognizing this relatively small group of patients is important because many respond well to treatment, provided the diagnosis is made early and appropriate management started promptly. The key to making a diagnosis is having a high index of clinical suspicion such that important features of the syndrome are identified (see Box 21.3.9 for a case study). The hallmarks of a RPGN are rapidly declining renal function, haematuria and proteinuria on urine dipstick testing, dysmorphic red cells or red cell casts on urine microscopy, and crescentic and focal necrotizing glomerulonephritis on renal biopsy.

Clinical presentation A RPGN may present either de novo in a previously well patient or as a complication in a patient known to have a systemic disease (Box 21.3.10). The clinical features may be diverse. Occasionally,

Box 21.3.9 Case illustration—ANCA-associated vasculitis An 80-year-old woman presents with a 2-week history of increasing malaise and lethargy. On close questioning she also reported arthralgia in the small joints of her hands, and numbness in her hands and feet in the last few months.

Examination

- Subtle purpuric rash on both legs
- Bibasal crepitations
- Reduced pinprick sensation in a glove and stocking distribution

Investigations

- Creatinine: 854 $\mu\text{mol/litre}$ (56 $\mu\text{mol/litre}$ 10 months before)
- Urea: 45 mmol/litre
- Haemoglobin: 8.3 g/dl
- Urine dipstick test: blood 3+, protein 2+
- Urine microscopy: red cell casts

• Serological testing: perinuclear ANCA positive, with myeloperoxidase titre 78% • Renal biopsy: focal necrotizing glomerulonephritis
Diagnosis • AKI due to microscopic polyangiitis (an ANCA-associated vasculitis) with associated peripheral neuropathy
Comment The history is nonspecific, except that the onset of symptoms is recent and suggestive of a systemic disorder. The presence of a purpuric rash makes the diagnosis of vasculitis a possibility. Dipstick testing of the urine and checking the renal function are critical in making the diagnosis of AKI due to an inflammatory condition. Confirmation of a systemic vasculitis is made with a positive perinuclear ANCA and renal biopsy.
Box 21.3.10 Causes of a rapidly progressive glomerulonephritis • ANCA-associated vasculitis:

— Granulomatosis with polyangiitis

— Microscopic polyangiitis

— Eosinophilic granulomatosis with polyangiitis • Other primary systemic vasculitides (ANCA negative) • Other systemic disorders:

— Systemic lupus erythematosus

— Cryoglobulinaemia

— Henoch-Schönlein purpura • Infection-related glomerulonephritis:

— Postinfectious glomerulonephritis

— Infective endocarditis • Anti-GBM disease (Goodpasture's syndrome) • Crescentic phase of a primary glomerulonephritis:

— IgA nephropathy

— Mesangiocapillary glomerulonephritis

section 21 Disorders of the kidney and urinary tract 4774 patients may present with very few symptoms and signs, except for proteinuria and haematuria with a recent decline in renal function, and at the other end of the spectrum, patients may present with severe AKI associated with features of uraemia. Importantly, patients may also present with clinical features of systemic inflammation that indicate an underlying cause for glomerulonephritis. These range from the subtle, such as arthralgia or myalgia, to the florid, such as a purpuric rash (Fig. 21.3.4), haemoptysis, and peripheral neuropathy. Clinical features of specific inflammatory diseases associated with a RPGN are detailed in Table 21.3.1. In practice, specific features to elicit in patients presenting with an acute decline in renal function include arthralgia and arthritis, myalgia and muscle tenderness, rashes, eye symptoms (pain and redness), ear, nose, and throat symptoms (epistaxis, nasal crusting, and new deafness), haemoptysis (important, as it may indicate a life-threatening pulmonary haemorrhage), and neuropathic symptoms and signs. Conversely, the clinician should have a high index of suspicion for a RPGN in patients presenting with any of these features, and in this context suspicions are heightened by the presence of dysmorphic red cells and red cell casts on urinary microscopy (Fig. 21.3.5). If a RPGN is suspected, investigations should

include ANCA, anti-GBM antibodies, antinuclear and anti-double-stranded DNA antibodies, serum complement, antistreptolysin-O titre, and immunoglobulins and serum electrophoresis (including tests for cryoglobulins). It is almost certain that a patient with a RPGN will require a renal biopsy to confirm the diagnosis and to guide management. All patients with suspected RPGN should be referred urgently to a nephrologist. Presentation of renal disease associated with other underlying diseases Renal disease can present in many complex and diverse ways, and many renal problems arise as either direct or indirect complications of other diseases. Examples include AKI caused by sepsis, and progressive CKD due to diabetes (Box 21.3.11). This section illustrates some common and important presentations of renal disease. Diabetic nephropathy In the Western world, diabetes is the most common cause of renal disease, accounting for around 45% of new cases of ESKD in the United States of America and around 25% in the United Kingdom (Box 21.3.12). Diabetic nephropathy develops over the course of years and is preceded by a clinically silent phase of microalbuminuria, which is often detected as a result of diabetic screening programmes, enabling a targeted approach to management in which tight glycaemic control and blood pressure control with the use of agents to block the renin-angiotensin system aim to reduce the rate of progression of the nephropathy. As with other causes of progressive CKD, patients with diabetic nephropathy often only develop symptoms of kidney disease late in the course of their disease, but there is a tendency for those with this condition to become symptomatic, particularly in relation to anaemia and fluid retention, with lesser degrees of impairment of renal function than their nondiabetic counterparts. This leads to an earlier requirement for initiation of dialysis in patients with diabetic nephropathy. Screening patients with diabetes for microalbuminuria and hypertension enables early diagnosis of complications and intensive management of glucose and blood pressure. As eGFR falls below 30 ml/min per 1.73 m², patients should be referred to a nephrologist to plan for renal replacement therapy. Patients with diabetes are also subject to develop other microvascular and macrovascular complications, which may lead to superimposed renal atheroembolic disease and renal artery stenosis. These may present as an abrupt decline in renal function following the introduction of an ACE inhibitor or angiotensin receptor antagonist. Patients with diabetic nephropathy are also at increased risk of AKI or chronic renal failure, with common causes Fig. 21.3.4 Purpuric rash affecting the lower legs, consistent with a systemic vasculitis. Table 21.3.1 Key features of specific systemic inflammatory diseases causing a rapidly progressive glomerulonephritis

Feature	Type	Disease
Skin rashes	Purpuric	Lupoid
Any vasculitis		
Lupus	Ear, nose, and throat symptoms	Nasal crusting
	Deafness	Oral ulceration
	Granulomatosis with polyangiitis	Granulomatosis with polyangiitis
	Any vasculitis or lupus	Eye symptoms
	Scleritis and episcleritis	Any vasculitis, lupus, rarely Behçet's disease
	Myalgia, arthralgia, and arthritis	Any vasculitis, Henoch-Schönlein purpura, cryoglobulinaemia, lupus, rheumatoid arthritis, systemic sclerosis
Haemoptysis	Goodpasture's disease, any vasculitis, lupus	Neuropathy
	Any vasculitis, lupus, cryoglobulinaemia	

21.3 Clinical presentation of renal disease 4775 for this including use of radiocontrast media for investigations such as coronary or peripheral angiography, surgery (especially cardiac surgery), and in the context of diabetic emergencies, particularly diabetic ketoacidosis. See Chapter 21.10.1 for further discussion of diabetic renal disease. Renovascular disease Many patients with diffuse atherosclerosis have evidence of renal vascular disease. A history of cerebrovascular, coronary, or peripheral vascular disease makes a diagnosis of renovascular disease likely. Up to 24% of patients presenting with peripheral vascular (b) (a) Fig. 21.3.5 Phase contrast micrographs showing dysmorphic erythrocytes (a) and a red cell cast (b) within the urine. Box 21.3.11 Important and

common presentations of renal disease • Diabetic nephropathy with progressive CKD • Vascular disease:

— Renal atheroemboli

— Renal artery stenosis • Underlying malignancy:

— Urinary tract obstruction

— Membranous glomerulonephritis

— Myeloma

— Hypercalcaemia • Infection:

— Acute presentation with renal failure: (1) general syndromes— sepsis, rhabdomyolysis, HUS, postinfectious glomerulonephritis, tubulointerstitial nephritis; (2) specific syndromes—hantavirus, leptospirosis, malaria

— Chronic infections associated with renal disease: hepatitis B, hepatitis C, filaria, schistosomiasis, HIV • Systemic inflammatory disease:

— Systemic vasculitides

— Systemic lupus erythematosus

— Sarcoidosis • Drug-induced renal disease • Pregnancy Box 21.3.12 Case illustration—progressive CKD due to diabetic nephropathy A 66-year-old Asian man presents with nausea, anorexia, ankle swelling, and breathlessness. He has a 25-year history of type 2 diabetes mellitus, a 14-year history of hypertension, and had coronary artery bypass grafts 3 years ago. Insulin, furosemide, and ramipril are his only regular medications. Examination • Cardiovascular—blood pressure 167/88 mmHg, jugular venous pressure +3 cm, cardiomegaly, bibasal crepitations, and peripheral oedema to sacrum • Fundi—treated diabetic retinopathy • Neurological—reduced pinprick sensation in stocking distribution to knees, with absent ankle reflexes, proprioception, and vibration sensation Investigations • Urine dipstick test: protein 4+, no haematuria • Urine ACR: 1720 mg/mmol • Serum creatinine: 568 μ mol/litre (eGFR 9 ml/min per 1.73 m² body surface area) • Serum bicarbonate: 15 mmol/litre • Full blood count: haemoglobin (Hb) 9.8 g/dl • HbA1C: 10.2% Further history Five years previously, his blood pressure was 189/92 mmHg with creatinine of 154 μ mol/litre and protein+ on urine dipstick. At the time of his coronary surgery, blood pressure was 165/86 mmHg with creatinine 210 μ mol/litre. Over the last year he had felt well until the last 2 months, since when he had developed increasing lethargy, anorexia, and breathlessness on exertion, and noted increasing ankle swelling. Comment This man with long-standing diabetes presents with nonspecific symptoms and oedema. He also has evidence of end-organ damage, with cardiovascular disease, retinopathy, and neuropathy. Five years ago he had evidence of nephropathy with proteinuria and an eGFR of 43 ml/min (CKD stage 3). Since then his blood pressure and glycaemic control have been poor, which contributed to the progression of nephropathy to eGFR of 30 ml/min (CKD stage 3/4) 3 years ago, and now to CKD stage 5 with

symptoms of uraemia.

section 21 Disorders of the kidney and urinary tract 4776 disease have stenoses in both renal arteries, and up to 50% have more than 50% stenosis in at least one renal artery. The absence of peripheral pulses and the presence of a femoral bruit make the diagnosis of renovascular disease likely, although most of these patients remain asymptomatic from the renal point of view. Common presentations of renovascular disease are outlined in Box 21.3.13. See Chapter 21.10.10 for further discussion of renovascular disease. Myeloma and other malignancies Myeloma can cause AKI in a number of ways. Features suggestive of underlying myeloma in a patient presenting with unexplained renal failure are older age, bone pain (often nonspecific), hypercalcaemia (sometimes mild, and sometimes 'relative' considering the degree of renal impairment), anaemia (often inappropriately severe for the degree of renal impairment), an abrupt decline in renal function after a relatively minor prerenal 'insult', and unremarkable urine dipstick findings. Up to 50% of patients presenting with myeloma have impaired renal function at the time of diagnosis. This may be reversible and due to hypercalcaemia, dehydration, hyperuricaemia, or infection. Cast nephropathy accounts for 10% of all renal dysfunction in patients with myeloma and is characterized by the formation of tubular casts of excreted light chains and Tamm-Horsfall protein: these are thought to cause renal failure by obstructing the tubule and by direct tubular toxicity. The key to the diagnosis is to maintain a high index of suspicion, particularly in elderly patients presenting with renal failure and hypercalcaemia. Serum electrophoresis and urinary Bence Jones proteins and serum free light chains are the required investigations, leading on to bone marrow examination. Other malignancies may present with renal involvement through a number of mechanisms, including AKI due to urinary tract obstruction by pelvic or retroperitoneal tumour. Other possible causes are outlined in Box 21.3.14. See Chapters 21.10.5 and 21.10.9 for further discussion. Renal presentation of infectious diseases A wide range of systemic infections can affect the kidney and result in either AKI or CKD. The presentation of infection-related kidney disease varies worldwide, and in the developing world—in contrast to the developed world—infectious diseases are the leading cause of both AKI and CKD. AKI may occur as part of a general systemic syndrome induced by infection, such as sepsis and septic shock, haemolytic uraemic syndrome (HUS), rhabdomyolysis, postinfectious glomerulonephritis, and acute tubulointerstitial nephritis. Alternatively, an infectious agent may cause specific nephrotoxicity, for example, hantavirus, leptospirosis, or malaria. General systemic syndromes caused by infection In Western countries, the most common infectious cause for renal disease is sepsis, which accounts for 10% of all hospital-acquired renal failure and, if severe, may lead to AKI in the context of multiorgan failure. Other general syndromes that may be induced by infection include HUS and rhabdomyolysis. For example, the verotoxin of *Escherichia coli* O157:H7 causes (D+) HUS, which is a thrombotic microangiopathy characterized by diarrhoea, AKI, and thrombocytopenia. Patients with influenza, legionella, or streptococcal infection may present with fever, severe myalgia, and dark urine in the context of AKI due to rhabdomyolysis. Poststreptococcal glomerulonephritis is still one of the most common causes of AKI in the developing world, although now seen rarely in the United Kingdom and developed countries. Typical presentation is 10 days to a few weeks following a streptococcal infection of the throat or skin with a 'nephritic' syndrome characterized by hypertension, oedema, haematuria, proteinuria, and AKI. Specific nephrotoxicity caused by infection Hantavirus and leptospirosis Hantaviruses are endemic in specific rodent reservoirs and are transmitted to humans by inhalation of infectious aerosols or rodent excreta. In Europe, the main pattern of disease is haemorrhagic fever with renal syndrome. The disease presents in

four stages: (1) an abrupt febrile stage characterized by fever, loin or abdominal pain, nausea, vomiting, and periorbital oedema, lasting for 3 to 7 days; (2) a hypotensive phase associated with haemorrhages and ecchymoses, lasting hours to 2 days; (3) an oliguric phase for 3 to 14 days, with worsening AKI due to a tubulointerstitial nephritis and haemorrhage; and (4) a polyuric phase as renal function returns to normal. Leptospirosis may present with similar features to hantavirus. However, leptospirosis is endemic worldwide and is typically associated with jaundice and hepatomegaly. AKI occurs in 20 to 85% of patients due to acute tubulointerstitial nephritis. Malaria Severe infection with *Plasmodium falciparum* occurs in nonimmune adults. AKI may occur either in the acute phase of the disease or

Box 21.3.13 Common presentations of renovascular disease

- As part of the investigation for acute, severe, or refractory hypertension
- An acute rise (>20%) in creatinine following introduction of an ACE inhibitor or angiotensin receptor antagonist
- Incidental finding of asymmetric kidney size on renal ultrasonography
- As part of the investigation for progressive CKD
- Symptomatically as acute ('flash') pulmonary oedema in the absence of cardiac failure or fluid overload
- Postoperative AKI, especially following coronary artery bypass or aortic aneurysm surgery

Box 21.3.14 Renal presentations associated with malignancy

 - AKI:

- Urinary tract obstruction
- Hypercalcaemia
- Tumour lysis with urate nephropathy
- Chemotherapy (e.g. cisplatin, ifosfamide)
- Leukaemic infiltration
- Microangiopathy
- Paraneoplastic glomerular disease:
- Membranous
- Amyloid
- Mesangiocapillary glomerulonephritis

21.3 Clinical presentation of renal disease

4777 in the recovery phase. Sequestration of parasitized erythrocytes in the renal vasculature and proinflammatory cytokine release cause tubular cell ischaemia and injury. Rarely, patients with *falciparum* malaria present with 'blackwater fever' due to massive intravascular haemolysis, which often occurs following quinine administration in association with glucose-6-phosphate dehydrogenase deficiency. Infections and CKD In the developing world, CKD is commonly secondary to infectious disease, with the underlying infection often remaining subclinical until the presentation with renal manifestations. Examples of CKD secondary to infective agents include hepatitis B, hepatitis C, *P. malariae*, filaria, schistosomiasis, and HIV. Hepatitis B is classically associated with nephrotic syndrome due to membranous nephropathy, but occasionally it may result in a mesangiocapillary glomerulonephritis. Hepatitis B virus infection is also associated with the development of polyarteritis nodosa, although the reported frequency of this appears to be falling. Patients who develop such complications usually have chronic hepatitis, having contracted the virus in childhood. Hepatitis C is increasingly

recognized as a common cause for cryoglobulinaemia. This remains asymptomatic in most patients, with only a few developing clinical evidence of vasculitis. The associated mesangiocapillary glomerulonephritis can present as nephrotic syndrome or CKD. Many infectious agents endemic in sub-Saharan Africa may also cause a mesangiocapillary glomerulonephritis presenting as nephrotic syndrome. Most common is *P. malariae*, but filaria and schistosomiasis remain in the differential diagnosis. HIV-associated nephropathy (HIVAN) is an increasingly recognized complication of HIV infection, and it now accounts for around 1% of the dialysis population in the United States of America. Patients usually present with heavy proteinuria and nephrotic syndrome due to a collapsing form of focal segmental glomerulosclerosis. HIVAN predominates in young African American men. See Chapters 21.5, 21.10.8, and 21.11 for further discussion.

Systemic inflammatory diseases Patients with systemic inflammatory disease are at risk of developing renal disease. Sometimes this may be the presenting feature of the condition, such as systemic vasculitis or systemic lupus, and on other occasions renal disease may develop as a complication later in the course of disease. Examples of systemic inflammatory diseases associated with renal involvement are detailed in Box 21.3.15. The presentation of an acute glomerulonephritis and progressive renal failure due to systemic inflammatory diseases such as the vasculitides and systemic lupus erythematosus has been discussed earlier in the chapter, and further details can be found in Chapters 21.10.2 and 21.10.3. Other inflammatory diseases may present in different ways.

Sarcoidosis Renal disease is common in sarcoidosis and characterized histologically by granulomatous tubulointerstitial nephritis. The mean prevalence from biopsy studies is 35%, but this is likely to be an overestimate. Most renal disease is subclinical, but may be identified by the presence of proteinuria or tubular dysfunction with a renal tubular acidosis. However, sarcoidosis may present with AKI, which may be caused by an acute tubulointerstitial nephritis associated with an eosinophilia and eosinophiluria, or be precipitated by hypercalcaemia, which may be more common in summer months due to ultraviolet light exposure. The presence of extrarenal features of sarcoidosis (including bilateral hilar lymphadenopathy and erythema nodosum) helps to establish the diagnosis, but sometimes the diagnosis may only become apparent on finding a high level of serum ACE or following a renal biopsy for unexplained renal impairment. See Chapters 21.10.4 and 18.12 for further discussion of sarcoidosis.

Systemic sclerosis Systemic sclerosis may present with an acute crisis characterized by an abrupt rise in blood pressure (>160/90 mmHg) with hypertensive encephalopathy, AKI, and a microangiopathic haemolytic anaemia. This may occur before the onset of the cutaneous features of the disease. Patients are typically tachycardic, with evidence of heart failure and a high systemic vascular resistance. This diagnosis should be suspected in any patient presenting with malignant-phase hypertension and AKI. See Chapter 19.11.3 for further discussion of systemic sclerosis.

Systemic amyloidosis Systemic amyloidosis is characterized by extracellular deposition of insoluble fibrillar proteins that lead to organ dysfunction. In AL amyloidosis this arises from light chains produced by a malignant plasma cell clone. AA amyloidosis occurs in the setting of long-standing inflammation, the amyloidogenic protein being an N-terminal fragment of serum amyloid A (SAA), an acute phase reactant. Patients may present with heavy proteinuria or nephrotic syndrome. Renal involvement can be demonstrated by serum amyloid P scanning or by renal biopsy. See Chapter 12.12.3 for further discussion of the amyloidoses.

Drug-induced renal disease Numerous drugs have the potential for causing both AKI and CKD (Box 21.3.16). As well as prescribed and over-the-counter medication, renal disease may also arise from herbal and traditional Chinese medicines or illicit drugs. Mechanisms by which drugs cause renal disease include salt and water depletion, effects on renal perfusion, direct nephrotoxicity, and intrarenal obstruction.

Box 21.3.15 Systemic inflammatory

diseases associated with renal involvement • Typically associated with renal involvement:

- Systemic vasculitides
- Systemic lupus erythematosus
- Sarcoidosis
- Systemic sclerosis
- Henoch-Schönlein purpura
- Cryoglobulinaemia • Unusually associated with renal involvement:
- Relapsing polychondritis
- Ankylosing spondylitis
- Behçet's disease
- Rheumatoid arthritis • Renal complications of multisystem conditions:
- Amyloidosis (of AA type)

section 21 Disorders of the kidney and urinary tract 4778 Salt and water depletion AKI may follow hypotension and reduced renal perfusion due to sodium and water depletion. This may be caused by excess diuretic use or diarrhoea and vomiting as a drug side effect. Effect on renal perfusion and the regulation of intrarenal haemodynamics Overdose of any hypotensive agent may compromise renal perfusion and interfere with renal function. Agents which block the renin-angiotensin system, the ACE inhibitors, and angiotensin receptor blockers, require special consideration. These agents abrogate the effect of angiotensin II on efferent arteriole constriction, which is the normal adaptive response to any reduction in renal perfusion. A small and acceptable deterioration in renal function (up to a 20% increase in serum creatinine) often occurs following the introduction of an ACE inhibitor. A greater increase in serum creatinine may indicate underlying renal artery stenosis, for which further investigation may need to be carefully considered. These agents are implicated in a significant proportion of cases of AKI in patients with sepsis and dehydration. This is because renal perfusion is frequently compromised in these settings and the kidney is unable to autoregulate its blood flow in the presence of renin-angiotensin system blockade. NSAIDs have numerous renal effects, including disturbances of autoregulation of intrinsic renal haemodynamics. These effects are mediated by inhibition of prostaglandin synthesis from arachidonic acid by nonspecific blocking of the enzyme cyclooxygenase. This may lead to vasoconstriction and reversible renal impairment in volume-contracted states. Long-term use of NSAIDs may cause chronic renal impairment, with selective COX-2 inhibitors seeming to confer no renal advantage. Direct nephrotoxicity The mechanisms of drug toxicity on the kidney include direct tubulotoxicity, drug-induced tubulointerstitial nephritis, tubular dysfunction, and glomerular disease. Common nephrotoxic drugs and mechanism are outlined in Box 21.3.16. Tubulointerstitial nephritis is classically caused by penicillins, NSAIDs, and proton pump inhibitors but most drugs

have the potential to cause the condition. Drug-induced tubulointerstitial nephritis usually occurs days to weeks after starting the drug. Symptoms may be nonspecific, with malaise, fatigue, and anorexia. A low-grade fever, fleeting rash, and arthralgia may also be reported. Investigations show a variable degree of renal dysfunction along with proteinuria and nonvisible haematuria. Urine microscopy may show white and red cell casts, and there may be a blood eosinophilia. However, in practice, the key is to suspect the diagnosis, stop the potentially offending drug (or drugs), and proceed with a renal biopsy if renal function is severe or does not improve. Obstruction Specific drugs, such as aciclovir and the protease inhibitor indinavir, may precipitate as crystals within the tubule, causing obstruction and sometimes renal failure. This is more likely to occur if the patient is dehydrated, hence adequate fluid input to achieve a high urinary volume is advised before these drugs are taken. See Chapter 21.19 for further discussion of drugs and the kidney. Pregnancy Pregnancy provides a unique set of circumstances in which renal disease may present. Pre-existing renal disease may be detected as part of screening for proteinuria and hypertension during the first trimester. Alternatively, de novo renal disease may be precipitated by pregnancy and present with specific syndromes, such as nephrotic syndrome or AKI due to pre-eclampsia. A summary of the presentation of renal disease in pregnancy is detailed in Box 21.3.17. Box 21.3.16 Adverse effects of drugs on the kidney AKI • Acute tubular cell injury (acute tubular necrosis, ATN)

- Aminoglycosides
- Amphotericin
- Cisplatin
- NSAIDs
- Radiocontrast media
- Paracetamol poisoning
- Statins (by inducing rhabdomyolysis) • Interstitial nephritis:
- Proton pump inhibitors
- β -Lactam antibiotics (penicillins, cephalosporins)
- NSAIDs
- Diuretics, particularly thiazides
- Allopurinol
- Sulphonamides
- Other antibiotics (e.g. ciprofloxacin, rifampicin)
- Indinavir

— Aristolochic acid ('Chinese herb nephropathy') Nephrotic syndrome • Membranous glomerulonephritis:

— High-dose captopril

— Gold

— Penicillamine

— Phenytoin • Minimal change:

— NSAIDs • Focal segmental glomerulosclerosis:

— Pamidronate

— Heroin Tubular dysfunction • Renal tubular acidosis:

— Acetazolamide

— Amphotericin

— Lithium • Nephrogenic diabetes insipidus:

— Lithium

— Demeclocycline Others • Renal papillary necrosis:

— Aspirin with phenacetin

— NSAIDs • Crystalluria with tubular obstruction

— Aciclovir

— Indinavir

— Methotrexate

— Sulphonamides

21.3 Clinical presentation of renal disease 4779 The clinical presentation of renal disease during pregnancy is often varied and nonspecific, but certain features may guide the diagnosis. Key points to note are as follows: • Is there evidence of pre-existing renal disease? • Were previous pregnancies complicated by hypertension or pre-eclampsia? • What was the time of onset of renal disease during pregnancy? Onset in late pregnancy implies that the renal disease is likely to be pregnancy induced. • Hypertension with proteinuria and oedema suggest pre-eclampsia or underlying renal disease (e.g. systemic lupus erythematosus). • Hypotension and hypovolaemia suggest sepsis or haemorrhage. See Chapter 14.5 for further discussion of renal disease in pregnancy. Pre-eclampsia and HELLP Pre-eclampsia classically presents with hypertension,

oedema, and proteinuria. Other recognized features include elevation of serum urate, liver transaminases, and haematocrit, along with thrombocytopenia. However, patients may not be hypertensive or demonstrate other features, hence distinguishing pre-eclampsia from pre-existing renal disease may be difficult, and the condition may occasionally present with heavy proteinuria and nephrotic syndrome. The HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) is a severe variant of pre-eclampsia that is commonly associated with renal failure, severe haemolysis, and coagulopathy, and may progress to multiorgan failure. See Chapters 14.4 and 14.9 for further discussion. Haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura HUS and thrombotic thrombocytopenic purpura are related disorders that are occasionally associated with pregnancy. Both can cause AKI. HUS usually occurs 2 days to 10 weeks postpartum and may cause severe renal failure. By contrast, thrombotic thrombocytopenic purpura usually presents in the first or second trimester with predominant neurological features and only mild proteinuria and haematuria. See Chapters 21.10.6, 22.7.3, and 22.7.5 for further discussion. FURTHER READING Bauer SR, Carroll PR, Grady D (2019). Hematuria practice guidelines that explicitly consider harms and costs. *JAMA Intern Med*, doi: 10.1001/jamainternmed.2019.2269. Cohen RA, Brown RS (2003). Clinical practice. Microscopic hematuria. *N Engl J Med*, 348, 2330–8. Doshi SM, Friedman AN (2017). Diagnosis and management of type 2 diabetic kidney disease. *Clin J Am Soc Nephrol*, 12, 1366–73. Hill NR, et al. (2016). Global prevalence of chronic kidney disease—a systematic review and meta-analysis. *PLoS One*, 11, e0158765. Joint Specialty Committee on Renal Medicine of the Royal College of Physicians of London and the Renal Association (2006). Chronic kidney disease in adults: UK guidelines for identification, management and referral. Royal College of Physicians of London, London. Keith DS, et al. (2004). Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*, 164, 659–63. Kodner C (2016). Diagnosis and management of nephrotic syndrome in adults. *Am Fam Physician*, 93, 479–85. Krogsbøll LT (2014). Guidelines for screening with urinary dipsticks differ substantially—a systematic review. *Dan Med J*, 61, A4781. Lamb EJ, Stevens PE (2014). Estimating and measuring glomerular filtration rate: methods of measurement and markers for estimation. *Curr Opin Nephrol Hypertens*, 23, 258–66. Leung N, Nasr SH (2014). Myeloma-related kidney disease. *Adv Chronic Kidney Dis*, 21, 36–47. Lopez-Vargas PA, et al. (2013). Prevention, detection and management of early chronic kidney disease: a systematic review of clinical practice guidelines. *Nephrology (Carlton)*, 18, 592–604. Moroni G, Ponticelli C (2014). Rapidly progressive crescentic glomerulonephritis: early treatment is a must. *Autoimmun Rev*, 13, 723–9. National Institute for Health and Care Excellence (2014). Chronic kidney disease in adults: assessment and management. Clinical Guideline 182. <http://www.nice.org.uk/guidance/cg182> Niemi MA, Cohen RA (2015). Evaluation of microscopic hematuria: a critical review and proposed algorithm. *Adv Chronic Kidney Dis*, 22, 289–96. Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C (2017). Diabetic nephropathy in type 1 diabetes: a review of early natural history, pathogenesis, and diagnosis. *Diabetes Metab Res Rev*, 33, e2841. Radhakrishnan J, Perazella MA (2015). Drug-induced glomerular disease: attention required! *Clin J Am Soc Nephrol*, 10, 1287–90. Raghavan R, Eknayan G (2014). Acute interstitial nephritis—a reappraisal and update. *Clin Nephrol*, 82, 149–62. Box 21.3.17 Renal disease in pregnancy AKI in pregnancy • Hypovolaemia:

— Hyperemesis

— Haemorrhage

- Sepsis
- Abruptio • Infection:
- Pyelonephritis
- Septic abortion
- Puerperal sepsis • Obstruction:
- Gravid uterus • Endothelial dysfunction:
- Pre-eclampsia
- Acute fatty liver of pregnancy
- HELLP syndrome
- HUS Exacerbation of pre-existing renal disease • CKD of any cause with deterioration of function, proteinuria, and pre-eclampsia • Flare of systemic and renal disease (systemic lupus erythematosus and systemic sclerosis) New-onset nephrotic syndrome • Pre-eclampsia • Systemic lupus erythematosus • Minimal change disease

section 21 Disorders of the kidney and urinary tract 4780 Siew ED, Davenport A (2015). The growth of acute kidney injury: a rising tide or just closer attention to detail? *Kidney Int*, 87, 46–61. Tesar V, Hruskova Z (2013). ANCA-associated renal vasculitis—an update. *Contrib Nephrol*, 181, 216–28. Torres PA, et al. (2015). Rhabdomyolysis: pathogenesis, diagnosis, and treatment. *Ochsner J*, 15, 58–69. van der Velde M, et al. (2009). Screening for albuminuria identifies individuals at increased renal risk. *J Am Soc Nephrol*, 20, 852–62. Webster AC, et al. (2017). Chronic kidney disease. *Lancet*, 389, 1238–52. Webster P, et al. (2017). Pregnancy in chronic kidney disease and kidney transplantation. *Kidney Int*, 91, 1047–56. Wingo CS, Clapp WL (2000). Proteinuria: potential causes and approach to evaluation. *Am J Med Sci*, 320, 188–94. Zubair AS, et al. (2016). Loin pain hematuria syndrome. *Clin Kidney J*, 9, 128–34.

Revision #1

Created 2026-01-22 16:41:33 UTC by Omar Ayman

Updated 2026-01-22 16:41:33 UTC by Omar Ayman