1 The Approach to the Patient with Kidney Disease

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Clinical Scenario

A 40 year old female international traveller presents with a history of fever, dysuria and a serum creatinine of 208 μmol/L (2.35 mg/dL). She is assessed as confused in the emergency department, but has been found to be haemodynamically stable, with a temperature of 37 °C (98.6 °F), a blood pressure of 130/75 mmHg, and pulse of 70 beats per minute. She has indicated that she is due to fly back home in 2 days' time.

How would you proceed?

Introduction

Kidney disease is increasing in incidence worldwide, with increasing numbers of patients on kidney replacement therapy; more kidney patients are looked after by internists, general practitioners and other specialties than by nephrologists. Furthermore, kidney disease is now the 12th leading cause of death worldwide, and a staggering 14.5 million people are estimated to require kidney replacement therapy by 2030 [1, 2]. The initial approach to diagnosis of kidney disease, and management of patients on kidney replacement therapy requires a careful history, physical exam and initial laboratory tests, which are emphasised in this chapter.

Common Kidney Patient Presentations

Kidney patients present may with symptoms, signs and abnormal investigations, with a hitherto unknown kidney disease. Careful history taking and a full physical examination can help the clinician to arrive at a provisional diagnosis for the kidney condition - these include common kidney syndromes, such as nephrotic syndrome, nephritic syndrome, chronic kidney disease and acute kidney injury (Fig. 1.1). A tailored investigation with urinalysis, blood tests and imaging can help to identify the cause of kidney disease, and formulate a management plan.

Patients with known kidney disease, on kidney replacement therapy may also present with complications of chronic kidney disease, or complications of their modality of kidney replacement therapy. For example, haemodialysis patients may present to the emergency department with shortness of breath—particularly following a prolonged interdialytic period, such as

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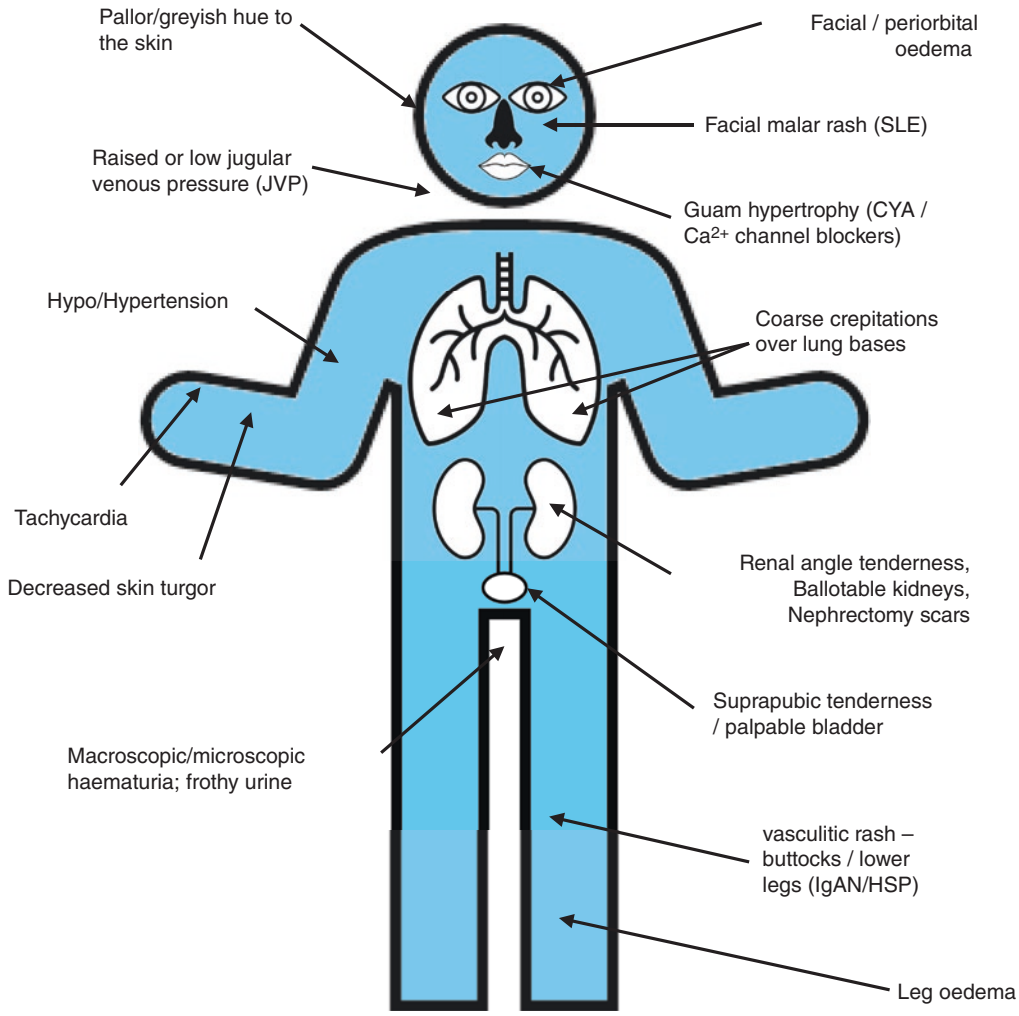

Also inspect groins, neck, precordium, and abdomen for scars/evidence suggestive of current or previous kidney replacement therapy (haemodialysis (arteriovenous fistula/dialysis catheter) /peritoneal dialysis (tenchkoff catheter) access and/or transplantation (J-shaped/Rutherford-Morrison scar)).

SLE – systemic lupus erythematosus; CYA – cyclosporin; Ca^{2+} channel blockers – Calcium channel blockers; IgAN – IgA nephropathy; HSP – Henoch Schonlein Purpura

Fig. 1.1 Physical signs that can be associated with kidney disease

after the weekend; peritoneal dialysis patients and kidney transplant patients may present with fever and abdominal pain, both requiring careful history and physical examination to arrive at a likely differential diagnosis, and start immediate treatment if necessary. Kidney replacement therapy is available in all countries; and patients are frequently managed by clinicians other than nephrologists, hence a good working knowledge about how to make a prompt diagnosis, and man-

Table 1.1 The approach to the kidney patient depends on the presence of a past history of kidney replacement therapy

Patients with no known kidney disease	Patients on dialysis, with kidney transplantation
Presents with symptoms or signs such as oedema, oliguria suggestive of kidney disease or urine abnormalities and rising creatinine	Presentation with general signs and symptoms such as breathlessness, fever or chest/abdominal pain in patients on kidney replacement therapy
Requires a careful history and physical examination to formulate a differential diagnosis from common kidney syndromes such as nephrotic syndrome, nephritic syndrome, chronic kidney disease or acute kidney injury	Requires a careful history and physical examination to formulate a differential diagnosis for causes of breathlessness, fever and chest/abdominal pain

age complications is important amongst nephrologists and non-nephrologists alike, in all regions of the world (Table 1.1).

Common Kidney Syndromes and Definitions

Haematuria: Abnormal number of red blood cells (RBCs) in the urine, either visible or detected on urine examination, >3 RBCs/high power field under the microscope.

Nephrotic syndrome: Significant proteinuria (>3 g/day), with oedema, hypoalbuminaemia, hypercholesterolaemia, and a hypercoagulable state.

Nephritic syndrome: Glomerular haematuria with proteinuria, dysmorphic RBCs, red cell casts, often a raised serum creatinine, and hypertension.

Acute kidney injury: A sudden rise in serum creatinine over hours or days (>50% from baseline).

Chronic kidney disease: Gradual, progressive and irreversible rise in serum creatinine over at least 3 months.

Kidney stones: Colicky loin pain, haematuria with graveluria.

Urinary tract obstruction: Inability to pass urine, with structural and functional abnormalities with urinary retention.

Kidney tubule defects: Abnormalities of electrolytes, acid-base in blood and urine.

Urinary tract infections: Infections of kidney, ureter, urinary bladder, prostate or urethra.

Anatomical Localisation of Kidney Diseases

The presenting signs, and symptoms, and presence of blood and urinary abnormalities are dependent on the anatomical structure of the urinary tract involved, as shown in the Table 1.2.

Table 1.2 Clinical features of kidney diseases, as determined by anatomical involvement of the urinary organs

Anatomical structure	Clinical features of presentation
Kidneys	Loin pain, hematuria, frothy urine, renal angle tenderness, oliguria, polyuria, nocturia, raised creatinine, electrolyte abnormalities
Ureters	Loin to groin pain, colicky in nature, haematuria, graveluria
Urinary bladder	Lower abdominal pain, dysuria, hematuria, suprapubic tenderness, leukocyturia
Urethra	Dysuria, hematuria at the initiation of micturition

Aetiology of Kidney Syndromes

Understanding the common causes of kidney syndromes can help to inform the approach to diagnosis and management. Some of the aetiologies may present with acute or chronic kidney diseases, the understanding of which helps with determining the reversibility of the pathological process and urgency of treatment (Table 1.3).

Table 1.3 Common causes of kidney syndromes

Kidney syndrome	Site affected	Causes
Haematuria	Kidney	Inflammation, infection, cancer, stone
	Kidney outflow tract	Stone, cancer, infection, inflammation
Nephrotic syndrome	Kidney limited (or idiopathic)	Minimal change, membranous, focal segmental glomerulosclerosis (FSGS)
	Systemic (or secondary)	Diabetes, mellitus lupus, Amyloidosis, Cancer: Lymphoma, Myeloma, Drugs: Gold, Antibiotics, NSAIDS, Heroin, Penicillamine, Infections: HIV, Hepatitis B, Hepatitis C, Malaria, Syphilis, Alport's syndrome, Nail-Patella syndrome
Nephritic syndrome	Kidney limited (or idiopathic)	IgA nephropathy, kidney limited vasculitis
	Systemic (or secondary)	Lupus, ANCA-associated vasculitis (AAV)
Kidney stones		Calcium oxalate, urate, struvite, cysteine
Urinary tract obstruction	Ureter	Stones, cancer
	Urethra/ bladder outflow	Stones, prostate cancer
Kidney tubular disorder	Acidosis	Renal tubular acidosis
Urinary tract infection (UTI)	Bacterial	*Escherichia coli, Klebsiella pneumoniae*
	Fungal	*Candida albicans*
	Viral	Cytomegalovirus (CMV), BK virus, adenovirus
Acute kidney injury	Pre-renal	Volume depletion, haemorrhage
	Renal	Acute interstitial nephritis (AIN), Acute Glomerulonephritis
	Post-renal	Urethral/bladder outflow obstruction
Chronic kidney disease		Diabetes mellitus, Hypertension, chronic glomerulonephritis, inherited kidney diseases

Approach to a Patient with Kidney Disease

A careful history and physical exam is necessary to identify the kidney syndrome and identify the cause. The duration of illness is important to determine the syndrome: for example, acute kidney injury (AKI) develops in hours to days, and chronic kidney disease (CKD) over months. The presence of fever, skin rash and joint pains indicates systemic disease. Visible haematuria indicates glomerular or renal tract bleeding. The presence of oedema may be associated with nephrotic syndrome, fluid retention or end stage kidney disease (ESKD). The physical is followed by tests of blood and urine (Tables 1.4 and 1.5).

Table 1.4 Approach to common kidney syndromes

Kidney syndrome	History	Physical examination	Investigations
Haematuria	Age of onset (malignancy if>50 years), gender (bladder cancer and prostate cancer is commoner in males, infection in females), associated symptoms: Fever, dysuria, flank pain, family history (Alport's), travel history (schistosomiasis), smoking, anticoagulation, pharyngitis (IgA nephropathy)	Hypertension, oedema, abdominal mass, palpable bladder	Urine microscopy for RBCs, dysmorphic RBCs, RBC casts, urinalysis for blood, leucocytes & nitrites (infection), proteinuria, test for myoglobin. Ultrasound, computerised tomography (CT), cystoscopy
Nephrotic syndrome (and non-nephrotic proteinuria)	Peripheral and facial oedema, frothy urine. History of diabetes mellitus, diabetic retinopathy. Fever, iv drug use, high risk sexual behaviour, malaria, filaria; drugs NSAIDS, gold, penicillamine	Dependent oedema, malar rash, scarring alopecia, telangiectasia, erythema nodosum, jaundice, spider naevi, leukonychia, yellow nails, dystrophic nails	Urine protein, albumin, cells, casts, lipids, urinary bence jones protein (BJP). Serum creatinine, liver function, full blood count. ANA, ANCA, anti-GBM, complement* (Table 1.5), ASOT, cryoglobulins, hepatitis B, C & HIV serology, ultrasound, kidney biopsy
Nephritic syndrome	Dark brown, tea-coloured or smoky urine, sore throat (IgA nephropathy) respiratory, skin infections (post-streptococcal), family history (Alport's syndrome), fever, skin rash, joint pain (lupus nephritis), haemoptysis (vasculitis)	Hypertension, oedema, hearing impairment (Alport's syndrome), skin lesion (Lupus, henoch-schonlein purpura (HSP), vasculitis, Fabry's disease)	Urine microscopy: dysmorphic RBC, casts, proteinuria >0.5 g/day, full blood count, serum creatinine, liver profile, ANA, ANCA, anti-GBM, complement*, ASOT, cryoglobulins, hepatitis B, C & HIV serology, ultrasound, kidney biopsy
Kidney stones	Haematuria, loin to groin pain, nausea, vomiting. High oxalate, high protein, high salt diet. Drugs triamterene, sulphonamides, indinavir. Hyperparathyroidism, sarcoidosis, bile salt depletion, short gut. Reduced fluid, excessive sweat	Fever, costo-vertebral 'renal angle' tenderness	Full blood count, serum calcium, phosphate, urate, pH Urinary RBC, WBC, pH, crystals. 24 h urine calcium, urate, citrate, oxalate, sodium Non-contrast helical CT of the kidneys, ureters and bladder (KUB), renal tract ultrasound
Urinary tract obstruction	Flank pain, suprapubic pain, suprapubic fullness. Urine frequency and urgency (partial obstruction). Anuria (urethral). Haematuria (stones, cancer) suprapubic fullness, frequency nocturia	Enlarged urinary bladder, enlarged prostate, uterine prolapse	Urine RBC, WBC, raised serum creatinine, hyperkalaemia, acidosis, renal tract ultrasound and CT scan

(continued)

Table 1.4 (continued)

Kidney syndrome	History	Physical examination	Investigations
Kidney tubular disorder	Renal stones, short stature, family history		Blood pH, electrolytes, urine electrolytes, pH
Urinary tract infection (UTI)	Urinary frequency and urgency, dysuria, cloudy urine, smelly urine, fever, flank pain	Suprapubic tenderness, flank pain/renal angle tenderness, signs of sepsis (fever, tachycardia, hypotension)	Urinalysis for blood, leucocytes & nitrites (infection), MSU culture to isolate causative organisms, FBC, blood urea, serum creatinine, electrolytes, CRP and blood culture if immune suppressed or signs of systemic sepsis. Ultrasound ± CT scan if obstruction or stones suspected, recurrent, or failure to resolve with first line therapy
Acute kidney injury	History of salt and water loss, drug history, fever, history of CKD, rash, hair loss, joint pain	Blood pressure & pulse, postural drop on assessing lying/standing blood pressure, dry mucus membranes, rash, alopecia, jaundice, ulcers, palpable bladder	Blood urea, serum creatinine, electrolytes. Urinary sodium, creatinine, osmolality, blood, protein, microscopy, RBC, casts, eosinophil Ultrasound of the renal tract, kidney biopsy
Chronic kidney disease	History of hypertension, diabetes, AKI, lupus, hepatitis, scleroderma, vasculitis, familial CKD. Polyuria, nocturia, haematuria, proteinuria. Anorexia, nausea vomiting	Blood pressure, pulse lying/standing, oedema, wasting, retinal exam, palpable kidney, urinary bladder	Full blood count, serum creatinine, electrolytes, calcium, phosphate, liver function, lipids. Urine protein, ultrasound of the renal tract

Table 1.5 Conditions causing abnormalities in complement levels

Complement levels	Condition
Low C3, Low C4	Lupus nephritis Cryoglobulinaemia Infective endocarditis Shunt nephritis Type 1 mesangio-proliferative glomerulonephritis (MPGN)
Low C3, Normal C4	Type 2 mesangio-proliferative glomerulonephritis (MPGN) Post-infective/post-streptococcal glomerulonephritis

Radiological Abnormalities

Radiological abnormalities of the urinary tract may be picked up incidentally, and should prompt further history taking, physical examination and tests to establish a diagnosis.

Haematuria

Haematuria is defined as an abnormal number of red cells in the urine i.e. more than 3 red blood cells seen under one high power field under the laboratory microscope. Haematuria may originate from the kidneys, or from the urinary tract. Table 1.6 can help with differentiating between the two:

Investigations for haematuria will be guided by the presentation, but may include urine microscopy, urinary protein quantification, ultrasound of the kidneys and urinary tract, and CT and cystoscopy if necessary (Tables 1.7 and 1.8).

Table 1.6 Clinical features of haematuria from kidney compared to that from urinary outflow tract

	Haematuria originating from the kidneys	Haematuria originating from the urinary outflow tract: ureters, urinary bladder & urethra
Age at presentation	Could be at any age	Usually >50 years
Urine colour	Dark red, brown, smoky	Bright red
Urinary clots	No	Yes
Mixed with urine	Yes	May be at beginning or end of micturition
Lower urinary tract symptoms	No	Yes
Proteinuria	Yes	No
Dysmorphic red blood cells (RBCs)	Yes	No
Oedema	Yes	No
Raised serum creatinine	Yes	No
Hypertension	Yes	No
Fever, rash, chest symptoms	Yes	No

Table 1.7 Common causes of haematuria

Category	Cause
Benign	Renal masses (angiomyolipoma (AML), oncocytoma Benign prostatic hypertrophy (BPH) Urethral strictures
Stones	Staghorn calculi Calcium stones Uric acid stones
Infective	Pyelonephritis Cystitis Urethritis
Trauma	Pelvic trauma Renal injuries Foreign bodies
Renal	IgA nephropathy Thin basement membrane disease Hereditary nephritis Medullary sponge kidney
Iatrogenic	Recent endoscopic procedure (e.g. transurethral resection of the prostate (TURP) Transrectal ultrasound (TRUS) guided prostate biopsy Traumatic catheterisation Radiation Indwelling ureteric stents Renal biopsy Extracorporeal shockwave lithotripsy (ECSWL)
Malignant	Renal cell carcinoma Transitional cell carcinoma Squamous cell carcinoma Urothelial cell carcinoma Prostate acinar adenocarcinoma

Table 1.8 Causes of red or brown urine

Endogenous substances	Foods	Drugs
Red blood cells Haemoglobin Myoglobin Bilirubin Porphyrins Melanin	Food colouring Beetroot Blackberries, Blueberries Fava beans Paprika Rhubarb	Rifampicin Adriamycin Chloroquine Deferoxamine Levodopa Methyldopa Metronidazole Nitrofurantoin Phenytoin Prochlorperazine Quinine Sulfonamides

Presentation of Kidney Failure Patients on Kidney Replacement Therapy

Common presenting features for kidney failure patients on kidney replacement therapy include, fever, breathlessness, chest pain, confusion, fatigue, falls and abnormal blood tests such as hyperkalaemia and rising serum creatinine in a kidney transplant patient. Infection and malfunction of dialysis vascular access are very common causes of acute admissions for patients on haemodialysis and peritoneal dialysis, followed by breathlessness due to fluid volume overload. Rapid ultrafiltration on haemodialysis and obligatory ultrafiltration with peritoneal dialysis can alternatively lead to volume depletion, hypotension and falls, particularly in elderly dialysis patients. Fatigue and tiredness due to anaemia and malnutrition are also common complaints in patients on renal replacement therapy.

A rising serum creatinine on routine blood test results is a common reason for hospital attendance in kidney transplant recipients, which could be due to acute transplant rejection, urinary infection, transplant urinary tract obstruction, transplant renal artery stenosis, or most commonly volume depletion (Table 1.9).

Table 1.9 Common causes to consider based on symptoms and blood results in patients on kidney replacement therapy

Common symptoms	Haemodialysis	Peritoneal dialysis	Kidney transplantation
Fever	Dialysis access related infection Infections of chest and urine	PD catheter exit site infection, peritonitis Infections of chest and urine	Urinary tract infection atypical infection of chest and blood stream e.g. CMV, EBV, TB
Breathlessness	Fluid overload Chest infection Anaemia, loss of native renal function	Fluid overload Chest infection Anaemia, loss of native renal function	Fluid overload Chest infection Anaemia
Fatigue	Anaemia Malnutrition	Anaemia Malnutrition	Anaemia
Falls	Hypotension due to excess ultrafiltration on dialysis Drug-induced hypotension Cardiac arrythmias, infection	Hypotension due to excess ultrafiltration on dialysis Drug-induced hypotension Cardiac arrythmias, infection	Volume depletion, infection
Hyperkalaemia	Missed dialysis High potassium diet	High potassium diet, underlying high cell turnover state	Tacrolimus High potassium diet Kidney transplant failure

Conclusions

Returning to the clinical scenario from the beginning of the chapter, the differential diagnosis with the available information is extremely broad, and includes an acute kidney injury, chronic kidney disease, a new presentation with glomerulonephritis, urinary tract infection, or an infective complication of known end stage kidney disease. Further clarification is only really possible through eliciting a careful medical history, and performing a thorough physical examination, which will in turn determine the most appropriate next investigations, and an appropriate, safe plan for management, including whether she is likely to be fit to fly home:

The patient had been assessed as confused because she was having difficulty communicating with staff in the emergency department: thankfully, one of the hospital nursing team was able to speak with her coherently in her native language. She shows the assessing clinician a letter from her nephrology team at home, which on translation, indicates that she has end stage kidney disease due to IgA nephropathy, and was transplanted with a deceased donor (donation after circulatory death (DCD)) kidney 5 years ago, and is chronically immune suppressed with tacrolimus and mycophenolate mofetil. Her most recent serum creatinine level was 200 μmol/L (2.26 mg/dL) 2 months ago, and she has a history of recurrent transplant urinary tract infections, most recently an *Escherichia Coli,* fully sensitive to standard antimicrobial agents.

A full physical examination reveals—in addition to the findings reported previously—a non-functioning right radiocephalic arteriovenous fistula from previous haemodialysis, a right-sided Rutherford-Morrison scar, overlying a non-tender mass. There is mild suprapubic tenderness. There was no peripheral oedema, but she had a mild resting tremor. Neither her white cell count nor CRP were raised; her tacrolimus trough level was 6 ng/mL, and her blood sugar was 5.6 mmol/L; Her urinalysis was positive for leukocytes and nitrites, but was otherwise clear. A transplant renal tract ultrasound revealed no evidence of obstruction, a small post-micturition bladder residual volume of 60 mL, and normal resistive indices (RIs) of 0.68.

A clinical diagnosis of kidney transplant urinary tract infection is made: given the absence of haemodynamic compromise, and a clear history of similar presentations, with a serum creatinine at her baseline, and on agreement with both the local nephrology, and her home nephrology teams, it

was deemed appropriate to manage her in an ambulatory manner—avoiding admission—and encouraging oral fluid intake of 2–3 litres of fluid per day, and commencement of a course of oral antibiotics (amoxycillin + clavulanic acid 6750 mg orally tds for a 5 day course), with a view to being re-assessed by her local nephrology team in a week's time, on return to her native country.

Questions

1. A 22 year old black female presented with weakness, tiredness. On examination her pulse was 82/min, blood pressure was 165/80 mmHg and she had a red rash over her face. Urine examination showed blood and protein. Blood test showed low haemoglobin and creatinine was 187 µmol/L.

   What is most likely diagnosis

   A. Henoch Schulein purpura
   B. Systemic amyloidosis
   C. Systemic lupus erythematosus
   D. Essential cyroglobinimia
   E. Systemic vasculitis

Correct answer: young woman with low haemoglobin, haemo-proteinura and rash is most likely to be lupus.

2. A 45 year old black man presented with tiredness and frothy urine. On examination his pulse was 89/min, blood pressure was 130/82 mmHg. He had a white deposit over his tongue and inner side of his cheek. His urine protein:creatinine ratio was 300 mg/mol (Normal < 15). His kidney ultrasound showed bilateral normal size bright echogenic kidneys.

   What is the likely cause of his nephrotic syndrome?

   A. Amyloidosis
   B. Type 2 diabetes
   C. Hypertension
   D. HIV associated nephropathy
   E. Systemic lupus nephritis

3. A 23 year old female with lupus nephritis, end stage kidney failure on haemodialysis presented with fever and lethargy. She denied Joint pain, dysuria, cough, diarrhoea or rash. On examination pulse was 100/min, temperature 38 °C, blood pressure 110/60 mmHg. The exit site of her tunneled catheter was clean. Blood cultures were sent. Her white cell and CRP were raised.

   What is next best plan of management?

   A. Investigations for lupus nephritis.
   B. Investigations for lymphoma
   C. Start antibiotics for catheter related bacteremia
   D. Start oral steroids
   E. Start intravenous cyclophosphamide

Correct answer: C mostly cause of fever is catheter related bacteremia and lupus id less likely.

4. A 55 year old asymptomatic man was admitted to hospital from the transplant clinic with rising creatine 15 days post kidney transplant from 150 to 230 µmol/L. He was on mycophenolate 250 mg bd and tacrolimus 2 mg bd. His tacrolimus level was 5 ng/mL (target 10–15). His pulse was 78/min, blood pressure 130/60 mmHg. His urine had no blood pr protein. Ultrasound of the transplanted kidney was normal.

   What is the likely cause of his AKI

   A. Acute rejection
   B. Acute intestinal nephritis
   C. Tacrolimus toxicity
   D. Thrombotic microangiopathy related to tacrolimus
   E. Urinary tract infection

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