

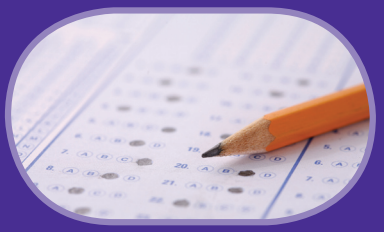

CCU CLINICAL CASES UNCOVERED

Nephrology

Menna Clatworthy

WILEY Blackwell

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Contents

Preface

Renal medicine is often viewed as a complex, 'hard-core' medical specialty, mastered by a small minority of intellectual physicians. The lasting impression of many medical students (and indeed non-renal specialists) is of a list of glomerulonephritides (GNs), which have random and difficult names and blur into one incomprehensible mass. In reality, nephrology is actually relatively simple and logical.

In the first section of the book, I have provided a broad introduction to nephrology. Where possible, I have tied together a clinical presentation with underlying pathology and immunology, using diagrams to distil the important points. I have also provided an 'ABC of GN', which offers a simple framework in which to place the GNs so that they can be understood.

The main part of this book consists of 31 cases, which have been chosen because they reflect the bread and butter of day-to-day life as a nephrologist. Nephrology is a fantastic specialty which allows the physician to deal with a wide variety of clinical problems, ranging from the critically unwell patient with acute renal failure to those with multisystem immune-mediated disease or tubular dysfunction, and those with chronic disease who we sometimes look after for decades on dialysis or following transplantation. For the junior doctor on a 4-month renal attachment (or even the junior renal trainee), the cases I have presented will be surprisingly similar to those which you see (and the questions that follow will reflect those which your consultant will ask). For the purposes of clarity, the cases are divided into seven sections according to clinical presentation: those presenting with acute renal failure, nephrotic syndrome, hypertension, urine dipstick abnormalities, acid–base disturbances, chronic kidney disease/dialysis-associated problems and renal transplant-related problems.

The kidneys are often involved in diseases which are primarily the remit of other specialties, for example, infectious diseases, oncology or haematology. Thus, the renal physician needs to maintain a breadth of medical knowledge, and is perhaps one of the few remaining generalists. This is deliberately reflected in some of the cases, whose presentation begins with a symptom or sign which appears unrelated to the kidneys. As a result, this book will also help you polish up on some basic general medical facts.

Another concept which I have tried to convey in this text is that the kidneys are 'sensitive' organs, and can frequently become acutely dysfunctional in the context of a variety of pathologies. Thus, all doctors, regardless of their specialty or career choice, will encounter patients with acute renal failure (acute kidney injury). On the average 'medical take' or surgical/orthopaedic ward, there will always be a handful of patients with acute renal failure. These patients can be very unwell but if managed promptly and appropriately, may regain their renal function. These are typified by the 10 cases of acute renal failure, starting with common causes and moving to rarer, to illustrate the principles of investigation, management and diagnosis of this important problem.

Chronic kidney disease (CKD) is now widely diagnosed, due to the increased availability of measurements of renal function, in particular eGFR. General practitioners need to be aware of the complications associated with CKD and the appropriate time for referral to nephrology services. I have therefore presented a number of cases of patients with CKD, which touch upon the practicalities of managing associated complications and of providing renal replacement therapy for the increasing number of patients diagnosed with CKD. For those with CKD reaching end-stage renal failure, dialysis and renal transplantation are no longer limited to the lucky, 'fit' few but are available to all. Very few textbooks provide practical advice on the management of these patients and I hope that students (and junior doctors) asked to deal with these chronic nephrology patients will find the cases in this book of genuine practical use. On a more pragmatic note, patients with CKD are often well with stable clinical signs and are therefore frequent attendees at

student clinical examinations (with an arteriovenous fistula, palpable kidneys or a transplanted kidney). This text should allow you to really fly through those stations of the exam. The MCQs, EMQs and SAQs also provide practical help to test your nephrology knowledge prior to examinations.

In summary, nephrology need not be feared and can be understood. Over the last 10 or so years, I have taught many students clinical medicine at the bedside. There is no substitute for this but in this text, I have tried to recreate some of these cases in an attempt to convey some of the important concepts and, I hope, to make renal medicine accessible to all.

Menna Clatworthy
Cambridge

Acknowledgements

There are a number of people to whom I owe a great deal of thanks. First and foremost to the many patients and students who have been involved in my teaching sessions over the last decade, who have provided a stimulus to clarify some of the more tricky aspects of renal medicine for the purposes of teaching. In terms of direct assistance with this book, my sincere thanks go, in particular, to Dr Meryl Griffiths (histopathologist, Addenbrooke's Hospital, Cambridge) for the many renal biopsy pictures featured in this book. To the patients who consented to photographs, especially those in the transplant clinic and dialysis unit at Addenbrooke's Hospital, Cambridge. To Dr Liz Wallin, for tirelessly tracking down and retrieving a number of radiology images, drug and fluid charts for illustrations, as well as proof reading Part 1. To Dr Lisa Willcocks (for assistance with renal biopsy pictures), to Sister Angela Green (for help in gathering PD-related pictures), to Mr Chris Watson (for formatting assistance and general wisdom) and to Sarah Harford (for cheerfulness, encouragement, tea and scanning skills). To many of the renal SpRs at Addenbrooke's for proof reading and providing comments on the cases contained within this book, including Dr Lisa Willcocks, Dr Eoin McKinney, Dr Andy Fry, Dr Thomas Heimstra, Dr Elaine Jolly and Dr Sharon Mulroy. Finally, to my family back in South Wales, who tolerated a whole Christmas holiday of writing with patience and provided a constant source of support and encouragement.

How to use this book

Clinical Cases Uncovered (CCU) books are carefully designed to help supplement your clinical experience and assist with refreshing your memory when revising. Each book is divided into three sections: Part 1, Basics; Part 2, Cases; and Part 3, Self-assessment.

Part 1 gives you a quick reminder of the basic science, history and examination, and key diagnoses in the area. Part 3 contains many of the clinical presentations you would expect to see on the wards or cropping up in exams, with questions and answers leading you through each case. New information, such as test results, is revealed as events unfold and each case concludes with a handy case summary explaining the key points. Part 3 allows you to test your learning with several question styles (MCQs, EMQs and SAQs), each with a strong clinical focus.

Whether reading individually or working as part of a group, we hope you will enjoy using your CCU book. If you have any recommendations on how we could improve the series, please do let us know by contacting us at: medstudentuk@oxon.blackwellpublishing.com.

Disclaimer

CCU patients are designed to reflect real life, with their own reports of symptoms and concerns. Please note that all names used are entirely fictitious and any similarity to patients, alive or dead, is coincidental.

List of abbreviations

AAA	abdominal aortic aneurysm
AAV	ANCA-associated vasculitis
ABG	arterial blood gas
ABPI	Ankle Brachial Pressure Index
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin/creatinine ratio
ADH	anti-diuretic hormone
ADPKD	autosomal dominant polycystic kidney disease
AF	atrial fibrillation
AGE	advanced glycosylation end products
aHUS	atypical haemolytic uraemic syndrome
AKI	acute kidney injury
ALG	antilymphocyte globulin
ALP	alkaline phosphatase
ANA	anti-nuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibody
ANP	atrial natriuretic peptide
APD	automated peritoneal dialysis
APKD	adult polycystic kidney disease
APTT	activated partial thromboplastin time
AR	atrial regurgitation
ARB	angiotensin receptor blockers
ARF	acute renal failure
ASO	anti-streptolysin-O
ATG	anti-thymocyte globulin
ATN	acute tubular necrosis
AVF	arteriovenous fistula
AVM	arteriovenous malformation
BCC	basal cell carcinoma
BFT	bone function tests
BHS	British Hypertension Society
BM	basement membrane
BMI	Body Mass Index
BP	blood pressure
BPH	benign prostatic hypertrophy
bpm	beats per minute
CAD	coronary artery disease
CAH	chronic active autoimmune hepatitis
CAPD	continuous ambulatory peritoneal dialysis
cCa	corrected calcium
CCF	congestive cardiac failure
CCPD	continuous cyclic PD
CI	confidence interval
CIN	contrast-induced nephropathy
CIT	cold ischaemic time
CK	creatine kinase
CKD	chronic kidney disease
CKD-BMD	chronic kidney disease-bone and mineral disorder
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPM	central pontine myelinolysis
CRP	C-reactive protein
CSA	ciclosporin-A
CT	computed tomography
CVA	cerebrovascular accident
CVP	central venous pressure
CVS	cardiovascular system
CXR	chest X-ray
DGF	delayed graft function
DIC	disseminated intravascular coagulopathy
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DVT	deep vein thrombosis
EBV	Epstein–Barr virus
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EH	essential hypertension
EM	electron microscopy
ENT	ear, nose and throat
EPO	erythropoietin
EPS	encapsulating peritoneal sclerosis

ESR	erythrocyte sedimentation rate
ESRF	end-stage renal failure
FBC	full blood count
FFP	fresh frozen plasma
FGF23	fibroblast growth factor 23
FH	family history
FMD	fibromuscular dysplasia
FOB	faecal occult blood
FSGS	focal segmental glomerular sclerosis
GAG	glycosaminoglycans
GCS	Glasgow Coma Score
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GI	gastrointestinal
GN	glomerulonephritis
HAART	highly active antiretroviral therapy
HD	haemodialysis
HDU	high-dependency unit
HELLP	haemolysis, elevated liver enzymes, low platelets
HHV	human herpes virus
HIV	human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HLA	human leucocyte antigen
HPV	human papilloma virus
HR	heart rate
HS	heart sounds
HSP	Henoch–Schönlein purpura
HUS	haemolytic uraemic syndrome
IC	immune complex
ICP	intracranial pressure
ICU	intensive care unit
IGT	impaired glucose tolerance
INR	international normalised ratio
IP	intraperitoneal
IPD	intermittent peritoneal dialysis
ITP	immune thrombocytopaenic purpura
ITU	intensive treatment unit
IVC	inferior vena cava
IVDU	intravenous drug use
JVP	jugular venous pressure
LAD	left axis deviation
LFT	liver function tests
LN	lymph node
LV	left ventricle/ventricular
LVH	left ventricular hypertrophy
MAC	membrane attack complex
MAHA	microangiopathic haemolytic anaemia
MAP	mean arterial pressure
MCGN	mesangiocapillary glomerulonephritis
MCP	membrane co-factor protein
MCV	mean corpuscular volume
MDT	multidisciplinary team
MEN	multiple endocrine neoplasia
MI	myocardial infarction
MM	multiple myeloma
MMF	mycophenolate mofetil
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MR	mitral regurgitation
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MSU	midstream urine
NAD	no abnormality detected
NBM	nil by mouth
NPBP	nephritis plasmin-binding protein
NIPD	nightly intermittent peritoneal dialysis
NSAID	non-steroidal anti-inflammatory drugs
NSAP	nephritis strain-associated protein
NSF	nephrogenic systemic fibrosis
OCP	oral contraceptive pill
OPD	outpatients department
ORG	obesity-related glomerulopathy
PAAg	preabsorbing antigen
PAMP	pathogen-associated molecular patterns
PAN	polyarteritis nodosa
PBC	primary biliary cirrhosis
PCA	patient-controlled analgesia
PCP	*Pneumocystis carinii* pneumonia
PCR	polymerase chain reaction
PCr	protein/creatinine ratio
PD	peritoneal dialysis
PE	pulmonary embolism
PEX	plasma exchange
PKD	polycystic kidney disease
PMH	past medical history
pmp	per million people
PND	paroxysmal nocturnal dyspnoea
POP	plaster of Paris
PPI	proton pump inhibitor
PR	per rectum
PSA	prostate-specific antigen
PT	prothrombin time
PTH	parathyroid hormone
PTHrP	parathyroid hormone related-protein
PTLD	post-transplant lymphoproliferative disorder

PVD	peripheral vascular disease
RAA	renin-angiotensin-aldosterone
RAS	renal artery stenosis
RBC	red blood cell
RF	rheumatoid factor
RHF	right heart failure
rpm	respirations per minute
RR	respiratory rate, relative risk
RRT	renal replacement therapy
RTA	renal tubular acidosis
RVH	right ventricular hypertrophy
SAA	serum amyloid A
SAH	subarachnoid haemorrhage
SAP	serum amyloid P
SCC	squamous cell carcinoma
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	systemic lupus erythematosus
SOB	shortness of breath
STEC	shigatoxin-producing *E. coli*
SV	stroke volume
TCC	transitional cell carcinoma
TIA	transient ischaemic attack
TIN	tubulointerstitial nephritis
TLR	Toll-like receptors
TNF	tumour necrosis factor
TPD	tidal peritoneal dialysis
TPR	total peripheral resistance
TTP	thrombotic thrombocytopaenic purpura
U&E	urea and electrolytes
UF	ultrafiltration
URR	urea reduction ratio
US	ultrasound
UTI	urinary tract infection
WBC	white blood cells
WG	Wegener's granulomatosis

Normal range for investigations

Haematology

Full blood count (FBC):
Haemoglobin (Hb) 11.5–16 g/dL (female), 13.5–18 g/dL (male)
White blood cells (WBC) 4–11 × 10^9/L
Platelets (plats) 150–400 × 10^9/L

Biochemistry

Sodium (Na) 135–145 mmol/L
Potassium (K) 3.5–5.3 mmol/L
Urea (U) 2.5–6.7 mmol/L
Creatinine (Creat) 50–120 μmol/L (varies according to muscle bulk and diet)
Corrected calcium (cCa) 2.18–2.6 mmol/L
Phosphate (PO_4) 0.8–1.45 mmol/L
Glucose (Glu) 3.5–5.5 mmol/L
Albumin (Alb) 35–50 g/L
Alkaline phosphatase (ALP) 30–300 iu/L
C-reactive protein (CRP) <6 mg/L
Creatine kinase (CK) 25–195 iu/L
Serum osmolality 278–305 mosmol/kg
pH 7.25–7.45
Bicarbonate (HCO_3) 24–28 mmol/L
Chloride (Cl) 95–105 mmol/L
Parathyroid hormone (PTH) <65 pg/mL
pO_2 10–13 kPa
pCO_2 4.9–6.1 kPa

Basic science

The structure of the kidney has evolved to effectively accomplish its main tasks, which include a number of functions that do not obviously relate to its main blood-cleaning role. They are:

- control of water balance
- control of electrolyte balance
- excretion of water-soluble waste
- control of acid–base balance
- control of blood pressure (through both control of water and electrolyte balance and production of renin)
- the production of active vitamin D (through the action of 1α-hydroxylase) and hence control of calcium-phosphate metabolism
- the production of erythropoietin, and hence control of haemoglobin level.

When the kidneys become diseased or dysfunctional, the symptoms with which a patient presents arise because of the failure to perform one or more of the above tasks. Before considering the clinical presentation of renal diseases, it is useful to put them in the context of basic renal anatomy, histology, physiology and biochemistry.

Anatomy

Most individuals have two kidneys, which lie in the retroperitoneum on either side of the midline (at vertebral level T12–L3). In adults, the kidneys measure around 10–12 cm in bipolar length and the upper poles are protected by the 11th and 12th ribs. The kidneys are pushed down into the abdomen during deep inspiration as the lungs expand and the diaphragm flattens. The adrenal glands rest on the upper poles of the kidneys and both organs are encased by two layers of fat (the peri- and pararenal fat) and a layer of fascia. The kidneys are surrounded by a tough capsule and are made up of an outer cortex and inner medulla. In older adults, cysts may form but these should number less than five per kidney.

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Given that the kidneys play a major role in clearance of circulating waste products and drugs, it is unsurprising that they receive a large volume of blood (25% of cardiac output) via the renal arteries, branches of the abdominal aorta. Each renal artery divides into progressively smaller vessels (arcuate, interlobular, then afferent arterioles). Blood is drained via the renal veins into the inferior vena cava, and urine via the ureter, which winds through the retroperitoneum to the bladder. Here the urine is stored and finally expelled through the urethra, which is longer in the male, thus reducing the risk of bladder infections. In males the urethra is encircled by the prostate gland, which may become enlarged in later life, causing obstruction to the outflow of urine (Figure A).

The functioning unit of the kidney is the nephron (Figure B), of which there are about a million per kidney. The nephron is made up of a glomerulus, proximal tubule, loop of Henle, distal tubule and collecting duct. Each capillary loop within the glomerulus has a layer of fenestrated endothelium surrounded by the glomerular basement membrane, which is in turn enveloped by an epithelial cell, the podocyte (Figure C). Each capillary loop is supported by a mesangial cell with surrounding matrix. Inflammation of the glomeruli (glomerulonephritis (GN)) tends to cause proliferation of one or more of the component cells of the glomerular capillary loop; for example, in IgA nephropathy, there is proliferation of the mesangial cells, in cresecentic GN there is proliferation of the epithelial cells to form a cellular crescent. Basic descriptions of these histological changes are used to define the different types of GN (see later).

Physiology

An overview of tubular function is given in Figure D.

Glomerular function

Blood arrives at the glomerulus via the afferent arteriole and around 20% of the plasma (and none of the cellular components of blood) is filtered into Bowman's capsule

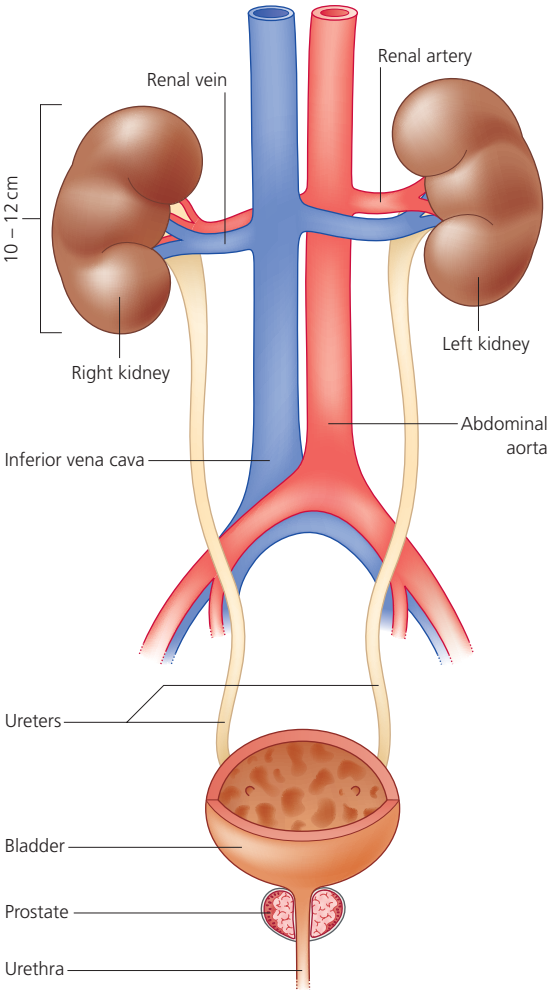


Figure A Anatomy of the renal tract.

as it passes through the glomerular capillary loops. The filtered blood leaves the glomerulus via the efferent arteriole which subsequently divides to form the peritubular capillaries. Filtration is a passive process which is driven by the hydrostatic pressure acting across glomerular capillaries and is countered by the oncotic pressure exerted by circulating proteins such as albumin. It is also in part dependent on the permeability of the glomerulus (which can increase if the podocyte becomes diseased, leading to proteinuria, or decrease in many conditions, e.g. if there is thickening of the basement membrane). Glomerular filtration is a key requirement for the blood-cleaning and water-handling functions of the kidneys. Thus, the glomerular filtration rate (GFR) is the main measure of kidney function used by nephrologists. GFR varies but is around 130 mL/min/1.73 m^2 in men and 120 mL/min/1.73 m^2 in women. GFR remains constant until around the age of 40 years, but thereafter gradually declines (by approximately 1 mL/min/1.73 m^2 per year) (1.73 m^2 is the average body surface area of an adult).

The simplest way of estimating GFR is to measure the serum creatinine. Creatinine is constantly being produced by muscle cells and is filtered by the kidney. If GFR declines, then serum creatinine will increase.

Tubular physiology (Figure D)

The normal GFR of 120–30 mL/min/1.73 m^2 requires the renal tubules to reabsorb vast quantities of water and electrolytes. For example, 180 litres of water are filtered at glomeruli per day. The total body (intracellular and extracellular) water volume is around 40 litres. If tubular reabsorption of water ceased, then the total plasma volume would be urinated in around 30 minutes.

Solutes such as Na^+, K^+, bicarbonate, and Cl^- and amino acids filtered at the glomerulus into Bowman's capsule need to be reabsorbed by tubular cells, or else they would all be lost in the urine (with severe consequences). Soluble waste products such as urea are also reabsorbed, but only partially, in contrast to the 'useful' solutes listed above, which are almost completely reabsorbed. In addition, tubular cells are involved in the secretion of waste products (such as creatinine, uric acid and H^+) into the urinary/tubular space. Thus, tubular cells express a number of surface pumps, allowing them to move molecules from the urinary space into the interstitium, and vice versa. These pumps require energy to function properly, so the metabolic needs of tubular cells are high and they are extremely susceptible to ischaemic injury, as seen in acute tubular necrosis (ATN).

The fine tuning of Na^+ and water balance is achieved in the distal tubule and collecting duct (via the influence of aldosterone and antidiuretic hormone (ADH)). Normal urine volume is around 1.5–2 litres/day.

Table A shows the average values of water and some electrolytes handled by the kidneys.

Proximal tubules

The main role of the proximal tubule is reabsorption of water and filtered electrolytes, glucose and amino acids, including:

- 60–80% of water
- 60–70% of filtered sodium (via the Na/K-ATPase)
- 90% of potassium
- 90% of bicarbonate

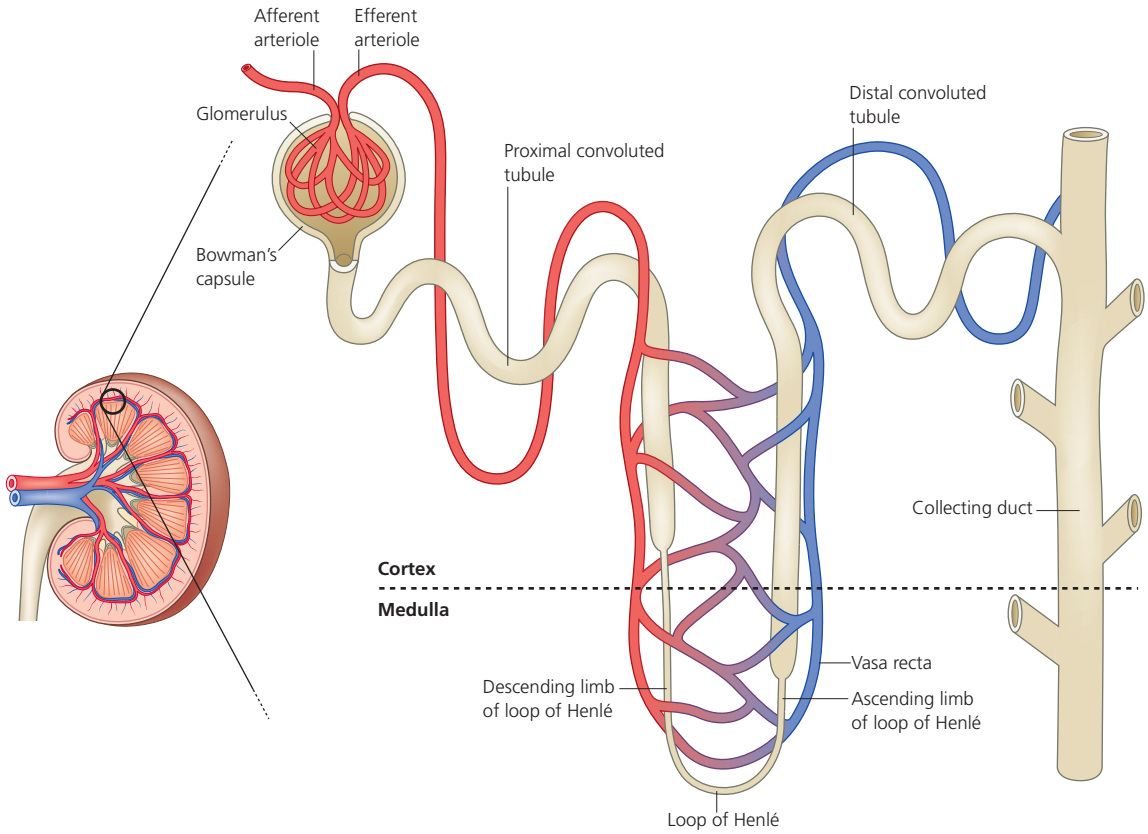


Figure B The nephron.

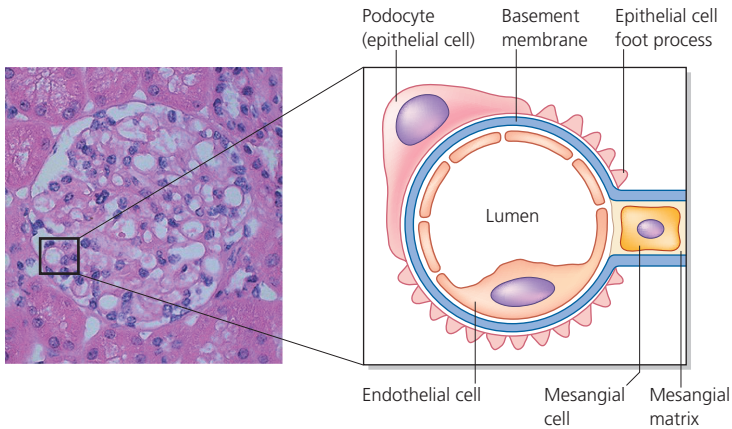


Figure C The glomerulus. Left panel shows typical histological appearance of the glomerulus. A single capillary loop is boxed and the structures within identified in the right-hand panel.

- 100% of glucose
- 100% of amino acids
- variable quantity of chloride, calcium and magnesium
- variable quantity of phosphate (dependent on parathyroid hormone (PTH) concentration).

Waste products secreted into the tubular space in the proximal tubule include creatinine and uric acid.

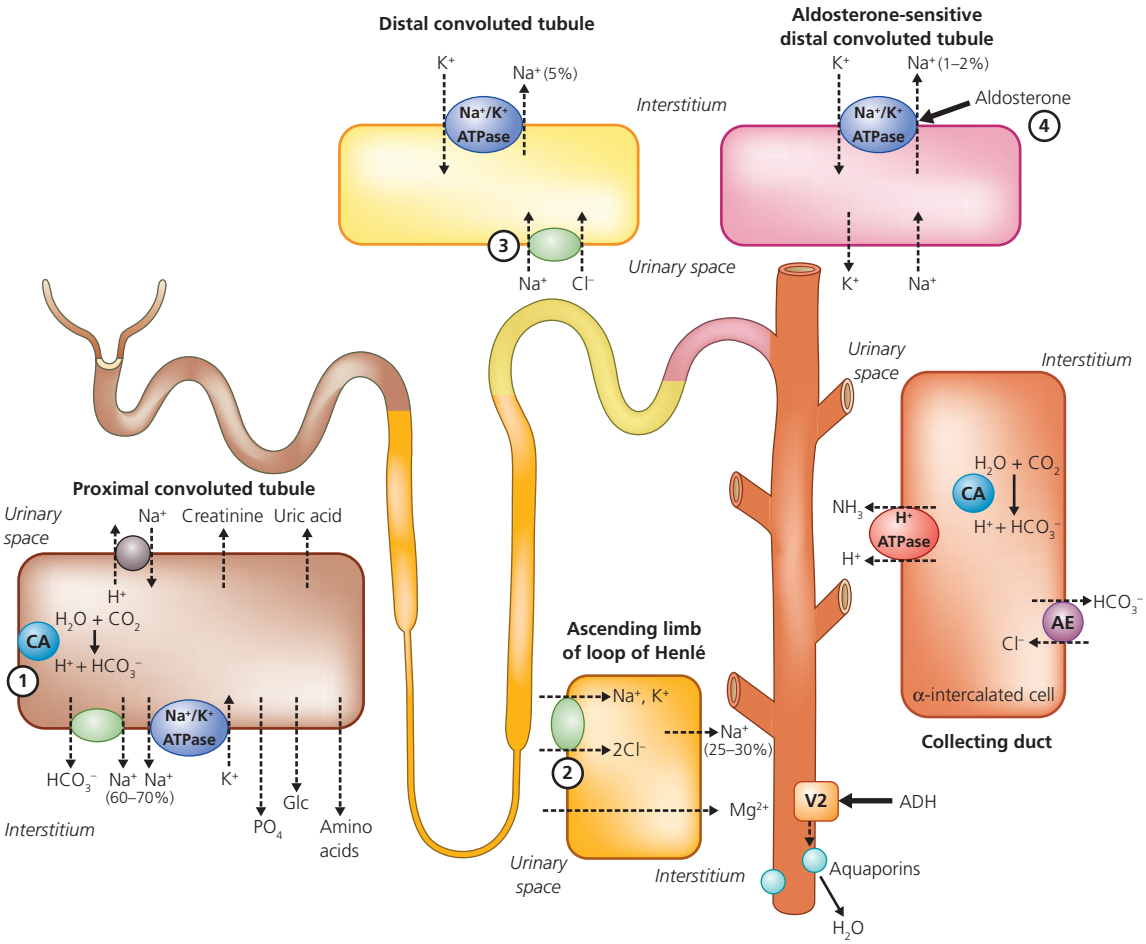


Figure D Tubular function (see text for detailed description).

Table A Renal water and solute handling

Substance	Amount filtered/day	Amount excreted/day	% reabsorption
Water (litres)	180	1.8	99
Sodium (g)	630	3.2	99.5
Glucose (g)	180	0	100
Urea (g)	56	28	50

If there is proximal tubule dysfunction (e.g. in type II (proximal) renal tubular acidosis) then there is glycosuria, aminoaciduria and acidosis (due to loss of bicarbonate).

Loop of Henle

The main role of the loop of Henle is to generate an interstitial sodium gradient between the cortex (low concentration Na^+) and inner regions of the medulla (high concentration Na^+). This concentration gradient is generated by virtue of the fact that the ascending limb of the loop of Henle is impermeable to water.

Twenty to 40% of sodium is reabsorbed from the tubular space into the interstitium in the loop of Henle by the NaK2Cl co-transporter and around 10% of filtered water. This generates a high concentration of Na^+ in the interstitium but water is unable to follow, due to the impermeable ascending limb. The high interstitial Na^+ concentration provides a gradient which allows urine to be concentrated as it flows through the collecting tubules (the permeability of which is controlled by ADH).

The NaK2Cl co-transporter is inhibited by loop diuretics, the effect of which is to reduce sodium reabsorption, and hence the concentration gradient generated, so that a more dilute urine is produced. In addition to sodium transport, the majority of magnesium is also absorbed in the ascending limb of the loop.

At the end of the loop of Henle, as it arrives back up in the cortex, lie the cells of the macula densa. These cells sense luminal sodium concentration and are involved in controlling the release of renin, and hence systemic blood pressure (see below).

Distal tubule

The distal tubule plays a role in fine tuning the final urine sodium concentration (and hence determines how dilute or concentrated it will be). Around 5% of sodium is reabsorbed here via the NaCl co-transporter, which is inhibited by thiazide diuretics.

Collecting duct

A further 2% of sodium is reabsorbed by the aldosterone-sensitive sodium channels found within the distal convoluted tubule and the collecting duct.

Acid secretion is performed by the α-intercalated cells of the collecting tubule and involves two pumps: H^+ATPase and the basolateral Cl^-:HCO_3^- anion exchanger 1 (AE-1) and an enzyme (carbonic anhydrase 2 (CA2); see Figure D for details.

Box A The determinants of mean arterial pressure (MAP)

MAP = cardiac output (CO) × total peripheral resistance (TPR)
CO = stroke volume (SV) × heart rate (HR)

Antidiuretic hormone (ADH) exerts its effects on this portion of the nephron, causing the insertion of aquaporins into the luminal membrane, thus facilitating the reabsorption of water, which travels from the tubular space into the interstitium as a result of the concentration gradient generated by the loop of Henle.

The physiology of blood pressure control

When considering the ways in which the kidneys are involved in blood pressure control, it is important to bear in mind the basic physiological principle that mean arterial pressure (MAP) is dependent on cardiac output (CO) and total peripheral resistance (TPR) (Box A). CO is affected by stroke volume and hence venous return. As tubular function declines in chronic kidney disease (CKD), the kidney retains fluid and the venous return increases, causing a rise in MAP. Thus CKD is often associated with hypertension.

Renin-angiotensin-aldosterone (RAA) pathway (Figure E)

Renin is released from the juxtoglomerular apparatus of the kidney in response to reduced renal perfusion or low sodium delivery to the distal part of the loop of Henle. Renin coverts angiotensinogen (made in liver) to angiotensin I. This is converted to angiotensin II by angiotensin-converting enzyme (ACE), found principally in the pulmonary vasculature. Angiotensin II is a potent vasoconstrictor and will thus increase TPR and MAP. It also causes the release of aldosterone from the adrenal cortex, which acts on the distal tubule to cause retention of sodium, and thus water, expanding volume and increasing venous return, CO and MAP.

In addition, angiotensin II leads to the release of ADH from the posterior pituitary. ADH increases permeability of the collecting duct by stimulating the insertion of water channels (aquaporins) into the apical (luminal) membrane of principal cells of the collecting duct. This is achieved through the action of ADH on V2 receptors, G protein-coupled receptors on the basolateral (intersti-

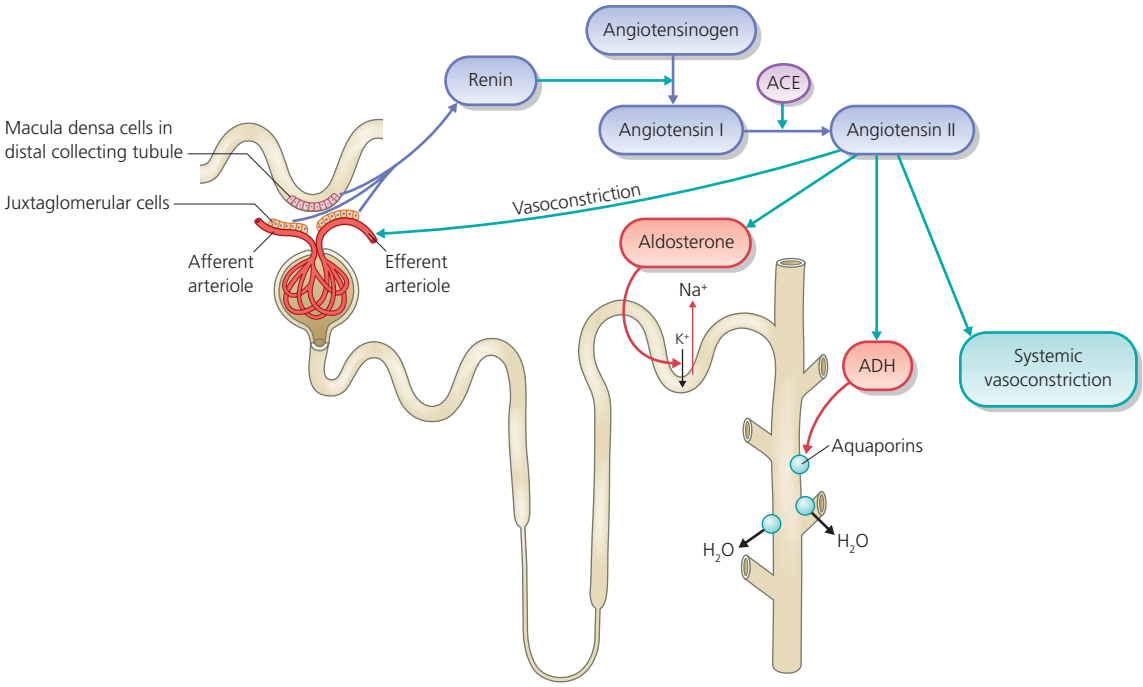


Figure E The renin-angiotensin-aldosterone system.

tial) membrane of principal cells. Following binding, activation of the cAMP cascade leads to the release of aquaporins from storage vesicles by exocytosis. The aquaporins are then inserted into the apical (luminal) membrane, allowing water to pass out of the distal convoluted tubules and the collecting tubules into the interstitium, and back into the blood. The net effect is to increase the concentration of urine and expand blood volume, causing a rise in MAP.

Biochemistry

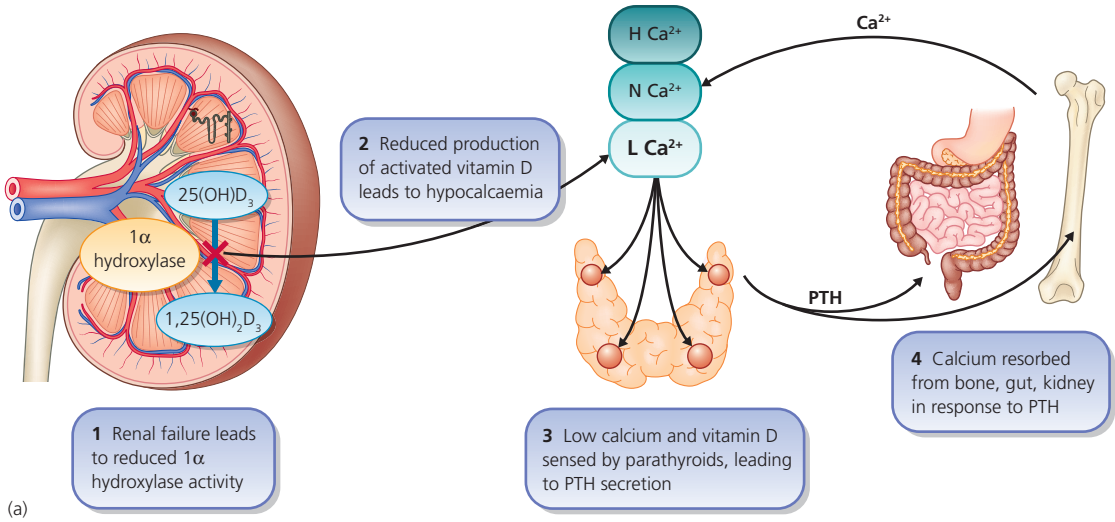
Endocrine functions of the kidney

Vitamin D metabolism

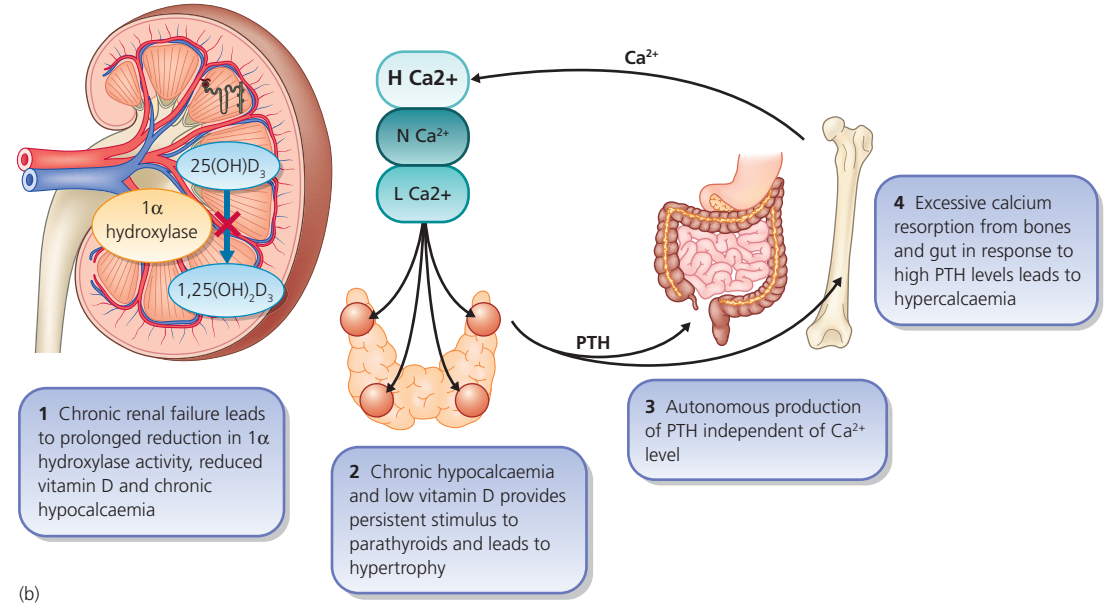
Naturally occurring vitamin D requires hydroxylation, first in the liver to 25,OH-vitamin D and then in the kidney to 1,25$(OH)_2$-vitamin D via the action of the enzyme 1α-hydroxylase. If the kidneys are diseased, there is a reduction in production of active vitamin D (1,25$(OH)_2$-vitamin D). This results in reduced absorption of calcium from the gut, impaired bone mineralisation and hypocalcaemia. The low levels of calcium and 1,25$(OH)_2$-vitamin D (as well as high phosphate) are sensed by cells of the parathyroid gland, which increase the production of PTH in an attempt to restore normocalcaemia, a state known as secondary hyperparathyroidism. If there is chronic kidney dysfunction and persistent hypocalcaemia, the parathyroid glands hypertrophy and begin to function autonomously, i.e. independently of blood calcium level, leading to hypercalcaemia (tertiary hyperparathyroidism) (Figure F).

Erythropoietin production

Endogenous erythropoietin (EPO) is produced by peritubular cells. It acts on erythroid precursors within the bone marrow, stimulating proliferation and maturation. Damage to the kidney leads to reduced EPO production and can be seen when GFR falls to <50 mL/min. Anaemia in CKD patients is exacerbated by impaired intestinal absorption of iron and reduced iron intake. Prior to the introduction of recombinant EPO, anaemia was a major cause of morbidity and mortality in patients with end-stage renal failure, and was associated with cardiovascular complications in particular. In some renal conditions, e.g. polycystic kidney disease or renal cell carcinoma, the production of EPO may increase, leading to polycythaemia.



(a)



(b)

Figure F (a) Secondary hyperparathyroidism. (b) Tertiary hyperparathyroidism.

Approach to the patient

History

Specific features related to renal disease

1. Urine abnormalities

- *Amount*
  - A reduced amount of urine (<300 mL/day) is termed oliguira.
  - An absence of urine production is termed anuria. Oliguria occurs in nephritic syndrome, acute renal failure (ARF) and chronic end-stage renal failure (ESRF). Absolute anuria suggests a complete obstruction to the outflow of urine (e.g. prostatic disease), a vascular catastrophe or acute cortical necrosis.
  - An increased production of urine is termed polyuria (urine output >3 L/24 h). This may occur as a result of:
    - diuretic agents
    - reduced ADH secretion (cranial diabetes insipidus, alcohol)
    - insensitivity to ADH (nephrogenic diabetes insipidus)
    - psychogenic polydipsia
    - atrial natriuretic peptide (ANP) release (e.g. associated with cardiac arrhythmias, cardiac failure)
    - osmotic diuresis (hyperglycaemia, hypercalciuria)
    - chronic kidney disease (CKD) (inability of the diseased tubular cells to appropriately move Na and hence concentrate urine)
- *Nocturia*: adults do not normally pass urine at night, although there is some variability. Nocturia occurs in CKD, in conditions where an osmotic agent is found in the urine (e.g. glucose in diabetes mellitus (DM), calcium in conditions associated with hypercalciuria) or in prostatic disease.
- *Urinary frequency* can occur in DM, hypercalciuria and urinary tract infections (UTI).
- *Poor urinary stream*: this is a symptom of prostatic disease or sphincter dysfunction.
- *Colour*: urine should be clear to light yellow in colour (depending on concentration). 'Coke-coloured' is seen in nephritic syndrome, where there is glomerular haematuria. 'Tea-coloured' urine is seen in myoglobinuria (usually secondary to rhabdomyolysis). Macroscopic haematuria (where urine is obviously blood-stained) may be due to bleeding in the upper (e.g. IgA nephropathy) or lower urinary tract (e.g. bladder cancer, renal calculi). Frothy urine is observed if there is heavy proteinuria. Other causes of discoloured urine include rifampicin or beetroot ingestion (pink-red) and cholestatic jaundice (bright/strongly coloured yellow). Discolouration of urine on standing may occur in alkaptonuria or porphyria.
- *Dysuria* (pain whilst passing urine): this classically occurs in UTI or in urethritis (e.g. in gonococcal infection).

2. Loin pain: this can occur due to renal calculi (stones), infection, IgA nephropathy, loin pain haematuria, and polycystic kidney disease. Renal colic (due to the passage of a renal calculus through the ureter) is usually agonisingly painful, and patients often require opiates to relieve the pain.

3. Oedema: occurs if there is volume overload (increased hydrostatic pressure) or in nephrotic syndrome where heavy proteinuria leads to reduced oncotic pressure.

4. Symptoms of hypertension, e.g. headache, blurred vision or fitting (if severe).

5. Symptoms of anaemia (secondary to erythropoietin (EPO) deficiency), e.g. tiredness, dyspnoea.

6. Symptoms of uraemia such as nausea/vomiting, chest pain associated with pericarditis or confusion due to uraemic encephalopathy.

7. Symptoms of hyperphosphataemia such as itchiness, lethargy.

Nephrology: Clinical Cases Uncovered. By M. Clatworthy. Published 2010 by Blackwell Publishing.

Symptoms 4–7 occur if there is a decline in renal function such that the kidney cannot perform its basic tasks.

Past medical history (PMH)

Has the patient ever had any renal problems previously? Have they ever had their kidney function assessed? This is useful if trying to delineate between acute and chronic renal failure.

Is there a PMH of diseases which can cause chronic kidney disease?

- Diabetes mellitus (diabetic nephropathy)
- Hypertension (can be a cause of, or occur as a result of renal impairment)
- Vascular disease, including peripheral vascular disease, myocardial infarction, cerebrovascular disease. A past history of such diseases marks out the patient as an arteriopath who may also have renovascular disease
- Prostatic hypertrophy (obstructive uropathy)
- Recurrent UTI (chronic pyelonephritis)
- Recurrent renal calculi (nephrocalcinosis)

Is there a PMH of diseases which can cause acute renal failure?

- Systemic lupus erythematosus (SLE) (50–60% of patients with SLE have renal involvement)
- Vasculitis
- Infections (hepatitis B/C, HIV)
- Myeloma

Is there a PMH of diseases which can cause nephrosis (heavy proteinuria)?

- Diabetes mellitus
- SLE
- Amyloid
- Infections (hepatitis B/C, HIV)
- Myeloma

Systems review

It is important to ascertain whether the patient had any other illness prior to presentation, e.g. pharyngitis (which may be associated with IgA nephropathy or post-streptococcal glomerulonephritis (GN)), vomiting/diarrhoea/blood loss (all of which predispose to volume depletion and pre-renal failure), sepsis (risk factor for pre-renal failure/ATN) or back pain (which can be associated with myeloma).

Many autoimmune diseases are systemic and affect multiple organ systems. Thus, there may be non-specific symptoms such as fever, night sweats, lethargy and malaise. A failure to enquire about or recognise the importance of such relatively non-specific systemic symptoms can lead to a delay in diagnosis of some serious autoimmune diseases, particularly systemic vasculitis. In addition to systemic symptoms, there may also be evidence of inflammation in other systems such as joints (arthralgia), eyes (red eyes due to anterior uveitis, dry eyes due to keratoconjunctivitis sicca), gastrointestinal tract (mouth ulcers, abdominal pain), genitourinary ulcers, skin (photosensitivity rash, discoid lupus, purpuric rash of vasculitis) or symptoms typical of a systemic vasculitis (e.g. sinusitis, ear ache, hearing loss, shortness of breath, haemoptysis). The occurrence of pulmonary haemorrhage in association with acute renal failure secondary to a rapidly progressive glomerulonephritis is known as pulmonary-renal syndrome, and is important to recognise (the causes are described in detail in case 8).

Drug history

- Has the patient started on any new drugs? Such a history may suggest acute tubulointerstitial nephritis (TIN), particularly if associated with a rash. Some drugs are associated with the development of SLE (e.g. hydralazine).
- Is the patient taking any nephrotoxic medications? Angiotensin-converting enzyme inhibitors (ACEI), non-steroidal anti-inflammatory drugs (NSAID), ciclosporin-A (alter renal blood flow); gentamicin, lithium, amphotericin, cisplatin (directly toxic to tubules); NSAID, antibiotics, proton pump inhibitors (PPI) (associated with interstitial nephritis); gold, penicillamine (can cause proteinuria).
- Is the patient taking any drugs which are predominantly excreted by the kidneys, e.g. digoxin or allopurinol? In such cases, the dose of the drug should be reduced if there is a significant renal impairment. The *British National Formulary* (BNF) has a specific section indicating which drugs require a dosage adjustment in patients with renal impairment.

Social history

- Employment history: certain occupations are associated with an increased risk of developing diseases which can present with renal problems. For example, livestock and arable farming is associated with an increased risk of developing anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

• Smoking history: smoking is a risk factor for renovascular disease and is associated with pulmonary haemorrhage in patients with Goodpasture's disease). In contrast, smoking is protective in pre-eclampsia.
• Intravenous drug use (IVDU) is a risk factor for hepatitis B/C/HIV, which are associated with a variety of GN.

Family history

Monogenic disorders which affect the kidneys

• The most common genetic disorder affecting the kidneys is adult (autosomal dominant) polycystic kidney disease (APKD). New mutations occur in only 5% of cases, although many patients will not be aware of a positive family history of disease. Closer questioning or discussion with older relatives may prompt recall of a family member who died of 'kidney trouble' or 'brain haemorrhage'. APKD is caused by mutations in one of two genes, PKD1 (chromosome 16p) and PKD2 (chromosome 4q), encoding polycystin 1 and polycystin 2 respectively. Mutations in PKD1 are more common than PKD2, accounting for 85% of cases of APKD.
• Alport's syndrome presents with a nephritic syndrome and is often associated wth sensorineural deafness. It occurs due to mutations in the genes encoding collagen chains (mainly type IV) and can be inherited in an autosomal recessive or X-linked fashion.
• Some forms of focal segmental glomerular sclerosis (FSGS) are also familial, occurring due to mutations in the genes encoding podocin or nephrin (components of the slit diaphragm of podocytes).

Polygenic disorders which affect the kidneys

Some disorders occur due to the presence of polymorphisms in more than one susceptibility gene. These polymorphisms are often found as relatively common variants in the general population, and it is the inheritance of a specific combination of a number of these susceptibility genes which predisposes to disease. Examples of such polygenic diseases include autoimmune conditions such as diabetes mellitus and SLE. Some genetic polymorphisms confer susceptibility to a number of different autoimmune diseases. Therefore a history of one autoimmune disease (e.g. rheumatoid arthritis) in a family member increases the likelihood of another family member developing a different autoimmune disease (e.g. type I diabetes mellitus).

Examination

General features

• Is the patient sick or stable? It is important to identify this early as some patients with acute renal failure may require high-dependency or intensive treatment unit (ITU) care.
• *Temperature*: a fever may indicate infection or systemic autoimmune disease.
• *Nails, hands, and feet*: examining for the presence of splinter haemorrhages, nailfold infarcts, necrotic areas (signs of vasculitis/endocarditis). Leuconychia (associated with hypoalbuminaemia which may be secondary to liver failure, nephrotic syndrome or chronic inflammatory disease). Small joints of the hands for signs of arthritis (heat, swelling, pain, erythema, the classic signs of inflammation; see Box B) which can occur in some systemic autoimmune diseases that affect the kidney, e.g. SLE, rheumatoid arthritis.
• *Skin rashes*: purpuric lesions (associated with vasculitis), photosensitivity rash (usually on sun-exposed areas such as dorsum of forearms, neck and face – seen in SLE), maculopapular erythematous rash (drug associated), petechial rash (associated with thrombocytopaenia, e.g. as seen in haemolytic uraemic syndrome).
• *Legs*: peripheral oedema (evidenced by swelling of the ankles/legs or by the presence of sacral oedema in bed-bound patients). Peripheral oedema may occur secondary to an increase in hydrostatic pressure (e.g. right heart failure or volume overload) or if there is a reduction in oncotic pressure (e.g. liver failure, nephrosis, malabsorption).
• *Eyes*: conjunctivitis and anterior uveitis both present with red eyes and can occur in autoimmune conditions which are also associated with renal involvement (e.g. rheumatoid arthritis can cause a keratoconjunctivitis and may be associated with amyloidosis). In addition, fundoscopy should be performed in order to assess whether there is retinopathy associated with hypertension or diabetes mellitus. The presence of diabetic retinopathy indicates significant microvascular disease, and such patients will usually also have diabetic nephropathy.

Box B The classic signs associated with inflammation

The first four were described by Celsus in around 30 BC. The fifth was added by Virchov in 1870.

1. Calor – Heat
2. Dolor – Pain
3. Rubor – Redness
4. Tumor – Swelling
5. Functio laesa – loss of /reduced function

• *Mouth*: in a renal transplant patient, there may be gingival hypertrophy if the patient is on long-term ciclosporin. SLE and Behçet's disease are associated with mouth ulceration. Amyloidosis is associated with macroglossia.

Cardiovascular system

• Assess intravascular volume status, as volume depletion is a cause of ARF and fluid overload can occur as a consequence of oligoanuria. Volume status should be assessed by examining skin turgor, dryness of mucous membranes, jugular venous pressure (JVP) (elevated JVP suggests volume overload, low JVP suggests volume depletion) and blood pressure (BP) (if low or postural drop then it is likely that there is hypovolaemia). A high BP can cause CKD or may be associated with CKD of any cause.

• *Heart sounds*: murmurs may be audible in endocarditis (which can be associated with GN due to deposition of circulating immune complexes in the glomeruli). Mitral regurgitation or mitral valve prolapse is associated with APKD. An aseptic endocarditis can occur in SLE (Libmann Sachs endocarditis).

• Severe uraemia can lead to pericarditis and a pericardial rub (sounds like feet crunching in the snow).

Respiratory system

• Pleural effusion (ipsilateral reduced expansion, reduced breath sounds, stony dull percussion note) can occur in nephrotic syndrome and if there is fluid overload secondary to acute or chronic renal failure.

• Pulmonary oedema (increased respiratory rate, reduced oxygen saturations, bibasal crepitations) can occur if there is volume overload. Coarse inspiratory crepitations may also occur if there is pulmonary haemorrhage (seen in Goodpasture's disease and ANCA-associated vasculitis).

• Pulmonary fibrosis (reduced oxygen saturations, reduced expansion, fine end-inspiratory crepitations) can be associated with ANCA-associated vasculitis.

Abdominal system

• Hepatosplenomegaly may occur secondary to cirrhosis with portal hypertension secondary to hepatitis B/C (both associated with GN) or secondary to amyloidosis (can affect the kidney, causing nephrotic syndrome and renal impairment). Splenomegaly may be observed in SLE.

• *Palpable kidneys*: occurs in APKD or renal tumour, or occasionally in amyloidosis.

• Abdominal aortic aneurysm (associated with renovascular disease and retroperitoneal fibrosis).

• Renal bruits +/– femoral bruits: associated with renovascular disease.

• Renal transplant *in situ* (usually a palpable mass in the left or right iliac fossa, with overlying 'hockey-stick' scar) (Figure G). There may also be a scar visible from previous peritoneal dialysis catheter insertion.

Nervous system

• Uraemia can be associated with encephalopathy (i.e. impairment of conciousness +/– confusion).

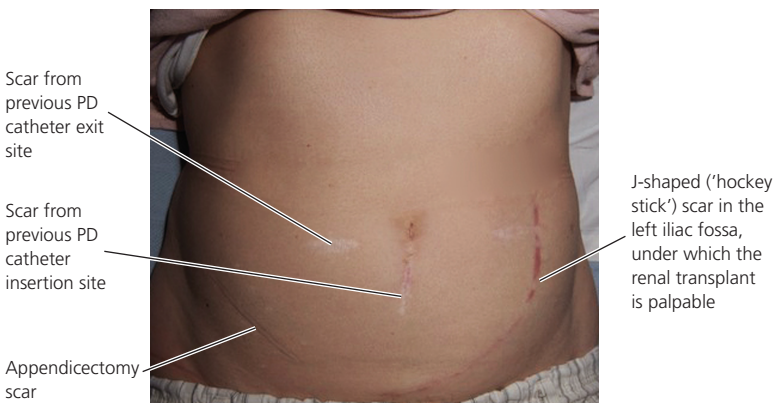


Figure G Abdominal examination in a renal transplant patient. Other signs which should be specifically sought in a renal transplant patient include: blood glucose 'finger-prick' test marks (DM is one of the most common causes of ESRF); skin and gums for signs of long-term immunosuppression (e.g. gingival hypertrophy associated with ciclosporin); evidence of tunnelled line insertion in the neck/upper chest (used for temporary haemodialysis); evidence of arteriovenous fistula formation in the upper limbs; enlarged kidneys or liver (as seen in patients with APKD).

• Deafness (usually conductive) may occur in ANCA-associated vasculitis (particularly Wegener's granulomatosis). Sensorineural deafness is a feature of Alport's syndrome and some rare tubular diorders (where the same pumps are found in the ear as in tubular cells).
• Patients with long-standing diabetes with associated microvascular disease may have signs of neuropathy (peripheral or autonomic) as well as nephropathy.
• Vasculitides (particularly Churg-Strauss syndrome) are associated with peripheral neuropathy or mononeuritis multiplex.
• Some patients with SLE have neuropsychiatric features, including poor memory and depression.
• Systemic amyloidosis is associated with peripheral neuropathy (peripheral nerves may enlarge and become palpable) and/or autonomic neuropathy (evidenced by loss of heart rate variability and an increase in postural drop).