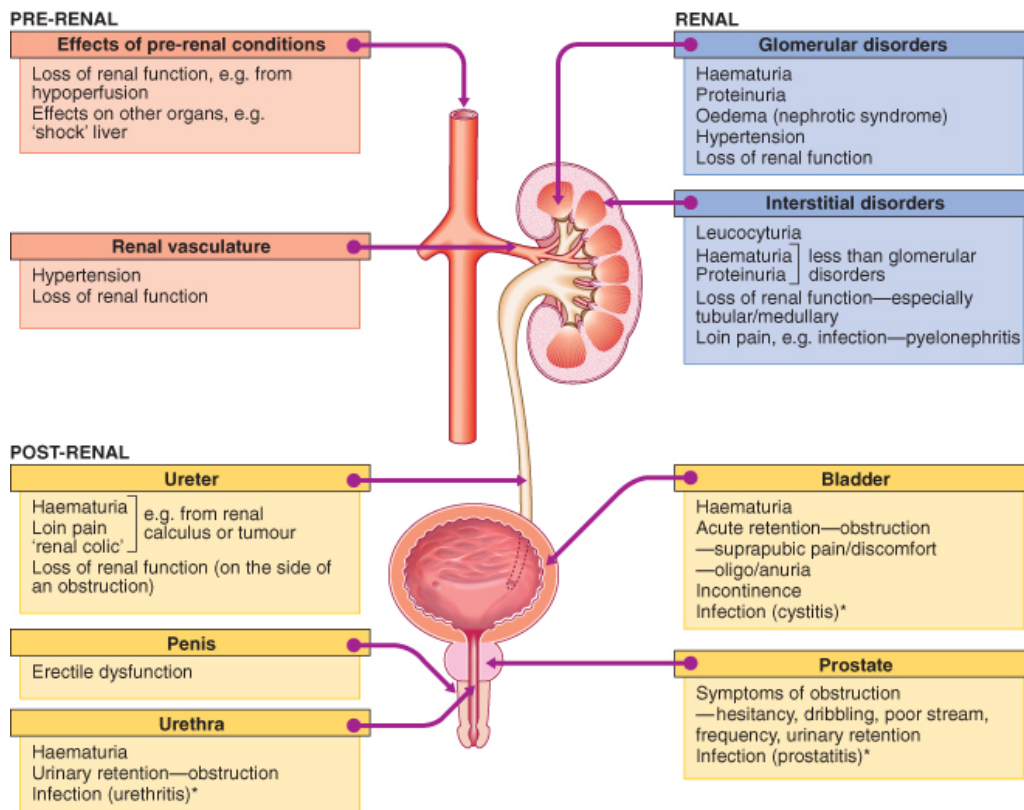


Renal And Urinary Tract Disease

Learning Objectives :

1. to appreciate the range of disorders that can affect the kidney and associated structures;
2. to understand the common clinical presentations of renal disease;
3. to understand the factors which may contribute to the development of renal disease
4. to appreciate the role of transplantation in managing renal disease

The broad categories of renal and urinary tract disease, and their typical manifestations, are illustrated in the following figure :



Symptoms from the lower urinary tract are an extremely common group of presenting complaints. Less commonly, urinary tract disorders lead to obstruction to urinary flow, which may present with pain or with loss of renal function.

The term 'renal failure' is used to denote failure of renal excretion leading to retention of nitrogenous waste products of metabolism including creatinine and urea. Other aspects of renal function may fail at the same time, including the regulation of fluid and electrolyte status and the endocrine functions of the kidney. A wide range of clinical manifestations may therefore occur. The most fundamental categorisation of renal failure is into acute or chronic types, and this is aided by knowledge of previous renal function for comparison.

Non-inflammatory and subacute inflammatory/proliferative glomerular disorders may present with substantial proteinuria resulting in nephrotic syndrome. Inflammatory glomerular disorders more typically cause haematuria in association with early signs of disturbed renal function, such as hypertension. If progressive, obvious signs of impaired excretion of water and solutes develop. The onset of these features in close succession has been described as the nephritic syndrome, but in pure form this condition is rarely seen, except in countries where post-infectious glomerulonephritis is common. Mixed inflammatory and nephrotic features are more common. It is important to recognise such disease, especially if renal impairment is progressing, as the inflammatory group includes some renal disorders which are amenable to treatment.

1. Cystitis And Urinary Tract Infection

Urinary tract infection (UTI) is the most common bacterial infection managed in general medical practice and accounts for 1-3% of consultations. Up to 50% of women have had a UTI at some time. The prevalence of UTI in women is about 3% at the age of 20, increasing by about 1% in each subsequent decade. In males UTI is

uncommon, except in the first year of life and in men over 60, in whom urinary tract obstruction due to prostatic hypertrophy may occur. UTI causes morbidity and, in a small minority of cases, renal damage and chronic renal failure.

When the urinary tract is anatomically and physiologically normal, and local and systemic defence mechanisms are intact, bacteria are confined to the lower end of the urethra. UTI is defined as multiplication of organisms in the urinary tract and is usually associated with the presence of neutrophils.

Organisms causing UTI in the community include:

- *Escherichia coli* derived from the gastrointestinal tract (about 75% of infections)
- *Proteus*
- *Pseudomonas* species
- streptococci
- *staphylococcus epidermidis*

In hospital, *E. coli* still predominates, but *Klebsiella* or streptococci are more common than in the community. Certain strains of *E. coli* have a particular propensity to invade the urinary tract.

The first stage in the development of UTI is colonisation of the peri-urethral zone with pathogenic organisms. Urine is an excellent culture medium for bacteria; in addition, the urothelium of susceptible persons may have more receptors to which virulent strains of *E. coli* become adherent. In women, the ascent of organisms into the bladder is easier than in men because of the relatively short urethra and absence of bactericidal prostatic secretions. Sexual intercourse may cause minor urethral trauma and transfer bacteria from the perineum into the bladder. Instrumentation of the bladder may also introduce organisms. Multiplication of organisms then depends on a number of factors, including the size of the inoculum and virulence of the bacteria.

Some patients, usually female, have symptoms suggestive of urethritis and cystitis but no bacteria are cultured from the urine (the 'urethral syndrome'). Possible explanations include infection with organisms not readily cultured by ordinary methods (e.g. *Chlamydia*, certain anaerobes), intermittent or very low-count bacteriuria, reaction to toilet preparations or disinfectants, symptoms related to sexual intercourse, or post-menopausal atrophic vaginitis. Antibiotics are not indicated.

Typical features of cystitis and urethritis include:

- abrupt onset of frequency of micturition
- scalding pain in the urethra during micturition (dysuria)
- suprapubic pain during and after voiding
- intense desire to pass more urine after micturition, due to spasm of the inflamed bladder wall (urgency)
- urine that may appear cloudy and have an unpleasant odour
- microscopic or visible haematuria.

Systemic symptoms are usually slight or absent. However, infection in the lower urinary tract can spread; prominent systemic symptoms with fever and loin pain suggest the presence of acute pyelonephritis and may be an indication for hospitalisation. Prostatitis is suggested by systemic symptoms and prostatic tenderness. The differential diagnosis includes urethritis due to sexually transmitted disease, or Reiter's syndrome.

Antibiotics are recommended in all cases of proven UTI. If urine culture has been performed, treatment may be started while awaiting the result. Treatment for 3 days is the norm and is less likely to induce antibiotic resistance than more prolonged therapy. Trimethoprim is the usual choice for initial treatment. Between 10% and 40% of organisms causing UTI are resistant to trimethoprim, the lower rates being seen in community-based practice. Nitrofurantoin, quinolone antibiotics such as ciprofloxacin and norfloxacin, and cefalexin are also generally effective. Co-

amoxiclav or amoxicillin should only be used when the organism is known to be sensitive. Penicillins and cephalosporins are safe to use in pregnancy but trimethoprim, sulphonamides, quinolones and tetracyclines should be avoided.

A fluid intake of at least 2 litres/day is usually recommended, although this is not based on evidence and may make matters worse for patients with severe dysuria. Urinary alkalinising agents such as potassium citrate (bought as over-the-counter preparations) may help symptomatically but are not of proven efficacy.

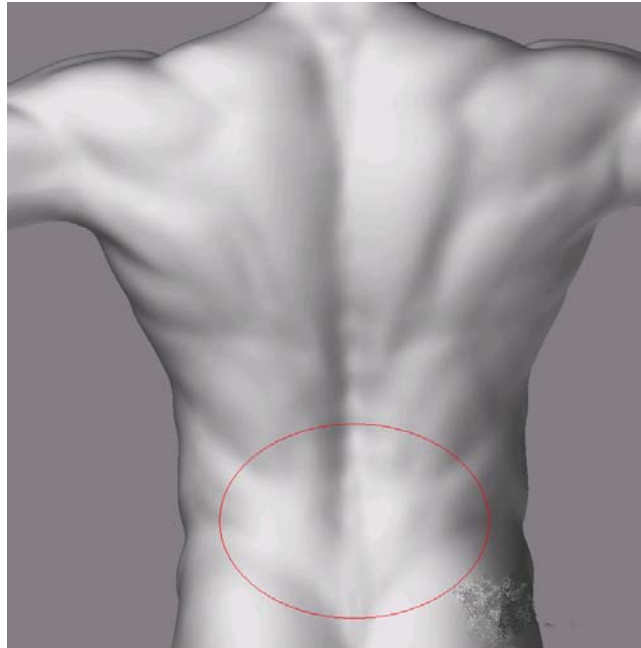
Asymptomatic Bacteriuria

This is defined as $> 10^5$ /ml organisms in the urine of apparently healthy asymptomatic patients. Approximately 1% of children under the age of 1, 1% of schoolgirls, 0.03% of schoolboys and men, 3% of non-pregnant adult women and 5% of pregnant women have asymptomatic bacteriuria. It is increasingly common in those aged over 65. There is no evidence that this condition causes renal scarring in adults who are not pregnant and have a normal urinary tract, and in general, treatment is not indicated. Up to 30% of patients will develop symptomatic infection within 1 year. In infants and pregnant women, treatment is required and investigation is indicated. Where the urinary tract is abnormal, asymptomatic bacteriuria is also more significant and may require intervention.

2. Loin Pain.

Dull ache in the loin is rarely due to renal disease but may be due to renal stone, renal tumour, acute pyelonephritis or obstruction of the renal pelvis. This is most commonly caused by a congenital abnormality of the pelvi-ureteric junction where typically the pain is precipitated by a large fluid intake. More rarely, upper urinary tract obstruction is caused by retroperitoneal fibrosis, a sloughed renal papilla, tumour or blood clot.

The usual site of loin pain is indicated by the red oval on the diagram below :



Acute Pyelonephritis

The kidneys become infected in a minority of patients with lower urinary tract infection or bacteriuria, although the exact proportion is unknown. Acute renal infection (pyelonephritis) presents as a classic triad of loin pain, fever and tenderness over the kidneys. The renal pelvis is inflamed and small abscesses are often evident in the renal parenchyma. Histological examination shows focal infiltration by neutrophils, which can often be seen within the tubules.

Renal infection is almost always caused by organisms ascending from the bladder, and the bacterial profile is the same as for lower urinary tract infection. Rarely, bacteraemia may give rise to renal or perinephric abscesses, most commonly due to staphylococci. One or more complicating factors are often present; pre-existing renal damage, such as cyst formation or scarring, facilitates infection. The renal medulla may be particularly susceptible to infection because of the low oxygen tension, high osmolality and high concentrations of H^+ and ammonia, which impair leucocyte

function. The high osmolality favours conversion of bacteria to antibiotic-resistant L-forms.

There is usually acute onset of pain in one or both loins, which may radiate to the iliac fossae and suprapubic area and is associated with tenderness and guarding in the lumbar region. About 30% of patients have dysuria due to associated cystitis. Fever is usually present and may be associated with rigors, vomiting and hypotension. Examination of urine reveals neutrophils, organisms, red cells and tubular epithelial cells.

Rarely, acute pyelonephritis is associated with papillary necrosis. Fragments of renal papillary tissue are passed per urethra and can be identified histologically. They may cause ureteric obstruction, and if this occurs bilaterally or in a single kidney, may cause acute renal failure. Predisposing factors include diabetes mellitus, chronic urinary obstruction, analgesic nephropathy and sickle-cell disease.

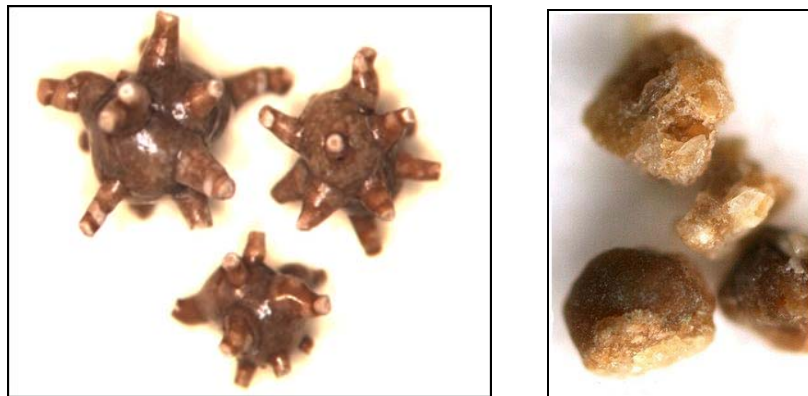
The differential diagnosis of acute pyelonephritis includes acute appendicitis, diverticulitis, cholecystitis and salpingitis. In perinephric abscess, there is marked pain and tenderness and often bulging of the loin on the affected side. Patients are extremely ill, with fever, leucocytosis and positive blood cultures. Urinary symptoms are absent, and urine contains neither pus cells nor organisms.

Antibiotics are continued for 7-14 days. Severe cases require intravenous therapy, with a cephalosporin, quinolone or gentamicin, later switching to an oral agent. In less severe cases, oral antibiotics can be used throughout. Penicillins and cephalosporins are safe in pregnancy; other antibiotics should usually be avoided.

Renal Colic

Acute loin pain radiating to the groin ('renal colic'), together with haematuria, is typical of ureteric obstruction most commonly due to calculi, although a sloughed renal papilla, tumour or blood clot may be responsible.

Urinary calculi consist of aggregates of crystals containing small amounts of proteins and glycoprotein. Different types vary in frequency around the world, probably as a consequence of dietary and environmental factors, but genetic factors may also contribute. In Europe, 80% of renal stones contain crystals of calcium (most commonly as oxalate, but also as phosphate). About 15% contain magnesium ammonium phosphate, and small numbers of pure cystine or uric acid stones are found. Rarely, drugs may form stones (e.g. indinavir, ephedrine).



In developing countries, bladder stones are common, particularly in children. In developed countries, the incidence of childhood bladder stones is low; renal stones in adults are more common. In a North American survey, 12% of men and 5% of women had experienced a renal stone by the age of 70 years. It is surprising that stones and nephrocalcinosis are not more common, since some of the constituents are present in urine in concentrations which exceed their maximum solubility in water. However, urine contains proteins, glycosaminoglycans, pyrophosphate and citrate which help to keep otherwise insoluble salts in solution.

A number of risk factors are known for renal stone formation, however, in developed countries, most calculi occur in healthy young men in whom investigations reveal no clear predisposing cause.

When a stone becomes impacted in the ureter, an attack of renal colic develops. The patient is suddenly aware of pain in the loin, which radiates round the flank to the

groin and often into the testis or labium, in the sensory distribution of the first lumbar nerve. The pain steadily increases in intensity to reach a peak in a few minutes. The patient is restless, and generally tries unsuccessfully to obtain relief by changing position or pacing the room. There is pallor, sweating and often vomiting, and the patient may groan in agony. Frequency, dysuria and haematuria may occur.

The intense pain usually subsides within 2 hours, but may continue unabated for hours or days. It is usually constant during attacks, although slight fluctuations in severity may occur. Contrary to general belief, attacks rarely consist of intermittent severe pains coming and going every few minutes. Subsequent to an attack of renal colic there may be intermittent dull pain in the loin or back.

The immediate treatment of renal pain or renal colic is bed rest and application of warmth to the site of pain. Renal colic is often unbearably painful and demands powerful analgesia, e.g. morphine, pethidine intramuscularly or diclofenac as a suppository. Patients are advised to drink 2 litres per day. Around 90% of stones less than 4 mm in diameter will pass spontaneously, but only 10% of stones of more than 6 mm will pass and these may require active intervention. Immediate action is required if there is anuria or if severe infection occurs in the stagnant urine proximal to the stone (pyonephrosis).

Attempts to develop drugs that dissolve stones have so far been unsuccessful. However, most stones can now be fragmented by extracorporeal shock wave lithotripsy, in which shock waves generated outside the body are focused to the stone, breaking it into small pieces which can pass easily down the ureter. This requires free drainage of the distal urinary tract.

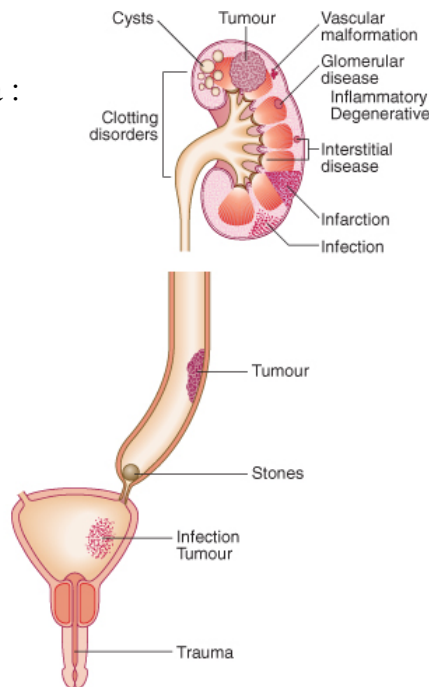
Management to prevent further stone formation should be guided by the results of investigations, but some general principles apply to almost every patient with calcium-containing stones. More specific measures apply to some stone types. Urate stones can be prevented by allopurinol, and this may also reduce calcium stone

formation in patients with a high urate excretion. Stones formed in cystinuria can be reduced by penicillamine therapy. It may be helpful to attempt to alter urine pH with ammonium chloride (low pH discourages phosphate stone formation) or sodium bicarbonate (high pH discourages urate and cystine stone formation).

3. Haematuria

Haematuria may be visible and reported by the patient (macroscopic haematuria), or invisible and detected on dipstick testing of urine (microscopic haematuria). It indicates bleeding from anywhere in the renal tract.

Causes of haematuria :



Microscopy shows that normal individuals have occasional red blood cells in the urine (up to 12,500 rbc/ml). The detection limit for dipstick testing is 15-20,000 rbc/ml, which is sufficiently sensitive to detect all significant bleeding. However, dipstick tests are also positive in the presence of free haemoglobin or myoglobin. Urine microscopy can be valuable in confirming haematuria and in establishing the

cause of bleeding. Other causes of red or dark urine may sometimes be confused with haematuria but produce negative dipstick tests and microscopy. True positive tests may occur during menstruation, infection or strenuous exercise, but persistent haematuria requires further investigation to exclude malignancy.

Macroscopic (visible) haematuria is more likely to be caused by tumours. Severe infections or renal infarction can also cause macroscopic haematuria, usually accompanied by pain. Recurrent episodes of painless gross haematuria in association with respiratory infections are characteristic of IgA nephropathy.

Investigation, whether microscopic or macroscopic, should be directed first at the exclusion of an anatomical bleeding lesion, particularly in older patients or others at risk of carcinoma of the bladder or other malignancy. If haematuria occurs with proteinuria or clinical features of renal disease, inflammatory renal disease should be considered and a renal biopsy may be indicated. Where there are no features of significant renal disease and malignancy has been excluded, patients with isolated microscopic haematuria may be managed by observation alone and biopsy is rarely warranted. Although this scenario occasionally precedes significant renal disease (e.g. Alport's syndrome, IgA nephropathy), it is commonly caused by the usually benign condition of thin basement membrane disease, insignificant vascular malformations, renal cysts or renal stones. In 'loin pain-haematuria' syndrome, benign glomerular bleeding is associated with loin pain. Management of haematuria depends upon the cause.

4. Proteinuria

Moderate amounts of low molecular weight protein do pass through the glomerular basement membrane (GBM). These proteins are normally reabsorbed by tubular cells so that less than 150 mg/day appears in urine. Greater amounts indicate renal damage; any renal disease or injury may cause proteinuria. Proteinuria is usually asymptomatic, although large amounts may make urine froth easily.

Relatively minor leakage of albumin into the urine may occur transiently after vigorous exercise, during fever or UTI and in heart failure. Such proteinuria does not reach nephrotic levels and tests should be repeated once the stimulus is no longer present. Occasionally, proteinuria occurs only during the day, and the first morning sample is negative. In the absence of other signs of renal disease, such 'orthostatic proteinuria' is usually regarded as benign.

Low molecular weight proteins may also appear in the urine in larger quantities than 150 mg/day, indicating failure of reabsorption by damaged tubular cells, i.e. 'tubular proteinuria'. This can be demonstrated by analysis of the size of excreted proteins or by specific assays for such proteins. The amounts of such protein rarely exceed 1.5-2 g/24 hours, and proteinuria greater than this almost always indicates significant glomerular disease.

The amount of protein in urine should be quantified to guide further investigations. Quantification in a 24-hour urine collection is the gold standard, but these collections are arduous and often inaccurate. Use of the protein/creatinine (mg/mmol) ratio in single samples makes allowance for the variable degree of urinary dilution and can allow extrapolation of 24-hour values. Changes in this ratio give valuable information about the progression of renal disease.

In many types of renal disease, the severity of proteinuria is a marker for an increased risk of progressive loss of renal function. There is circumstantial evidence that protein in the glomerular filtrate is toxic to the kidneys, and treatments that are effective at lowering the risk of progression of renal failure (e.g. angiotensin-converting enzyme (ACE) inhibitors in diabetic nephropathy) also reduce proteinuria.

Microalbuminuria

Microalbuminuria describes the urinary excretion of small amounts of normal albumin protein. The presence of albumin in the urine is a clear sign of glomerular abnormality and can identify the very early stages of progressive glomerular disease, e.g. in diabetic nephropathy. Because significant renal damage will have occurred before dipstick tests become positive, patients with diabetes mellitus should be screened regularly for microalbuminuria. Persistent microalbuminuria has also been associated with an increased risk of atherosclerosis and cardiovascular mortality; neither the mechanism of proteinuria nor an explanation of these associations has yet been found.

Nephrotic Syndrome

Nephrotic syndrome refers to the secondary phenomena that occur when substantial amounts of protein are lost in the urine. Dependent oedema accumulates predominantly in the lower limbs in adults, extending to the genitalia and lower abdomen as it becomes more severe. In the morning, the upper limbs and face may be more affected. In children, ascites occurs early and oedema is often seen only in the face. Blood volume may be normal, reduced or increased. Avid renal sodium retention is an early and universal feature.

The diseases that cause nephrotic syndrome always affect the glomerulus and tend to be non-inflammatory, or subacute examples of inflammatory glomerulonephritis. Diabetes mellitus and amyloidosis can also cause nephrotic syndrome. In children, because minimal change glomerulonephritis is the most common diagnosis, initial management includes administration of high-dose corticosteroids. In older patients, and in children where this therapy is unsuccessful, a renal biopsy is required unless there is strong evidence for a specific aetiology (e.g. a long history of diabetes with other microvascular complications and a demonstrated progression from microalbuminuria, and with hypertension but no haematuria).

KEY LEARNING POINTS.

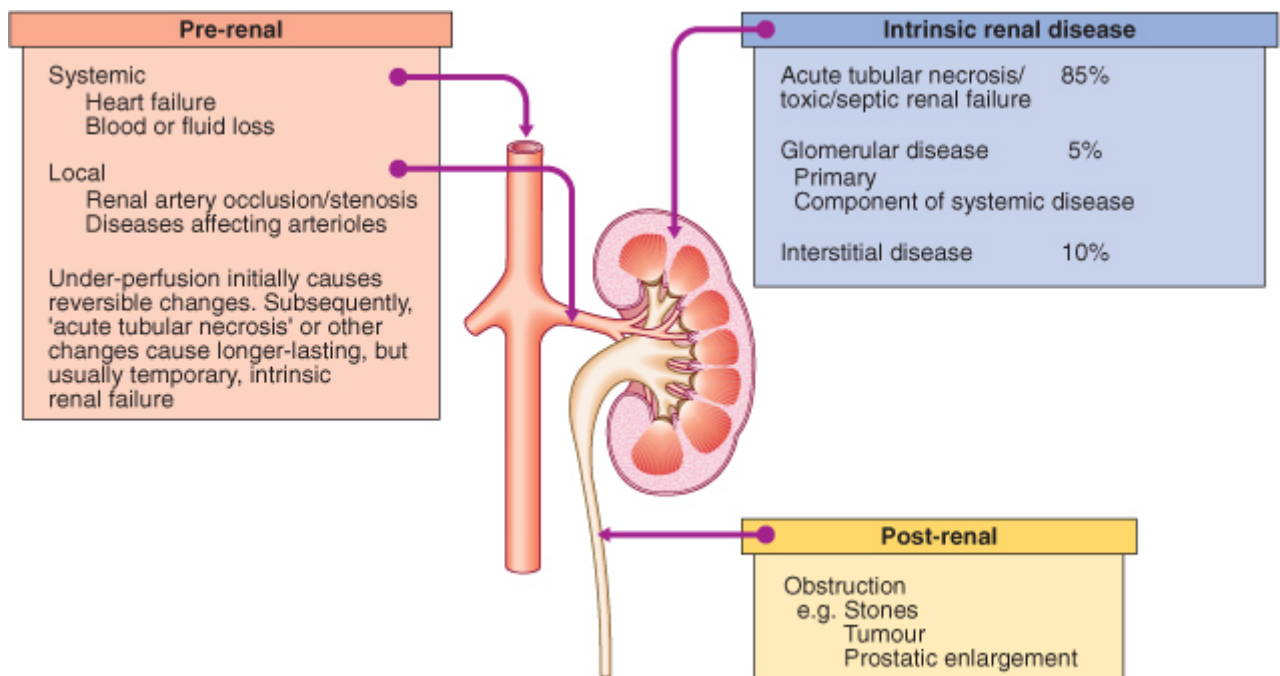


- 1. The term 'renal failure' denotes failure of renal excretion, leading to retention of nitrogenous waste products of metabolism, including creatinine and urea.**
- 2. Renal failure can be either acute or chronic.**
- 3. UTI's are the most common bacterial infection managed in general practice.**
- 4. Loin pain tends to be indicative of the presence of kidneys stones, or other kidney pathology.**
- 5. Acute pyelonephritis presents as a classic triad of loin pain, fever, and tenderness over the kidneys.**
- 6. Acute loin pain which radiates to the groin is known as renal colic.**
- 7. Renal colic is most commonly caused by renal calculi (stones).**
- 8. Haematuria is the presence of blood in urine.**
- 9. Proteinuria is the presence of protein in urine, and is indicative of loss of renal function.**
- 10. Nephrotic syndrome occurs when substantial amounts of protein are lost in the urine, resulting in odema in the lower limbs, and ascites. There is a link with the presence of long-standing diabetes mellitus.**

5. Acute Renal Failure

Acute renal failure (ARF) refers to a sudden and usually reversible loss of renal function, which develops over a period of days or weeks and is usually accompanied by a reduction in urine volume. There are many possible causes (Fig. 17.18) and it is frequently multifactorial. The clinical picture is often dominated by the underlying condition (e.g. septic shock, trauma). If the cause cannot be rapidly corrected and renal function restored, temporary renal replacement therapy may be required.

Causes of acute renal failure :



Reversible Pre-Renal Acute Renal Failure

Because haemodynamic disturbances can initially produce acute renal dysfunction that has the potential to be rapidly reversed, prompt recognition and treatment are important. This is considered separately from established acute renal failure.

The kidney can regulate its own blood flow and GFR over a wide range of perfusion pressures. When the perfusion pressure falls, as in hypovolaemia, shock, heart failure or narrowing of the renal arteries, the resistance vessels in the kidney dilate to facilitate flow. Vasodilator prostaglandins are important, and this mechanism is

markedly impaired by NSAIDs. If autoregulation of blood flow fails, the GFR can still be maintained by selective constriction of the post-glomerular (efferent) arteriole. This is mediated through the release of renin and generation of angiotensin II, which preferentially constricts this vessel. ACE inhibitors interfere with this response.

More severe or prolonged under-perfusion of the kidneys may lead to failure of these compensatory mechanisms and hence an acute decline in GFR. The renal tubules are intact and become hyperfunctional; that is, tubular reabsorption of sodium and water is increased, partly through physical factors associated with changes in blood and urine flow and partly through the influence of angiotensins, aldosterone and vasopressin. This leads to the formation of a low volume of urine which is concentrated but low in sodium. These urinary changes may be absent in patients with impaired tubular function, e.g. pre-existing renal impairment, or those who have received loop diuretics.

There may be marked hypotension and signs of poor peripheral perfusion, such as delayed capillary return. However, pre-renal ARF may occur without systemic hypotension, particularly in patients taking NSAIDs or ACE inhibitors. Postural hypotension (a fall in blood pressure $> 20/10$ mmHg from lying to standing) is a valuable sign of early hypovolaemia.

The cause of the reduced renal perfusion may be obvious, but concealed blood loss can occur into the gastrointestinal tract, following trauma (particularly where there are fractures of the pelvis or femur) and into the pregnant uterus. Large volumes of intravascular fluid are lost into tissues after crush injuries or burns, or in severe inflammatory skin diseases or sepsis. Metabolic acidosis and hyperkalaemia are often present.

In sepsis most patients, once volume-resuscitated, have a vasodilated systemic circulation; this leads to a relative under-filling of the arterial tree and the kidney responds as it would to absolute hypovolaemia. When it is severe or prolonged,

sepsis is an important cause of established ARF with acute tubular necrosis. The combination of sepsis and NSAIDs is a potent cause of ARF.

If treatment is given sufficiently early, renal function will usually improve rapidly; in such circumstances residual renal impairment is unlikely. In some cases, however, treatment is ineffective and renal failure becomes established.

Established Acute Renal Failure

Established ARF may develop following severe or prolonged under-perfusion of the kidney (pre-renal ARF). In such cases, the histological pattern of acute tubular necrosis is usually seen.

Acute tubular necrosis (ATN)

Acute necrosis of renal tubular cells may result from ischaemia or nephrotoxicity, caused by chemical or bacterial toxins, or a combination of these factors. Ischaemic tubular necrosis usually follows a period of shock, during which renal blood flow is greatly reduced. Even when systemic haemodynamics are restored, renal blood flow can remain as low as 20% of normal, due to swelling of the endothelial cells of the glomeruli and peritubular capillaries, and oedema of the interstitium. Blood flow is further reduced by vasoconstrictors such as thromboxane, vasopressin, noradrenaline and angiotensin II, partly counterbalanced by the release of intra-renal vasodilator prostaglandins. Thus, in ischaemic ATN there is reduced oxygen delivery to the tubular cells. These cells are vulnerable to ischaemia because they have high oxygen consumption in order to generate energy for solute reabsorption, particularly in the thick ascending limb of the loop of Henle.

The ischaemic insult ultimately causes death of tubular cells, which may shed into the tubular lumen causing tubular obstruction. Focal breaks in the tubular basement membrane develop, allowing tubular contents to leak into the interstitial tissue and cause interstitial oedema.

In nephrotoxic ATN a similar sequence occurs, but it is initiated by direct toxicity of the causative agent to tubular cells. Examples include the aminoglycoside antibiotics, such as gentamicin, the cytotoxic agent cisplatin, and the antifungal drug amphotericin B.

Fortunately, tubular cells can regenerate and re-form the basement membrane. If the patient is supported during the regeneration phase, kidney function usually returns. During recovery there is often a diuretic phase in which urine output increases rapidly and remains excessive for several days before returning to normal. This is due in part to loss of the medullary concentration gradient (counter current system), which normally allows concentration of the urine in the collecting duct, and which depends on continued delivery of filtrate to the ascending limb of the loop of Henle and active tubular transport. The medullary concentration gradient is gradually 'washed out' in ATN, and is not re-established until glomerular filtration and tubular function are restored. Not all patients have a diuretic phase, depending on the severity of the renal damage and the rate of recovery.

Features of established ARF

These reflect the causal condition, such as trauma, septicaemia or systemic disease, together with features of renal failure. The rate of rise in plasma urea and creatinine is determined by the rate of protein catabolism (tissue breakdown). In ARF associated with catabolic states, such as severe infections, major surgery or trauma, the daily rise in plasma urea often exceeds 5 mmol/l. At first the patient may feel well but, unless dialysis begins, the clinical features described below eventually appear.

Alterations in urine volume - Patients are usually oliguric (urine volume < 500 ml daily). Anuria (complete absence of urine) is rare and usually indicates acute urinary tract obstruction or vascular occlusion. In about 20% of cases, the urine volume is normal or increased, but with a low GFR and a reduction of tubular reabsorption

(non-oliguric ARF). Excretion is inadequate despite good urine output, and the plasma urea and creatinine increase.

Disturbances of water, electrolyte and acid-base balance - Hyperkalaemia is common, particularly with massive tissue breakdown, haemolysis or metabolic acidosis.. Dilutional hyponatraemia occurs if the patient has continued to drink freely despite oliguria or has received inappropriate amounts of intravenous dextrose. Metabolic acidosis develops unless prevented by loss of hydrogen ions through vomiting or aspiration of gastric contents. Hypocalcaemia, due to reduced renal production of 1,25-dihydroxycholecalciferol, is common.

Other features -

- 'Uraemic' features include initial anorexia, nausea and vomiting followed by drowsiness, apathy, confusion, muscle-twitching, hiccoughs, fits and coma.
- Respiratory rate may be increased due to acidosis, pulmonary oedema or respiratory infection. Pulmonary oedema may result from the administration of excessive amounts of fluids relative to urine output and because of increased pulmonary capillary permeability.
- Anaemia is common, due to excessive blood loss, haemolysis or decreased erythropoiesis. Bleeding is more likely because of disordered platelet function and disturbances of the coagulation cascade. Spontaneous gastrointestinal haemorrhage may occur, often late in the illness, although this is less common with effective dialysis and the use of agents that reduce gastric acid production.
- Severe infections may complicate ARF because humoral and cellular immune mechanisms are depressed.

Hyperkalaemia (a plasma K^+ concentration > 6 mmol/l) must be treated immediately, to prevent the development of life-threatening cardiac arrhythmias. This is often managed with the administration of glucose and insulin. Circulating blood volume should be optimised to ensure adequate renal perfusion.

Hypovolaemia must be treated as for reversible pre-renal ARF, with monitoring of central venous or pulmonary wedge pressure as required. Patients with pulmonary oedema usually require dialysis to remove sodium and water. Severe acidosis can be ameliorated with isotonic sodium bicarbonate (e.g. 500 ml of 1.26%) if volume status allows. In an anuric or volume-overloaded patient, renal replacement therapy may be required.

Addressing the underlying cause of the ARF

This may be obvious or revealed by simple initial investigations (e.g. ultrasound showing urinary tract obstruction). If not, a range of investigations, including renal biopsy, may be necessary. In many cases, more than one factor contributes to the renal dysfunction.

There is no specific treatment for ATN, other than restoring renal perfusion. Intrinsic renal disease may require specific therapy; for example, immunosuppressive drugs are of value in some causes of rapidly progressive glomerulonephritis, and plasma infusion and plasma exchange may be indicated in microangiopathic diseases.

'Post-renal' obstruction should be relieved urgently. If pelvic or ureteric dilatation is found and not explained by bladder outlet obstruction, percutaneous nephrostomy is undertaken to decompress the urinary system. With rapid intervention, dialysis can usually be avoided. Injection of dye through the nephrostomy tube (antegrade pyelography) reveals the site of the obstruction. Once obstruction has been relieved and blood chemistry is returning to normal, the underlying cause is treated whenever possible. Sometimes obstruction is caused by pelvic malignancies, such as carcinoma of the cervix, uterus or colon, which are so advanced that intervention is inadvisable.

Fluid and electrolyte balance - After initial resuscitation, daily fluid intake should equal urine output, plus an additional 500 ml to cover insensible losses; such losses are higher in febrile patients and in tropical climates. If abnormal losses occur, as in diarrhoea, additional fluid and electrolyte replacement is required. Measurement of

fluid intake and urine output is subject to error so the patient should be weighed daily. Large changes in body weight, the development of oedema or signs of fluid depletion indicate that fluid intake should be reassessed. Since sodium and potassium are retained, intake of these substances should be restricted.

Protein and energy intake - In patients in whom dialysis is likely to be avoided, accumulation of urea is slowed by dietary protein restriction (to about 40 g/day) and by suppression of protein catabolism by giving as much energy as possible in the form of fat and carbohydrate. Patients treated by dialysis may have more dietary protein (70 g protein daily, 10-12 g nitrogen). It is important to give adequate energy and nitrogen to hypercatabolic patients (e.g. sepsis, burns). In some patients, feeding via a nasogastric tube may be helpful. Parenteral nutrition may be required, especially in critically ill patients, because of vomiting or diarrhoea, or if the bowel is not intact.

Infection control - Patients with ARF are at risk of inter-current infection. Regular clinical examination and microbiological investigation, as clinically indicated, are required to diagnose and treat this complication promptly.

Drugs - Vasoactive drugs such as NSAIDs and ACE inhibitors may prolong ARF and temporary withdrawal should be considered. Many drugs are excreted renally and dose adjustment may be required in ARF to avoid accumulation.

Renal replacement therapy may be required as supportive management in ARF.

Recovery from ARF

This is usually indicated by a gradual return of urine output, and subsequently a steady improvement in plasma biochemistry. Some patients, primarily those with ATN or after relief of chronic urinary obstruction, develop a 'diuretic phase'. Fluid should be given to replace the urine output as appropriate. Supplements of sodium chloride, sodium bicarbonate and potassium chloride, and sometimes calcium,

phosphate and magnesium, may be needed to compensate for increased urinary losses. After a few days urine volume falls to normal as the concentrating mechanism and tubular reabsorption are restored.

In uncomplicated ARF, such as that due to simple haemorrhage or drugs, mortality is low even when renal replacement therapy is required. In ARF associated with serious infection and multiple organ failure, mortality is 50-70%. Outcome is usually determined by the severity of the underlying disorder and other complications, rather than by renal failure itself.

Acute Renal Failure In Old Age

- **Physiological change:** nephrons decline in number from the age of 30; creatinine clearance declines at a rate of about 10 ml/min per decade after the age of 50 years.
- **Creatinine:** as muscle mass falls with age, less creatinine is produced each day. Serum creatinine can be a misleading guide to renal function in poorly nourished older people.
- **Renal tubular function:** declines with age, leading to loss of urinary concentration, acidification and toxin excretion.
- **Drugs:** increased drug prescription in older people (e.g. diuretics, ACE inhibitors and NSAIDs) may contribute to loss of renal function.
- **Acute renal failure:** due to reduction in function, older people are susceptible to acute renal failure. Infection, renal vascular disease, prostatic obstruction, hypovolaemia and severe cardiac dysfunction are common causes.
- **Mortality from acute renal failure:** rises with age, primarily because of comorbid conditions.

6. Chronic Renal Failure

Chronic renal failure (CRF) refers to an irreversible deterioration in renal function which classically develops over a period of years. Initially, it is manifest only as a biochemical abnormality. Eventually, loss of the excretory, metabolic and endocrine functions of the kidney leads to the development of the clinical symptoms and signs of renal failure, which are referred to as uraemia. When death is likely without renal replacement therapy, it is called end-stage renal failure (ESRF). The social and economic consequences of CRF are considerable. In the UK, over 37 000 patients (632 per million) are kept alive by renal replacement therapy and approaching 110 new patients per million of the adult population are accepted for long-term dialysis treatment each year. Of these, 50% are aged over 65. The incidence of CRF is much higher in some countries due to differences in regional and racial incidences of disease, as well as differences in medical practice. For example, in the USA, incident rates are over 300 per million population, with nearly half of these patients having a primary diagnosis of diabetes mellitus.

CRF may be caused by any condition which destroys the normal structure and function of the kidney. A precise diagnosis is not always established. Disturbances in water, electrolyte and acid-base balance contribute to the clinical picture in patients with CRF, but the exact pathogenesis of the clinical syndrome of uraemia is unknown. Many substances present in abnormal concentration in the plasma have been suspected as being 'uraemic toxins', and uraemia is probably caused by the accumulation of various intermediary products of metabolism.

Renal failure may present as a raised blood urea and creatinine found during routine examination, often accompanied by hypertension, proteinuria or anaemia. When renal function deteriorates slowly, patients may remain asymptomatic until GFR falls below 30 ml/minute. Nocturia, due to the loss of concentrating ability and increased osmotic load per nephron, is often an early symptom. Thereafter, due to the widespread effects of renal failure, symptoms and signs may develop that are

related to almost every body system. Patients may present with complaints which are not obviously renal in origin, such as tiredness or breathlessness.

In ESRF patients appear ill and anaemic. They do not necessarily retain fluid, and may show signs of sodium and water depletion. There may be unusually deep respiration related to metabolic acidosis (Kussmaul's respiration), anorexia and nausea. Later, hiccoughs, pruritus, vomiting, muscular twitching, fits, drowsiness and coma follow.

Retarding the progression of CRF

Once the plasma creatinine exceeds about 300 $\mu\text{mol/l}$, there is usually progressive deterioration in renal function, irrespective of aetiology. The rate of deterioration is very variable between patients but is relatively constant for an individual patient.

Control of blood pressure - In many types of renal disease, but particularly in diseases affecting glomeruli, control of blood pressure may retard deterioration of GFR. This has been proven for diabetic nephropathy, but is probably true for other diseases as well, particularly those associated with heavy proteinuria. No threshold for this effect has been found; reduction of any level of blood pressure is beneficial. Various target blood pressures have been suggested: for example, 130/85 mmHg for CRF alone, lowered to 125/75 mmHg for those with proteinuria $> 1 \text{ g/day}$. Achieving these targets often requires multiple drugs and may be limited by toxicity or non-compliance. The very high incidence of left ventricular hypertrophy, heart failure and occlusive vascular disease in patients with long-standing renal disease also justifies vigorous efforts to control blood pressure.

ACE inhibitors have been shown to be more effective at retarding the progression of renal failure than other therapies which lower systemic blood pressure to a similar degree. This may be because they reduce glomerular perfusion pressure by dilating the efferent arteriole, although this causes an immediate reduction in GFR when therapy is initiated. Reduction in proteinuria is a good prognostic sign, but it is not

clear whether this is causally related to prognosis. ACE inhibitors should be used in all patients with incipient or overt diabetic nephropathy or proteinuria > 1 g/day independent of the presence of hypertension. Angiotensin II receptor antagonists also reduce glomerular perfusion pressure, and the same effect may be achieved by certain non-dihydropyridine calcium antagonists.

Diet - In animals, progressive renal disease can be retarded by various manipulations of diet, most notably by restricting dietary protein. In humans results are less clear-cut; low-protein diets are difficult to adhere to and carry a risk of inducing malnutrition. This remains a controversial area but, for most patients living in areas where renal replacement therapy is available, severe protein restriction is not recommended. Moderate restriction (to 60 g protein per day) should be accompanied by an adequate intake of calories to prevent malnutrition. Anorexia and muscle loss may indicate a need to commence dialysis treatment.

Limiting the adverse effects of CRF

Anaemia - Anaemia is common; it usually correlates with the severity of renal failure and contributes to many of the non-specific symptoms of CRF. Several mechanisms are implicated, including:

- relative deficiency of erythropoietin
- diminished erythropoiesis due to toxic effects of uraemia on marrow precursor cells
- reduced red cell survival
- increased blood loss due to capillary fragility and poor platelet function
- reduced dietary intake and absorption of iron and other haematinics.

Plasma erythropoietin is usually within the normal range and thus inappropriately low for the degree of anaemia. In patients with polycystic kidneys, anaemia is often less severe or absent, while in some interstitial disorders it appears disproportionately

severe for the degree of renal failure. This is probably because of the effects of these disorders on the interstitial fibroblasts that secrete erythropoietin.

Recombinant human erythropoietin is effective in correcting the anaemia of CRF. The target haemoglobin is usually between 100 and 120 g/l. Complications of treatment include increased blood pressure, and adjustment of antihypertensive medication is often necessary. There is also an increase in blood coagulability and an increased incidence of thrombosis of the arteriovenous fistulae used for haemodialysis. If anaemia is corrected slowly, these effects are less common. Erythropoietin is less effective in the presence of iron deficiency, active inflammation or malignancy, or in patients with aluminium overload which may occur in dialysis. These factors should be sought and, if possible, corrected before treatment. Iron supplementation should be used to keep ferritin > 100 µg/l and transferrin saturation > 20%.

Fluid and electrolyte balance - Due to the reduced ability of the failing kidney to concentrate the urine, a relatively high urine volume is needed to excrete products of metabolism and a fluid intake of around 3 litres/day is desirable. Some patients with so-called 'salt-wasting' disease may require a high sodium and water intake, including supplements of sodium salts, to prevent fluid depletion and worsening of renal function. This is most often seen in patients with renal cystic disease, obstructive uropathy, reflux nephropathy or other tubulo-interstitial diseases, and is not seen in patients with glomerular disease. These patients benefit from taking 5-10 g/day of sodium chloride by mouth. It is usual to start with 2-3 g/day and increase the dose as required. The limit for additional salt is set by the development of peripheral or pulmonary oedema, or aggravation of hypertension. Sodium bicarbonate may be substituted in part for sodium chloride when acidosis requires correction.

Limitation of potassium and sodium intake may be required in late CRF if there is evidence of accumulation. Disproportionate fluid retention in milder renal failure, sometimes leading to episodic pulmonary oedema, is particularly associated with renal artery stenosis.

Acidosis - Declining renal function is associated with metabolic acidosis, which is often asymptomatic. Sustained acidosis results in protons being buffered in bone in place of calcium, thus aggravating metabolic bone disease. Acidosis may also contribute to reduced renal function and increased tissue catabolism.

The plasma bicarbonate should be maintained by giving sodium bicarbonate supplements. The increased sodium intake may induce hypertension or oedema; calcium carbonate is an alternative that is also used to bind dietary phosphate.

Cardiovascular disease and lipids - CRF is an independent risk factor for occlusive cardiovascular disease. Atherosclerosis is common and may be accelerated by hypertension. Vascular calcification may develop and be sufficiently severe to cause limb ischaemia. Pericarditis is common in untreated or inadequately treated ESRF. It may lead to pericardial tamponade and, later, constrictive pericarditis.

Hypertension develops in approximately 80% of patients with CRF. In part, this is caused by sodium retention. Chronically diseased kidneys also tend to hypersecrete renin, leading to high circulating concentrations of renin, angiotensin II and aldosterone. This is exaggerated if there is renal under-perfusion related to renal vascular disease. Hypertension must be controlled, as it causes further vascular and glomerular damage and worsening of renal failure.

Hypercholesterolaemia is almost universal in patients with significant proteinuria, and increased triglyceride levels are also common in patients with CRF. It has been suggested that as well as influencing the development of vascular disease, this may accelerate the progression of chronic renal disease. HMG-CoA reductase inhibitors achieve substantial reductions in lipids in chronic renal disease, and long-term studies are under way in this group of patients. However, many believe that the high incidence of vascular disease in CRF justifies the treatment of these abnormalities in advance of proof from controlled trials.

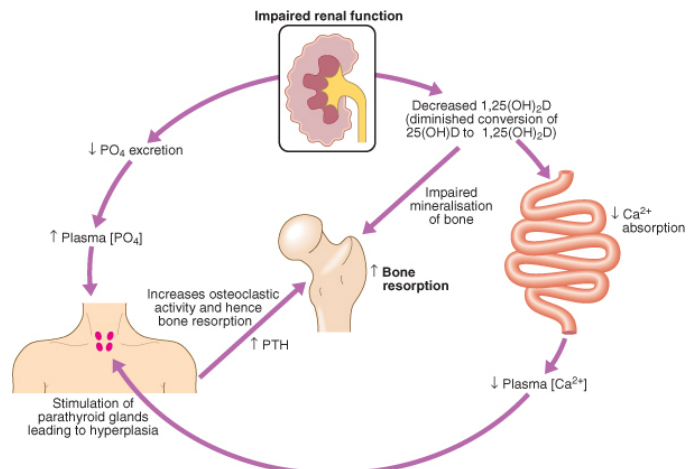
Infection - Cellular and humoral immunity are impaired, with increased susceptibility to infection. Infections are the second most common cause of death in

dialysis patients, after cardiovascular disease; they must be recognised and treated promptly.

Bleeding - There is an increased bleeding tendency in renal failure which manifests in patients with advanced disease as cutaneous ecchymoses and mucosal bleeds. Platelet function is impaired and bleeding time prolonged. Adequate dialysis treatment partially corrects the bleeding tendency.

Renal osteodystrophy - This metabolic bone disease which accompanies CRF consists of a mixture of osteomalacia, hyperparathyroid bone disease (osteitis fibrosa), osteoporosis and osteosclerosis. Osteomalacia results from diminished activity of the renal 1α -hydroxylase enzyme, with failure to convert cholecalciferol to its active metabolite, 1,25-dihydroxycholecalciferol. A deficiency of the latter leads to diminished intestinal absorption of calcium, hypocalcaemia and reduction in the calcification of osteoid in bone.

The parathyroid glands are stimulated by the low plasma calcium, and also by hyperphosphataemia, consequent upon reduced urinary phosphate excretion in CRF. Osteitis fibrosa results from this secondary hyperparathyroidism in the presence of hyperphosphataemia. In some patients tertiary or autonomous hyperparathyroidism with hypercalcaemia develops. Osteosclerosis is seen mainly in the sacral area, at the base of the skull and in the vertebrae; the cause of this unusual reaction is not known.



To minimise the effects of CRF on bone, plasma calcium and phosphate should be kept as near to normal as possible. Hypocalcaemia is corrected by giving 1α -hydroxylated synthetic analogues of vitamin D. The dose is adjusted to avoid hypercalcaemia. This will usually prevent or control osteomalacia, although it is sometimes resistant, presumably because of other factors inhibiting bone mineralisation. Calcitriol also binds to a receptor in the parathyroid glands, resulting in decreased PTH (parathyroid hormone) gene transcription. New calcimimetic agents also reduce PTH via a direct action on the parathyroid glands.

Hyperphosphataemia is controlled by dietary restriction of foods with high phosphate content (milk, cheese, eggs) and the use of phosphate-binding drugs administered with food. These agents form insoluble complexes with dietary phosphate and prevent its absorption (e.g. calcium carbonate and aluminium hydroxide). Newer polymer-based phosphate binders that are not associated with the problem of unwanted anion (Ca or Al) absorption are becoming available. Secondary hyperparathyroidism is usually prevented or controlled by these measures but, in severe bone disease with autonomous parathyroid function, parathyroidectomy may become necessary.

Myopathy - Generalised myopathy is due to a combination of poor nutrition, hyperparathyroidism, vitamin D deficiency and disorders of electrolyte metabolism. Muscle cramps are common, and quinine sulphate may be helpful. The 'restless leg syndrome', in which the patient's legs are jumpy during the night, may be troublesome and is often improved by clonazepam.

Other adverse effects - Neuropathy results from demyelination of medullated fibres, with the longer fibres being involved at an earlier stage. Sensory neuropathy may cause paraesthesiae. Amitriptyline and gabapentin may provide some symptom relief. Motor neuropathy may present as foot drop. Uraemic autonomic neuropathy may cause delayed gastric emptying, diarrhoea and postural hypotension. Clinical manifestations of neuropathy appear late in the course of CRF but may improve or even resolve once dialysis is established.

In addition to hyperparathyroidism, a number of hormonal abnormalities may be present. In both sexes there is loss of libido and sexual function, related at least in part to hyperprolactinaemia. The half-life of insulin is prolonged in CRF due to reduced tubular metabolism of insulin; insulin requirements may therefore decline in diabetic patients in end-stage CRF. However, there is also a post-receptor defect in insulin action, leading to relative insulin resistance. This latter abnormality is improved by dialysis treatment.

Gastrointestinal manifestations are common at low GFRs, including anorexia followed by nausea, and vomiting is commonly seen. There is a higher incidence of peptic ulcer disease in uraemic patients and H₂-receptor antagonists or proton pump inhibitors are commonly used.

Depression is common in patients on or approaching renal replacement therapy and support should be provided for both them and their relatives.

KEY LEARNING POINTS.



- 1. Acute renal failure refers to sudden, usually reversible loss of renal function, whereas chronic failure is irreversible loss of function.**
- 2. ARF is frequently associated with prolonged under-perfusion of the kidneys.**
- 3. Hyperkalaemia, hyponatraemia, and metabolic acidosis are features of ARF.**
- 4. Chronic renal failure can be caused by any condition which affects kidney function, and can eventually result in end stage renal failure (ESRF).**
- 5. Anaemia is a common complication of CRF, as are disturbances in electrolyte and fluid balance.**
- 6. Renal osteodystrophy results in the absorption of calcium from bone.**

7. Renal Replacement Therapy

The facility to replace some functions of the kidney artificially by dialysis has been available since the 1960s. Such treatment is now routine in patients with acute or chronic renal failure. It does not replace the endocrine and metabolic functions of the kidney, but aims to maintain the plasma biochemistry (uraemic toxins, electrolytes and acid-base status) at acceptable levels. Dialysis can also remove fluid from the circulation (ultrafiltration) to maintain euvolaemia. The major side-effects of dialysis relate to haemodynamic disturbance caused by fluid removal or the extracorporeal circulation of blood, and reactions between blood and components of the dialysis system (bioincompatibility).

The original renal replacement therapy (RRT) was haemodialysis, and this is still the most common form of treatment. A variety of other types have been developed, particularly for unstable patients with ARF.

Renal Replacement In Acute Renal Failure

The decision to institute RRT is made on an individual basis, taking account of other aspects of the patient's care. Guideline indications are as follows:

- *Increased plasma urea and creatinine.* Plasma urea > 30 mmol/l and creatinine > 600 μ mol/l are undesirable. At lower levels, if there is progressive biochemical deterioration and particularly if there is little or no urine output, it may be appropriate to commence dialysis. There is a trend towards earlier institution of dialysis in ARF, although trials of very early dialysis in post-operative or septic patients with oliguria have not shown consistent benefit compared with the more conventional strategy above.
- *Hyperkalaemia.* A plasma potassium > 6 mmol/l is hazardous. Elevated plasma potassium can usually be reduced by medical measures in the short term, but dialysis is often required for definitive control.

- *Metabolic acidosis*. This will often occur together with hyperkalaemia and raise the plasma potassium further.
- *Fluid overload and pulmonary oedema*. In patients with continued urine output, this may be controlled by careful fluid balance and use of diuretics, but in oligo/anuric patients may be an indication for RRT.
- *Uraemic pericarditis/uraemic encephalopathy*. These are features of severe untreated renal failure; they are uncommon in ARF but are strong indications for RRT

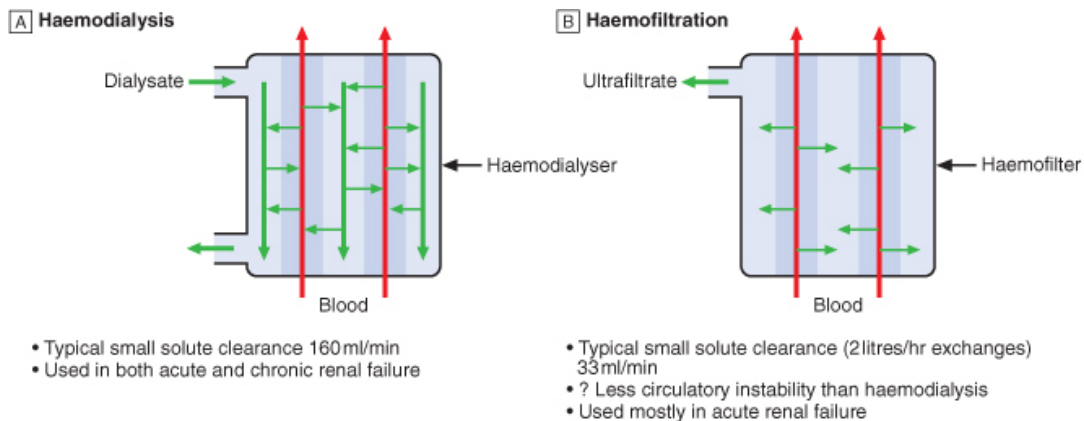
The principal options for RRT in ARF are haemodialysis, high-volume haemofiltration, continuous arteriovenous or venovenous haemofiltration, and peritoneal dialysis.

Intermittent haemodialysis - This modality offers the best rate of small solute clearance. In previously undialysed patients with ARF and elevated plasma urea, haemodialysis should be started gradually because of the risk of confusion and convulsions due to cerebral oedema (dialysis disequilibrium). Typically, 1 hour of treatment should be prescribed. Subsequently, patients with ARF who are haemodynamically stable can be treated by 3-4 hours of haemodialysis on alternate days, or 2-3 hours every day if they are severely catabolic. For patients at risk of bleeding, epoprostenol may be used instead of heparin for anticoagulation but can cause hypotension. For short dialyses or patients with abnormal clotting, it may be possible to avoid anticoagulation.

Haemofiltration - This may be either intermittent, with 15-30 litres of plasma ultrafiltrate exchanged for replacement fluid over 3-5 hours (high-volume haemofiltration), or continuous with 1-2 litres/hour of filtrate replaced (equivalent to a GFR of 15-30 ml/min); higher rates of filtration may be of benefit in patients with sepsis and multi-organ failure. In continuous arteriovenous haemofiltration (CAVH) the extracorporeal blood circuit is driven by the arteriovenous pressure difference. Poor filtration rates and clotting of the filter are common and this treatment has fallen out of favour. Continuous venovenous haemofiltration is pump-driven,

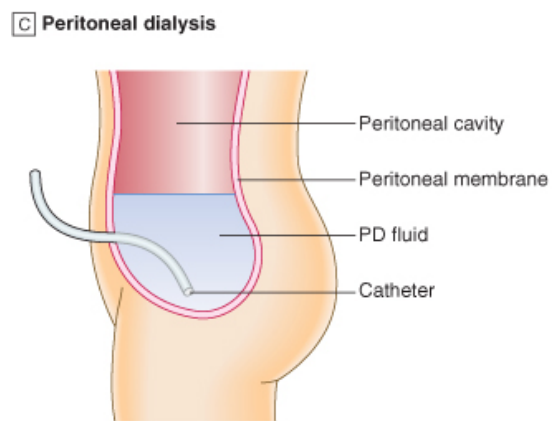
providing a reliable extracorporeal circulation. Issues concerning anticoagulation are similar to those for haemodialysis, but may be more problematic since longer or continuous anticoagulation is necessary.

Intermittent haemodiafiltration - This technique combines standard haemodialysis with the good small solute clearance and high ultrafiltration capacity of haemofiltration.



• **Access to the circulation** for haemodialysis or filtration is required. Arteriovenous fistulae, temporary or semi-permanent tunnelled central venous lines or arterio-venous shunts (e.g. Scribner shunt) may be used. The extracorporeal circuit requires anticoagulation, typically with heparin

Peritoneal dialysis - In ARF, this technique is rarely used. It is less efficient than haemodialysis, and seldom achieves adequate biochemical control in catabolic patients. It requires an intact peritoneal cavity and is not feasible after recent abdominal surgery.



- **Access to the peritoneal cavity** via 'Tenckhoff' catheter
- **Continuous ambulatory peritoneal dialysis (CAPD)**: typically 4 exchanges of 2 litres of fluid a day 4–6 hours apart
- **Automated peritoneal dialysis (APD)**: uses a machine to perform exchanges overnight (8–10 hours). Used mostly in chronic renal failure

In haemodialysis there is diffusion of solutes between plasma and dialysate across a semi-permeable membrane following a concentration gradient. Movement of solutes may be bi-directional and continues as long as the concentration gradient remains. The dialysate composition is chosen to achieve a suitable gradient. Fluid is removed by applying negative pressure to the dialysate side (ultrafiltration). In haemofiltration there is filtration of water from plasma to ultrafiltrate across a more porous semi-permeable membrane down a pressure gradient with removal of solutes by convection. 'Replacement' fluid of chosen electrolytic composition is added to the circuit after the filter. If fluid removal is required, less is replaced than filtered. Peritoneal dialysis uses peritoneum as a semi-permeable dialysis membrane. Solute move down a concentration gradient, and water down an osmotic gradient achieved by using an osmolar compound (typically glucose) in the dialysis fluid. In transplantation a functioning transplant replaces all of the functions of the failed kidneys. Some patients may elect not to dialyse and can be actively supported to control the symptoms of ESRF.

Renal Replacement In Chronic Renal Failure

When patients are known to have progressive CRF and are under regular clinic review, preparation for RRT should begin at least 12 months before the predicted start date. This involves psychological and social support, assessment of home circumstances and discussion about choice of treatment. The principal decisions required are the choice between haemodialysis and peritoneal dialysis, and referral for renal transplantation. In view of the historical high incidence of viral transmission in dialysis units, all such patients must be screened in advance for hepatitis B, hepatitis C and HIV, and have hepatitis B vaccine if they are not immune.

Of patients starting dialysis in the UK, 70% are treated by haemodialysis and 30% by peritoneal dialysis. Mortality figures indicate 78% survival at 1 year (87% counted from day 90 of treatment) and 45% at 5 years. Mortality is strongly influenced by

age; patients over 75 have a 15% survival at 5 years, whereas patients aged under 45 have an 83% survival at 5 years. Comorbid conditions such as diabetes mellitus (30% 5-year survival) and generalised vascular disease (34% 5-year survival) also have a strong influence

Comparison Of Haemodialysis And Peritoneal Dialysis :

Haemodialysis	Peritoneal dialysis
Efficient	Less efficient
4 hours three times per week usually adequate	Four exchanges per day usually required, each taking 30-60 minutes (continuous ambulatory peritoneal dialysis) or 8-10 hours each night (automated peritoneal dialysis)
2-3 days between treatments	A few hours between treatments
Requires visits to hospital (although home treatment possible for some patients)	Performed at home
Requires adequate venous circulation for vascular access	Requires an intact peritoneal cavity without major scarring from previous surgery
Careful compliance with diet and fluid restrictions required between treatments	Diet and fluid less restricted
Fluid removal compressed into treatment periods; may cause symptoms and haemodynamic instability	Slow continuous fluid removal, usually asymptomatic
Infections related to vascular access may occur	Peritonitis and catheter-related infections may occur
Patients are to some extent dependent on others	Patients can take full responsibility for their treatment

Intermittent haemodialysis - This is the standard blood purification therapy in ESRF. Haemodialysis is started when the patient has symptomatic advanced renal failure but before the development of serious complications, often with a plasma creatinine of 600-800 $\mu\text{mol/l}$. Vascular access is required; an arteriovenous fistula should be formed, usually in the forearm, when the patient reaches stage 4 kidney disease, so that the fistula has time to develop. After 4-6 weeks, increased pressure in the vein leading from the fistula causes distension and thickening of the vessel wall (arterialisation). Large-bore needles can then be inserted into the vein to provide access for each haemodialysis treatment. Preservation of arm veins is thus very important in patients with progressive renal disease who may require haemodialysis in the future. If this access is not possible, plastic cannulae in central veins can be used for short-term access.

Haemodialysis is usually carried out for 3-5 hours three times weekly. Most patients notice an improvement in symptoms during the first 6 weeks of treatment. Plasma urea and creatinine are lowered by each treatment but do not return to normal. Some patients are able to carry out their treatment at home. Many patients lead normal and active lives, and patient survival for more than 20 years is commonplace in young patients without extrarenal disease.

Continuous ambulatory peritoneal dialysis (CAPD) - CAPD is a form of long-term dialysis involving insertion of a permanent Silastic catheter into the peritoneal cavity. Two litres of sterile, isotonic dialysis fluid are introduced and left in place for approximately 6 hours. During this time, metabolic waste products diffuse from peritoneal capillaries into the dialysis fluid down a concentration gradient. The fluid is then drained and fresh dialysis fluid introduced. The inflow fluid is rendered hyperosmolar by the addition of glucose; this results in net removal of fluid from the patient on each cycle (ultrafiltration). This cycle is repeated four times daily, during which time the patient is mobile and able to undertake normal daily activities. CAPD is particularly useful in young children, and in elderly patients with cardiovascular instability. Its long-term use may be limited by episodes of bacterial

peritonitis and damage to the peritoneal membrane, but patients have been treated successfully for more than 10 years.

The use of automated peritoneal dialysis (APD) is now widespread. This system is similar to CAPD but uses a mechanical device to perform the fluid exchanges during the night, leaving the patient free, or with only a single exchange to perform, during the day.

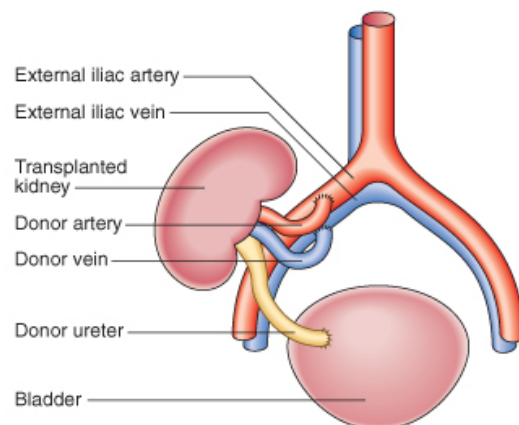
Conservative treatment of stage V chronic kidney disease

Partly as a result of survival data, there is an increasing trend to consider conservative non-dialytic treatment in patients in a high-risk category. Patients are offered full medical, psychological and social support to optimise and sustain their existing renal function for as long as possible, and appropriate palliative care in the terminal phase of their disease. Many of these patients enjoy a good quality of life for several years. It is also appropriate to discontinue dialysis treatment, with the consent of the patient, and to offer conservative therapy and palliative care when quality of life on dialysis is clearly inadequate.

Renal transplantation

Renal transplantation offers the best chance of long-term survival in patients with end-stage renal disease. It can restore normal kidney function and correct all the metabolic abnormalities of CRF. All patients should be considered for transplantation unless there are active contraindications.

Transplantation



- Successful transplantation extends the life expectancy of patients with end-stage CRF
- Requires long-term use of immunosuppressives with attendant risks

Contraindications To Renal Transplantation

Absolute

- Active malignancy-a period of at least 2 years of complete remission is recommended for most tumours prior to transplantation
- Active vasculitis or anti-GBM disease, with positive serology-at least 1 year of remission is recommended prior to transplantation
- Severe ischaemic heart disease
- Severe occlusive aorto-iliac vascular disease

Relative

- Age-while practice varies, transplants are not routinely offered to very young children (< 1 year) or older people (> 75 years)
- High risk of disease recurrence in the transplant kidney
- Disease of the lower urinary tract-in patients with impaired bladder function, an ileal conduit may be considered
- Significant comorbidity

Kidney grafts may be taken from a cadaver or from a living donor. Matching of a donor to a specific recipient is strongly influenced by immunological factors, since graft rejection is the major cause of failure of the transplant. ABO (blood group) compatibility between donor and recipient is essential, and the degree of matching for major histocompatibility (MHC) antigens-particularly HLA-DR-influences the incidence of rejection. T cells are the major cell involved in graft rejection; cytotoxic antibodies against HLA antigens, which may be present pre-transplant (sensitisation), are also important. A cytotoxicity test for these antibodies, and T- and B-cell cross-match tests (donor lymphocytes mixed with patient serum), are performed pre-transplant. Positive tests predict early rejection.

In the transplant operation, the donor vessels are anastomosed to the recipient iliac artery and vein, and the donor ureter to the bladder. Peri-operative problems include:

- *Fluid balance.* Careful matching of input to output is required.
- *Primary graft non-function.* Causes include hypovolaemia, acute tubular necrosis or other pre-existing renal damage, hyperacute rejection, vascular occlusion and urinary tract obstruction.
- *Sepsis* (related to immunosuppression).

Once the graft begins to function, normal or near-normal biochemistry is usually achieved within a few days. All transplant patients require regular life-long clinic follow-up to monitor renal function and immunosuppression.

Management after transplantation.

Immunosuppressive therapy is required to prevent rejection. Different therapeutic regimens are used; a commonly used one is triple therapy consisting of prednisolone, plus ciclosporin or tacrolimus and azathioprine. Newer immunosuppressive drugs such as mycophenolate mofetil and rapamycin are increasing in use. Rejection is treated by short courses of very high-dose corticosteroids in the first instance, although other more potent therapies, such as anti-lymphocyte antibodies or plasma exchange, are used in resistant episodes.

Immunosuppression, which must usually be taken throughout the life of the transplant, is associated with an increased incidence of infection, particularly opportunistic infections such as cytomegalovirus and *Pneumocystis carinii* (now *jirovecii*). There is also an increased risk of malignancy, especially of the skin. Approximately 50% of white patients develop skin malignancy by 15 years post-transplant. Lymphomas are rare but may occur early and are often related to infection with herpes viruses, especially Epstein-Barr virus.

The prognosis after kidney transplantation has improved significantly. Recent UK statistics for transplants from cadaver donors indicate 96% patient survival and 92% graft survival at 1 year, and 84% patient survival and 76% graft survival at 5 years. Even better figures are obtained with living donor transplantation (92% patient

survival and 86% graft survival at 5 years). Living donor operations are becoming more common in the UK and can now be successfully performed with genetically unrelated donors, such as spouses.

Quality of life studies indicate that transplantation offers the best hope of complete rehabilitation and is the most cost-effective treatment for end-stage CRF.

Renal Replacement Therapy In Old Age

- **Quality of life:** age itself is not a barrier to good quality of life on RRT.
- **Coexisting cardiovascular disease:** its high prevalence can make dialysis difficult. Older people are more sensitive to fluid balance changes, predisposing to hypotension during dialysis with rebound hypertension between dialyses. The ischaemic heart cannot cope with fluid overload and pulmonary oedema easily develops.
- **Provision of treatment:** only hospital-provided haemodialysis is suitable and older patients require more medical and nursing time.
- **Survival on dialysis:** difficult to predict for an individual patient, but is correlated with age, functional ability and co-morbid disease.
- **Withdrawal from dialysis:** a common cause of death in older patients with co-morbid disease.
- **Transplantation:** relative risks of surgery and immunosuppression, and limited organ availability exclude most older people from transplantation.
- **Conservative therapy:** i.e. without dialysis but with adequate support, may be a popular option for patients at high risk of complications from dialysis, who have a limited prognosis and little hope of functional recovery.

KEY LEARNING POINTS.



- 1. Dialysis is the replacement of some renal function by artificial means.**
- 2. Endocrine and metabolic kidney function is not replaced via dialysis.**
- 3. Haemodialysis and haemofiltration are the usual methods of dialysis. Peritoneal dialysis is less rarely used.**
- 4. Haemodialysis involves the exchange of solutes between plasma and the dialysing solution through a semi-permeable membrane.**
- 5. Renal transplantation currently offers the best chance of long-term survival in patients with ESRF.**
- 6. Immunosuppressive therapy is required post-transplant, leaving the patient at increased risk of opportunistic infection, such as CMV.**
- 7. Around 50% of white patients will develop skin malignancy within 15 years of undergoing transplant.**

8. Renal Vascular Diseases

Diseases which affect renal blood vessels may cause renal ischaemia, leading to acute or chronic renal failure or secondary hypertension. The rising prevalence of atherosclerosis and diabetes mellitus in ageing populations has made renovascular disease an important cause of ESRF.

Large-Vessel Disease: Renal Artery Stenosis

Presentations

Hypertension - Renal artery stenosis classically presents as hypertension if it affects a single kidney or as renal failure if it is bilateral. The hypertension is driven by activation of the renin-angiotensin system in response to renal ischaemia. In atherosclerotic renal artery disease, there is usually evidence of vascular disease elsewhere, particularly in the legs.

Deterioration of renal function on ACE inhibitors - When renal perfusion pressure drops, the renin-angiotensin-aldosterone system is activated and angiotensin-mediated glomerular efferent arteriolar vasoconstriction maintains glomerular filtration pressure. ACE inhibitors or angiotensin II receptor antagonists block this physiological response. A drop in GFR (> 20% rise in creatinine) on ACE inhibitors raises the possibility of renal artery stenosis. This is not a sensitive diagnostic test, however.

Flash pulmonary oedema - Repeated episodes of acute pulmonary oedema associated with severe hypertension, occurring without other obvious cause (e.g. myocardial infarction, dysrhythmia, anaemia, thyrotoxicosis) in patients with normal or only mildly impaired renal and cardiac function, can occur in renal artery stenosis. This presentation is characteristic of bilateral renovascular disease because in unilateral disease salt and water retention are partly corrected by increased

'pressure natriuresis' in the normal kidney. Episodes may be precipitated by a sudden increase in blood pressure, e.g. following sympathetic stimulation.

Acute renal infarction - Sudden occlusion of the renal arteries causes acute loin pain, usually with dipstick haematuria. It may be caused by local atherosclerosis (atheroembolic) or by thromboemboli from a distant source, e.g. mural cardiac thrombus. Bilateral occlusion (as in aortic occlusion-look for absent femoral pulses and reduced lower limb perfusion), or acute occlusion of the artery to a single kidney, will cause acute renal failure. Severe hypertension is common but not universal; presumably, some residual renal perfusion is required to generate renin release.

Aetiology

Reduction of renal blood flow is associated with > 70% narrowing of the artery, and commonly with a dilated region more distally (post-stenotic dilatation).

Atherosclerosis is the most common cause, especially in older patients. The characteristic lesion is an ostial stenosis that is associated with atherosclerosis within the aorta and affecting other major branches, particularly the iliac vessels. Renal impairment is not simply related to the degree of stenosis. The picture is often complicated by small-vessel disease in affected kidneys that may be related to subclinical atheroemboli, hypertension or other disease. As the stenosis becomes more severe, global renal ischaemia leads to shrinkage of the affected kidney: ischaemic nephropathy. However, the progression of stenosis is not easily predictable, and in many instances the outcome is determined by coronary, cerebral or other vascular disease. Some patients develop renal failure.

In younger patients (< 50 years), fibromuscular dysplasia is a more likely cause of renal artery stenosis. This is an uncommon congenital disorder of unknown cause affecting the media ('medial fibroplasia'), which narrows the artery but rarely leads to total occlusion. It may be associated with disease in other arteries; for example, those

who have carotid artery dissections are more likely to have this appearance in their renal arteries. It most commonly presents with hypertension in patients aged 15-30 years, and in women more frequently than men. Irregular narrowing ('beading') affects the distal renal artery, sometimes extending into intrarenal branches.

Rarely, large-vessel vasculitis, particularly Takayasu's arteritis, may involve renal arteries. Medium-sized arteries are more typically affected in polyarteritis nodosa.

Management

Untreated, atheromatous renal artery stenosis will progress to complete arterial occlusion and loss of kidney function in about 15% of cases. This figure is increased with more severe degrees of stenosis. If the progression is gradual, collateral vessels may develop and some function may be preserved, preventing infarction and loss of kidney structure. Conversely, at least 85% of patients with renal artery stenosis will not develop progressive renal impairment, and indeed in many patients the stenosis may be haemodynamically insignificant and not responsible for coexisting essential hypertension. Although investigations such as captopril renography or plasma renin activity have been advocated as predictors of the response to reversal of the stenosis, it remains difficult to predict which patients will respond.

Treatment options are:

- Medical management with blood pressure lowering, low-dose aspirin and lipid-lowering drugs. This will usually have been attempted before angiography is performed.
- Angioplasty, with placement of stents in atherosclerotic disease areas to improve primary patency rates and prevent rapid recurrence.
- Surgical resection of the stenosed segment and re-anastomosis. This is rarely undertaken now for atherosclerotic disease.

Angioplasty is widely used, but there may be substantial risks in patients with atherosclerosis: of contrast nephropathy, of renal artery occlusion and renal

infarction, and of atheroemboli from manipulations in a severely diseased aorta. Small-vessel disease distal to the stenosis may preclude substantial functional recovery. The overall effect on blood pressure, on renal function and on patient survival is far from clear, and trials are currently addressing this. Persisting with conservative medical treatment may be appropriate if there is widespread atheromatous disease of the aorta and elsewhere. Surgical mortality is significant in patients with atherosclerosis; when intervention is required, percutaneous procedures are generally preferred.

In non-atheromatous fibromuscular dysplasia, the renal artery stenosis is much more likely to be the cause of the presentation, and angioplasty has a high chance of success in improving blood pressure and protecting renal function.

Diseases Of Small Intrarenal Vessels

Microvascular disorders associated with acute renal damage :

- Thrombotic microangiopathy (haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura)
 - Associated with verotoxin-producing *E. coli*
 - Other (familial, drugs, cancer etc.)
- Disseminated intravascular coagulation
- Malignant hypertension
- Small-vessel vasculitis
- Systemic sclerosis (scleroderma)
- Atheroemboli ('cholesterol' emboli)

A number of conditions are associated with acute damage and occlusion of small blood vessels (arterioles and capillaries) in the kidney. They may be associated with similar changes elsewhere in the body. A common feature of these syndromes is microangiopathic haemolytic anaemia, in which haemolysis occurs as a consequence

of damage incurred to red blood cells during passage through the abnormal vessels; fragmented red cells can be seen on a blood film.

Thrombotic microangiopathy: HUS and TTP - Haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are types of thrombotic microangiopathy. Common features include damage to endothelial cells of the microcirculation, which is followed by cell swelling, platelet adherence and thrombosis. A severe microangiopathy causes a marked reduction in the platelet count and anaemia. Other features of intravascular haemolysis such as raised bilirubin and lactate dehydrogenase (LDH), decreased haptoglobins are also present. A reticulocytosis is often seen. The aetiology of the syndromes may be different, although there is substantial overlap. The kidney microcirculation tends to be most affected in HUS, with involvement of other organs (including the brain) in more severe cases. In TTP the brain is commonly affected and involvement of the kidney may be less severe.

E.coli associated HUS - Thrombotic microangiopathy associated with *E. coli* infection is associated with verotoxin-producing organisms. Although the bacteria live as commensals in the gut of cattle and other domestic livestock, they can cause haemorrhagic diarrhoea in humans when the infection is contracted from contaminated food products, water or other infected individuals. In a proportion of cases, verotoxin produced by the organisms enters the circulation and binds to specific glycolipid receptors that are expressed on the surface of microvascular endothelial cells. In children, this causes diarrhoea-associated (D+)HUS, although in more severe cases the brain and other organs are also affected. D+HUS is now the most common cause of ARF in children in developed countries. In adults, the disease may more closely resemble TTP. All patients usually recover, often after 5-15 days of dialysis. No specific treatments have been shown to help.

TTP and other HUS - Other causes of thrombotic microangiopathy have a less certain outlook and are more likely to recur (sometimes after renal transplantation).

Familial examples may reflect an abnormality of endothelial cell defence against damage or thrombosis, including deficiency of complement activation inhibitors (associated with familial HUS) or of von Willebrand protease (associated with TTP). The disease may occur post-partum, in response to certain drugs (especially chemotherapy), after bone marrow transplantation, in malignancy and apparently spontaneously. Plasma exchange using fresh frozen plasma is effective in many of these cases, probably by replacing a deficient substance (e.g. the von Willebrand protease).

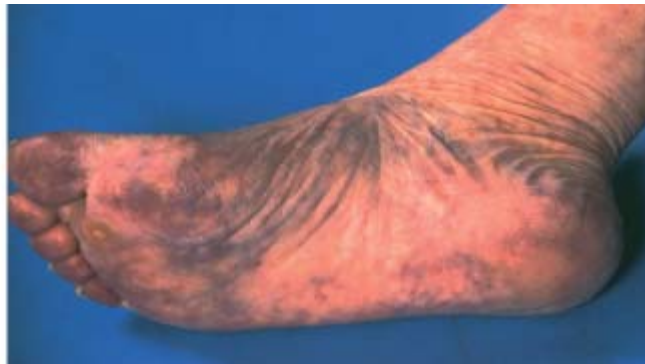
Disseminated intravascular coagulation - In this condition, consumption of clotting factors and platelets occurs due to uncontrolled thrombosis in the microvasculature, leading to a tendency to haemorrhage from larger vessels. Precipitating conditions include septic shock, in which bacterial endotoxin directly activates the coagulation cascade; obstetric complications; disseminated cancer; massive transfusion; and other causes of coagulation activation or depletion.

Accelerated phase ('malignant') hypertension - Hypertension is described as being in accelerated phase when it causes acute damage to renal and other arterioles. It is often symptomatic, with headache, impaired vision and, finally, manifestations of renal failure. Severe hypertensive retinopathy with papilloedema is almost always present, and it is usually associated with some of the features of microangiopathy described above. In the absence of a previous history, it may be difficult to distinguish these patients from those with HUS and hypertension. Patients usually respond to effective control of blood pressure, although renal function is permanently lost in 20% of cases.

Systemic sclerosis (scleroderma) - Renal involvement is a serious feature of this connective tissue disorder, and is characterised by intimal cell proliferation and luminal narrowing of intrarenal arteries and arterioles. Clinically, it usually presents as 'scleroderma renal crisis', with severe hypertension, microangiopathic features and progressive oliguric renal failure. There is intense intrarenal vasospasm, and plasma

renin activity is markedly elevated. Use of ACE inhibitors to control the hypertension has improved the 1-year survival from 20% to 75%; however, about 50% of patients continue to require RRT.

Atheroembolic renal disease ('cholesterol' emboli) - This is caused by showers of cholesterol-containing microemboli, arising in atheromatous plaques in major arteries. It occurs in patients with widespread atheromatous disease, usually after interventions such as surgery or arteriography but sometimes after anticoagulation. There is loss of renal function, haematuria and proteinuria, and sometimes eosinophilia and inflammatory features which may mimic a small-vessel vasculitis. Accompanying signs of microvascular occlusion in the lower limbs (e.g. ischaemic toes, livedo reticularis) are common but not invariable. There is no specific treatment.



Small-vessel vasculitis - Renal disease caused by small-vessel vasculitis usually affects the glomeruli.

9. Glomerular Diseases

Glomerular diseases account for a significant proportion of acute and chronic renal failure. Glomerular damage may follow a number of insults: immunological injury, inherited abnormality (e.g. Alport's syndrome), metabolic stress (e.g. diabetes mellitus), deposition of extraneous materials (e.g. amyloid), or other direct injury to

glomerular cells. The response of the glomerulus to injury varies according to the nature of the insult. At one extreme, specific injury to podocytes, or structural alteration of the glomerulus affecting podocyte function (for example, by scarring or deposition of excess matrix or other material), causes proteinuria and nephrotic syndrome. At the other end of the spectrum, inflammation leads to cell damage and proliferation, breaks form in the GBM and blood leaks into urine. In its extreme form, with acute sodium retention and hypertension, such disease is labelled nephritic syndrome.

Glomerulonephritis

Glomerulonephritis literally means 'inflammation of glomeruli', although inflammation is not apparent in all varieties.

Most types of glomerulonephritis seem to be immunologically mediated and several respond to immunosuppressive drugs. For some diseases there is direct evidence of this: for example, the anti-GBM antibodies seen in Goodpasture's disease.

Deposition of antibody occurs in many types of glomerulonephritis, but frequently the presumed mechanisms involve cellular immunity, which is more difficult to investigate. Although deposition of circulating immune complexes was previously thought to be a common mechanism of glomerulonephritis, it now seems that most granular deposits of immunoglobulin are formed 'in situ' by antibodies which complex about glomerular antigens, or about other antigens ('planted' antigens, e.g. viral or bacterial ones) that have localised in glomeruli

Membranous Nephropathy

This is the most common cause of nephrotic syndrome in adults. A proportion of cases are associated with known causes but most are idiopathic. Of this group, approximately one-third remit spontaneously, one-third remain in a nephrotic state, and one-third show progressive loss of renal function. Short-term treatment with high doses of corticosteroids and alkylating agents (e.g. cyclophosphamide) may improve both the nephrotic syndrome and the long-term prognosis. However, because of the

toxicity of these regimens, most nephrologists reserve such treatment for those with severe nephrotic syndrome or deteriorating renal function.

IgA Nephropathy And Henoch-Schönlein Purpura

IgA nephropathy is the most commonly recognised type of glomerulonephritis and can present in many ways. Haematuria is almost universal, proteinuria usual, and hypertension very common. There may be severe proteinuria and nephrotic syndrome, or in some cases progressive loss of renal function. The disease is a common cause of ESRF. A particular hallmark in some individuals is acute exacerbations, often with gross haematuria, in association with minor respiratory infections. This may be so acute as to resemble acute post-infectious glomerulonephritis, with fluid retention, hypertension and oliguria with dark or red urine. Characteristically, the latency from clinical infection to nephritis is short: a few days or less. These episodes usually subside spontaneously

In children, and occasionally in adults, a systemic vasculitis occurring in response to similar infections is called Henoch-Schönlein purpura. A characteristic petechial rash (cutaneous vasculitis, typically affecting buttocks and lower legs) and abdominal pain (gastrointestinal vasculitis) usually dominate the clinical picture, with mild glomerulonephritis being indicated by haematuria. When the disease occurs in older children or adults, the glomerulonephritis is usually more prominent. Renal biopsy shows mesangial IgA deposition and appearances indistinguishable from acute IgA nephropathy

Occasionally, IgA nephropathy progresses rapidly and crescent formation may be seen. The response to immunosuppressive therapy is usually poor. The management of less acute disease is largely directed towards the control of blood pressure in an attempt to prevent or retard progressive renal disease.

Glomerulonephritis Associated With Infection

Causes of glomerulonephritis associated with low serum complement :

- Post-infection glomerulonephritis
- Subacute bacterial infection-especially endocarditis
- SLE
- Cryoglobulinaemia
- Mesangiocapillary glomerulonephritis-usually type II

Bacterial infections, usually subacute (typically subacute bacterial endocarditis), may cause a variety of histological patterns of glomerulonephritis, but usually with plentiful immunoglobulin deposition and often with evidence of complement consumption. In the developed world, hospital-acquired infections are now a common cause of these syndromes. World-wide, glomerulonephritis associated with malaria, hepatitis B, hepatitis C, schistosomiasis, leishmaniasis and other chronic infections is very common. The usual histological patterns are membranous and mesangiocapillary lesions, although many other types may be seen. FSGS associated with HIV infection is prevalent in black races. Proving a causative relationship between renal disease and infection in individual cases is extremely difficult. Acute and chronic infections may also cause interstitial renal disease.

Acute post-infectious glomerulonephritis - This is most common following infection with certain strains of streptococcus and therefore is often called post-streptococcal nephritis, but it can occur following other infections. It is much more common in children than adults but is now rare in the developed world. The latency is usually about 10 days after a throat infection or longer after skin infection, suggesting an immune mechanism rather than direct infection. An acute nephritis of varying severity occurs. Sodium retention, hypertension and oedema, are particularly pronounced. There is also reduction of GFR, proteinuria, haematuria and reduced urine volume. Characteristically, this gives the urine a red or smoky appearance. Renal function begins to improve spontaneously within 10-14 days, and management

by fluid and sodium restriction and use of diuretic and hypotensive agents is usually adequate. Remarkably, the renal lesion in almost all children and most adults seems to resolve completely despite the severity of the glomerular inflammation and proliferation seen histologically.

Rapidly progressive glomerulonephritis - This describes an extreme inflammatory nephritis which causes rapid loss of renal function over days to weeks. Renal biopsy shows crescentic lesions often associated with necrotising lesions within the glomerulus (necrotising glomerulonephritis). It is typically seen in Goodpasture's disease, where there are specific anti-GBM antibodies, and in small-vessel vasculitides, but can also be seen in SLE and occasionally IgA and other nephropathies.

10. Interstitial Nephritis

A group of inflammatory, inherited and other diseases affect renal tubules and the surrounding interstitium. The clinical presentation is often renal failure, but electrolyte abnormalities are common, especially hyperkalaemia and acidosis. Proteinuria (and albuminuria) is rarely $> 1 \text{ g}/24 \text{ hrs}$ but low molecular weight proteinuria with haematuria and pyuria are common.

Acute Interstitial Nephritis (AIN)

Acute inflammation within the tubulo-interstitium is most commonly allergic, particularly to drugs, but other causes include toxins and a variety of systemic diseases and infections. Renal biopsies show intense inflammation, with polymorphonuclear leucocytes and lymphocytes surrounding tubules and blood vessels and invading tubules (tubulitis), and occasional eosinophils (especially in drug-induced disease).

Only a minority (perhaps 30%) of patients with drug-induced AIN have a generalised drug hypersensitivity reaction (e.g. fever, rash, eosinophilia) and dipstick testing of the urine usually shows little. However, leucocyturia is common, and eosinophils are found in the urine in up to 70% of patients. Deterioration of renal function in drug-induced AIN may be dramatic and resemble rapidly progressive glomerulonephritis. Renal biopsy is usually required to confirm the diagnosis. The degree of chronic inflammation in a biopsy is a useful predictor of the eventual outcome for renal function.

Some patients with drug-induced AIN recover following withdrawal of the drug alone, but corticosteroids (e.g. prednisolone 1 mg/kg/day) accelerate recovery and may prevent long-term scarring. Dialysis is sometimes necessary, but is usually only short-term.

Chronic Interstitial Nephritis

Chronic interstitial nephritis (CIN) can be caused by diseases such as SLE, sarcoidosis, drug reactions, or toxic substances such as some mushrooms and Chinese herbs. It is not uncommon for the condition to be diagnosed late and for no aetiology to be apparent.

Toxic causes of CIN - The combination of interstitial nephritis and tumours of the collecting system is seen in Balkan nephropathy, so called because of where cases are found, and has been controversially attributed to ingestion of fungal toxins, particularly ochratoxin A, present in food made from stored grain. A plant toxin, aristolochic acid, has been blamed for a rapidly progressive syndrome caused by mistaken identity of ingredients in herbal preparations.

Papillary necrosis and analgesic nephropathy - Long-term ingestion (years to decades) of analgesic drugs can cause renal papillary necrosis and CIN. As the papillae are at the end of the capillary distribution in the kidney, they become ischaemic most easily and may necrose in this condition, in sickle-cell disease and

occasionally in diabetes and other conditions. Necrosed papillae may cause ureteric obstruction and renal colic. In animals, lesions can be induced with almost any NSAID; however, there has been a dramatic fall in the incidence of this disease following withdrawal of phenacetin from compound analgesics. If it is diagnosed, cessation of analgesic intake may stop progression.

Most patients present in adult life with CRF, hypertension and small kidneys. CRF is often moderate but, because of tubular dysfunction, electrolyte abnormalities are typically more severe (e.g. hyperkalaemia, acidosis). Urinalysis abnormalities are non-specific. A minority of patients present with hypotension, polyuria and features of sodium and water depletion (e.g. low blood pressure and jugular venous pressure). Impairment of urine-concentrating ability and sodium conservation places patients with CIN at risk of superimposed ARF with even moderate salt and water depletion during an acute illness. Hyperkalaemia may be disproportionate in CIN or in diabetic nephropathy because of hyporeninaemic hypoaldosteronism. Renal tubular acidosis is seen most often in myeloma, sarcoidosis, cystinosis and amyloidosis.

Sickle-Cell Nephropathy

The longer survival of patients with sickle-cell disease means that a larger proportion live to develop chronic complications of microvascular occlusion. In the kidney these changes are most pronounced in the medulla, where the vasa recta are the site of sickling because of hypoxia and hypertonicity. Loss of urinary concentrating ability and polyuria are the earliest changes; distal renal tubular acidosis and impaired potassium excretion are typical. Papillary necrosis (as seen in analgesic nephropathy) is very common. A minority of patients develop ESRF. This is managed according to the usual principles, but response to recombinant erythropoietin is understandably poor. Patients with sickle trait have an increased incidence of unexplained microscopic haematuria, and occasionally overt papillary necrosis.

11. Polycystic Kidney Disease

Adult polycystic kidney disease (PKD) is a common condition (prevalence 1:1000) that is inherited as an autosomal dominant trait. Small cysts lined by tubular epithelium develop from infancy or childhood and enlarge slowly and irregularly.



Surrounding normal kidney tissue is progressively attenuated. Renal failure is associated with grossly enlarged kidneys.

Common clinical features are

- Vague discomfort in loin or abdomen due to increasing mass of renal tissue
- Acute loin pain or renal colic due to haemorrhage into a cyst
- Hypertension
- Haematuria (with little or no proteinuria)
- Urinary tract infection
- Renal failure

About 30% of patients with PKD have hepatic cysts, but disturbance of liver function is rare. Sometimes (almost always in women) this causes massive and symptomatic hepatomegaly, usually concurrent with renal enlargement, but occasionally with only minor renal involvement.

Berry aneurysms of cerebral vessels are an associated feature, and about 10% of patients have a subarachnoid haemorrhage. This feature appears to be largely restricted to certain families (and presumably specific mutations). Mitral and aortic regurgitation are frequent but rarely severe, and colonic diverticula and abdominal wall hernias may occur.

PKD is not a pre-malignant condition. The rate of renal malignancy is no different from that of other patients with renal failure (but is higher than the general population).

Nothing has yet been found to alter the rate of progression of renal failure in human PKD, although there are some potentially interesting approaches under investigation. Good control of blood pressure is important because cardiovascular morbidity and mortality are so common in renal disease, but there is no evidence that control of moderate hypertension retards the development of renal failure in PKD, in contrast to the evidence for glomerular diseases.

Patients with PKD are usually good candidates for dialysis and transplantation. Sometimes kidneys are so large that one or both have to be removed to make space for a renal transplant.

12. Tumours Of The Kidney

Tumours of the kidney account for 3% of all malignancies, and a variety of benign, malignant and secondary tumours can occur.

Renal Adenocarcinoma

This is by far the most common malignant tumour of the kidney in adults, with a prevalence of 16 cases per 100 000 population. It is twice as common in males as in females. The peak incidence is between 65 and 75 years of age and it is uncommon

before 40. The tumour arises from renal tubules. Haemorrhage and necrosis give the cut surface a characteristic mixed golden-yellow and red appearance.

Microscopically, 'clear cell' carcinomas are more common than 'granular cell' tumours. There is early spread of the tumour into the renal pelvis, causing haematuria, and along the renal vein, often extending into the inferior vena cava. Direct invasion of perinephric tissues is common. Lymphatic spread occurs to para-aortic nodes, while blood-borne metastases (which may be solitary) may develop almost anywhere in the body.

About 60% of cases present with haematuria, 40% with loin pain and only 25% with a mass. The triad of pain, haematuria and a mass is an important but late feature occurring in only 15% of cases. A range of systemic effects may be present, including fever, raised ESR, polycythaemia, disorders of coagulation, and abnormalities of plasma proteins and liver function tests. The patient may present with pyrexia of unknown origin or, rarely, with neuropathy. Systemic effects may be due to tumour secretion of products such as renin, erythropoietin, parathyroid hormone-related peptide and gonadotrophins. The effects disappear when the tumour is removed but may reappear when metastases develop, and so can be used as markers of tumour activity.

Radical nephrectomy that includes the perirenal fascial envelope and ipsilateral para-aortic lymph nodes is performed whenever possible. Renal adenocarcinoma is resistant to radiotherapy and chemotherapy but some benefit has been seen with immunotherapy using interferon and interleukin-2. Even when metastases are present, nephrectomy is always considered; not only may systemic effects disappear, but there may even be regression of any metastases. Solitary metastases tend to remain single for long periods and excision is often worth while.

If the tumour is confined to the kidney, 5-year survival is 75%. This falls to only 5% when there are distant metastases.

Tumours Of The Renal Pelvis, Ureters And Bladder

The vast majority of these tumours arise from the urothelium or transitional cell lining. The urothelium is exposed to chemical carcinogens excreted in the urine, such as naphthylamines and benzidine which were extensively used in the chemical and dye industries until their carcinogenic properties were recognised. Almost all tumours are transitional cell carcinomas. Squamous carcinoma may occur in urothelium that has undergone metaplasia, usually following chronic inflammation or irritation due to a stone or schistosomiasis.

The incidence of transitional cell carcinoma in the bladder in the UK is 45 cases per 100 000 population, and is three times more common in men than women. The appearance of a transitional cell tumour ranges from a delicate papillary structure to a solid ulcerating mass. The appearance correlates well with subsequent behaviour, in that papillary tumours are relatively benign cancers while those which ulcerate are much more aggressive.

More than 80% of patients have haematuria, which is usually visible and painless. It should be assumed that such bleeding is from a tumour until proved otherwise. A tumour at the lower end of a ureter or a bladder tumour involving the ureteric orifice may cause obstructive symptoms. Examination is usually unhelpful as rectal examination detects only very advanced tumours.

Small, large and even multiple superficial bladder tumours can be treated endoscopically by transurethral resection of the tumour(s) (TURBT). Intravesical chemotherapy (e.g. epirubicin, mitomycin C) is useful for treating multiple low-grade bladder tumours and for reducing their recurrence rate. Regular 'check' cystoscopies are required and recurrences can usually be controlled by diathermy; only rarely will cystectomy be required for superficial disease.

Transitional cell carcinoma of the renal pelvis and ureter is usually treated by nephroureterectomy and regular surveillance of the bladder, but if the tumour is

solitary and low-grade it may be treated endoscopically; surveillance remains problematic.

The prognosis of bladder tumours depends on tumour stage and grade. The 5-year survival rate varies from 50-60% in those with superficial tumours to 20-30% for those with deep muscle invasion. Overall, about one-third of patients survive for 5 years.

13. Renal Involvement in Systemic Disorders

The kidneys may be directly involved in a number of multisystem diseases or secondarily affected by diseases of other organs. Involvement may be at a pre-renal, renal (glomerular or interstitial) or post-renal level.

Diabetes Mellitus - In patients with diabetes, there can be a steady advance from microalbuminuria to dipstick-positive proteinuria, the development of hypertension and the progression to frank nephrotic syndrome. Few patients require renal biopsy to establish the diagnosis, but atypical features or progression should lead to suspicion that an alternative condition could be present. Management with ACE inhibitors and other hypotensive agents to slow progression has been dramatically effective. In some patients, proteinuria may be eradicated and progression completely halted, even if renal function is abnormal.

Hepatic-Renal Disease - IgA nephropathy is more common in patients with liver disease. Severe hepatic dysfunction may cause a haemodynamically mediated type of renal failure, hepatorenal syndrome. However, it also predisposes the kidney to develop acute renal failure (acute tubular necrosis) in response to relatively minor insults including bleeding and infection. Patients with such severe hepatic failure are often difficult to treat by dialysis and have a poor prognosis. Where treatment is

justified - eg if there is a good chance of recovery or of a liver transplant - very slow or continuous treatments are less likely to precipitate or exacerbate encephalopathy.

Pulmonary-Renal Disease - The pulmonary-renal syndrome is a dramatic presentation with renal and respiratory failure. Goodpasture's disease and small-vessel vasculitis can cause this presentation.

Tuberculosis Of The Kidney And Urinary Tract - Tuberculosis of the kidney is secondary to tuberculosis elsewhere and is the result of blood-borne infection. Initially, lesions develop in the renal cortex; these may ulcerate into the renal pelvis and involve the ureters, bladder, epididymis, seminal vesicles and prostate. Calcification in the kidney and stricture formation in the ureter are typical. Clinical features may include symptoms of bladder involvement (frequency, dysuria); haematuria (sometimes macroscopic); malaise, fever, night sweats, lassitude, weight loss; loin pain; associated genital disease; and chronic renal failure as a result of urinary tract obstruction or destruction of kidney tissue. Neutrophils are present in the urine but routine urine culture may be negative ('sterile pyuria'). Special techniques of microscopy and culture may be required to identify tubercle bacilli and are most usefully performed on early morning urine specimens. Bladder involvement should be assessed by cystoscopy. Radiology of the urinary tract and a chest X-ray to look for pulmonary tuberculosis are mandatory. Anti-tuberculous chemotherapy follows standard regimes. Surgery to relieve urinary tract obstruction or to remove a very severely infected kidney may be required.

Systemic Vasculitis - This causes a focal inflammatory glomerulonephritis, usually with focal necrosis, and often causes crescentic changes. It is usually associated with a systemic illness with acute phase response, weight loss and arthralgia, and characteristically in some patients causes pulmonary haemorrhage, which can be life-threatening. However, in other patients it presents as a kidney-limited disorder, with rapidly deteriorating renal function and crescentic nephritis. The most important causes of this syndrome, microscopic polyangiitis and Wegener's granulomatosis, are

usually associated with antibodies to neutrophil granule enzymes, but these antibodies are non-specific and cannot be relied upon to make the diagnosis so biopsy of the affected tissue may be required. Henoch-Schönlein purpura is associated with IgA nephropathy. Treatment of the primary types of small-vessel vasculitis with cyclophosphamide and corticosteroids is life-saving. Death from extrarenal manifestations of the disease is prevented and renal function can be salvaged in acute disease, even if the glomerulonephritis is so severe as to cause oliguria. In these circumstances, plasma exchange offers additional benefit. Vasculitis may also be seen in rheumatoid arthritis, SLE and cryoglobulinaemia, although SLE usually involves the kidney in different ways.

Systemic Lupus Erythematosus (SLE) - Subclinical renal involvement, with low-level haematuria and proteinuria but minimally impaired or normal renal function, is common in SLE. Usually this is due to glomerular disease, although serologically and sometimes clinically overlapping syndromes (e.g. mixed connective tissue disorder, Sjögren's syndrome) may cause interstitial nephritis. SLE can produce almost any histological pattern of glomerular disease and an accordingly wide range of clinical features, ranging from florid rapidly progressive glomerulonephritis to nephrotic syndrome. Many patients go into relative remission from SLE once ESRF has developed. This may be because ESRF itself is an immunosuppressed state, as indicated by the higher incidence of bacterial infections in ESRF from all causes. Patients with ESRF caused by SLE are usually good candidates for dialysis and transplantation. Although it may recur in renal allografts, the immunosuppression required to prevent allograft rejection usually controls SLE too.

Pregnancy - Pregnancy has important physiological effects on the renal system and is associated with a number of distinct disorders. Some conditions are more common in pregnancy, the manifestations of others are modified by the physiological changes of pregnancy, and a few diseases (e.g. pre-eclampsia) are unique to pregnancy. Physiological adaptations begin in the first few weeks. Peripheral vascular resistance declines, blood volume, cardiac output and GFR increase, and there is usually a

reduction in blood pressure and plasma creatinine and urea values in the first trimester. Recordings of baseline blood pressure and urine testing from the first antenatal clinic visit are valuable if problems arise later. Pyelonephritis is more common during pregnancy, perhaps because of dilatation of the urinary collecting system and ureters, so asymptomatic bacteriuria should be treated.

Proteinuria caused by glomerular disease is always exacerbated, and nephrotic syndrome may develop without any alteration in the underlying disease in individuals who had only slight proteinuria before pregnancy. This gives a particular risk of venous thromboembolism, which is now the leading cause of maternal deaths in developed countries.

Pre-eclampsia is a systemic disorder that occurs in or near the third trimester of pregnancy. Its aetiology is unknown, although a number of risk factors are described

- First pregnancy
- First pregnancy with a new partner or long inter-pregnancy interval
- Pre-eclampsia in previous pregnancies
- Age < 20 years or > 35 years
- Multiple pregnancy (singleton < twin < triplets etc.)
- Pre-existing hypertension
- Pre-existing renal disease

Pre-eclampsia is traditionally defined by the triad of oedema, proteinuria and hypertension. However, oedema is common in late pregnancy, proteinuria is a late sign and, while hypertension is usually present, it may be relative, mild or even absent. Furthermore, all these features occur in pre-existing renal disease exacerbated by pregnancy. Distinguishing pre-eclampsia from pre-existing renal disease is important. Pre-eclampsia presents progressively, increasing risks to mother and fetus which can be reversed almost immediately by early delivery. In contrast, in pre-existing renal disease, continuing the pregnancy for as long as possible may permit

delivery of a healthier, more mature baby. Proteinuria and hypertension in the first trimester of pregnancy suggest pre-existing renal disease.

The only effective management for pre-eclampsia is delivery. The role of antiplatelet therapy (low-dose aspirin) remains controversial. Hypertension is a consequence not the cause of the disorder, and treatment is only justified to lower it from severe and immediately dangerous levels (e.g. higher than 180/110 mmHg). Treating lower levels has been shown to confer no benefit and exposes the fetus to additional drugs. If life-threatening complications are not present and the baby is immature, corticosteroids may be given to induce maturation of fetal lungs, and delivery postponed while mother and baby are closely observed. Magnesium sulphate reduces the incidence of eclamptic convulsions. Maternal acute renal failure may occur in most of these syndromes, and may result from cortical necrosis (irreversible infarction of the renal cortex).

14. Drugs And The Kidney.

Many drugs and drug metabolites are excreted by the kidney so the presence of renal impairment alters the required dose and frequency.

Drug-Induced Renal Disease

The kidney is susceptible to damage by drugs because it is the route of excretion of many water-soluble compounds, including drugs and their metabolites. Some may reach high concentrations in the renal cortex as a result of proximal tubular transport mechanisms. Others are concentrated in the medulla by the operation of the counter-current system. The same applies to certain toxins. Very commonly, drugs contribute as one of multiple insults to the development of acute tubular necrosis. Numerically, reactions to NSAIDs and ACE inhibitors are the most important. Haemodynamic renal impairment, acute tubular necrosis and allergic reactions are usually reversible

if recognised early enough. However, other types, especially those associated with extensive fibrosis, are less likely to be reversible.

NSAIDs - NSAIDs have the predictable effect of impairing renal function in individuals in whom compensatory mechanisms are maintaining renal function (e.g. heart failure, cirrhosis, sepsis and renal impairment of almost any type), and may precipitate acute tubular necrosis in susceptible patients. This is a class effect that is related to alteration of essential prostaglandin-mediated vasodilatation. In addition, idiosyncratic immune reactions may occur: minimal change nephrotic syndrome and acute interstitial nephritis, which may occur together. Analgesic nephropathy is an occasional complication of long-term use.

ACE inhibitors - These abolish the compensatory angiotensin II-mediated vasoconstriction of the glomerular efferent arteriole that occurs to maintain glomerular perfusion pressure distal to a renal artery stenosis and in renal hypoperfusion. Monitoring of renal function before and after initiation of therapy is essential.

KEY LEARNING POINTS.



- 1. Renal ischaemia leads to both acute and chronic renal failure.**
- 2. Increased prevalence of atheroma and diabetes in an ageing population has made renovascular disease and important cause of ESRF.**
- 3. Hypertension is a major contributing factor to the development of renal vascular problems.**
- 4. Glomerular diseases may also contribute significantly to the development of ESRF.**
- 5. Drugs such as NSAIDs and ACE inhibitors are known to promote the development of renal failure.**