The Edren Textbook
The Edren (also known as Edrep) textbook is produced by members of the Renal Unit in Edinburgh, and the University of Edinburgh, in Edinburgh, Scotland.

Terms and conditions on our websites at www.edren.org and www.edrep.org. Contact us at renal@ed.ac.uk, but note that we cannot generally provide any info about management of individual cases.
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The Edren textbook is aimed at those with some medical knowledge who need to know the essentials on renal topics. Some medical knowledge is assumed but each section is intended to provide a short introduction to the topic.

The first version was conceived by Neil Turner and developed with Amit Adlakha, and Paddy Gibson (nephrologist, medical student, and nephrologist) in Edinburgh, in 2003. The content here is substantially rewritten and it may say at the foot of each page who the major author or latest editor is.

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Found something that's wrong, or could be better? Let us know.

Important - please note

Please note that although we have tried hard, we cannot guarantee that this material is free of mistakes, and opinions on best management may change with time, and in the presence of other factors. Be particularly cautious about accepting drug and dose recommendations, if you find any here. There is a further disclaimer at the foot of every page - we mean it. Please let us know if you think we've got something seriously wrong.

We regret that we cannot provide guidance on individual cases.

The authors

(no previous) >> Anaemia
Renal anaemia is a normochromic normocytic anaemia (normal sized red cells with normal Hb content) that increases in severity as GFR falls. There are a number of explanations for renal anaemia, but relative deficiency of erythropoietin is usually dominant. However many patients require more than physiological doses of erythropoietin. Causes include:

- Erythropoietin deficiency
- Reduced RBC lifespan
- Disordered iron utilisation
- Blood loss in patients on dialysis
- Inflammation - anaemia of chronic disease

As the graph shows, without effective treatments anaemia can be very severe. The lowest haemoglobins are found in patients who have had their native kidneys removed, and the highest in those with big kidneys - e.g. polycystic kidneys. Blood transfusions risk iron overload and sensitisation to transplantation antigens and before other effective treatments were available could only be used to prevent the most severe symptoms.

**Management of renal anaemia**

First look for other or contributing causes including deficiency of iron, folate etc. Then ...

**Erythropoietin** - is a glycosylated hormone produced mostly by the kidney in response to reductions in oxygen delivery, such as occur as in anaemia, or in living at high altitude. The natural molecule is small enough for glomerular filtration to be a significant route of clearance, and traces of EPO can be found in normal urine.

The availability of different EPO-type drugs means these are now more properly called 'erythropoiesis stimulating agents', ESAs. EPO-like drugs may be closely similar to native EPO (but not identical, as some athletes have found out to their cost) or engineered to be bigger and so have longer half lives and some other properties. So far all require injection, from 2-3 times weekly to injections one or several weeks apart for the larger molecules.

Blood pressure can rise as Hb rises. Development of EPO-neutralising antibodies to cause pure red cell aplasia (PRCA) is a very rare but serious complication of treatment with ESAs.

**Iron management** - Oral iron is poorly absorbed and utilised in patients with renal failure and periodic intravenous treatment is generally required. Higher ferritin values than usual are necessary to maximise erythropoiesis.

### What target haemoglobin?

Patients feel better and can do more with a higher haemoglobin, and patients with lower haemoglobins seem to have higher mortality. So you might assume that restoring Hb to the normal range is best practice. Randomised trials have not supported that and have even suggested extra risk from returning Hb to the normal range versus slightly lower targets of 10-11g/dl (100-110g/l). There are two chief hypotheses to explain this:

- Higher Hb values predispose to thrombosis - renal patients have a higher risk of cardiovascular disease so do better with lower Hb values.
- Against this, excess morbidity and mortality observed hasn't all been cardiovascular.
- The higher (supraphysiological) values of EPO required to generate normal Hb levels act on EPO receptors on other cells in addition to bone marrow cells, and produce some undesirable effects.

### Further info

- Anaemia management from the Edren Handbook

### More pages like this

- CRF (CKD 4-5)
Acute renal failure (ARF), and Acute kidney injury (AKI)

Go straight to: what do people with ARF die of?

A sudden deterioration of kidney function. ARF and AKI really mean the same thing. AKI has grades (e.g. RIFLE criteria) for milder degrees.

Traditionally and usefully divided into (see figure):

- **Prerenal** failure (see below) accounts for the majority in hospital
- **Post-rental** - i.e. obstruction accounts for a lot. See obstruction page
- **Renal** - intrinsic renal disease - glomerulonephritis and interstitial nephritis - accounts for a minority, but needs active treatment to recover renal function.

Pre-rental ARF and acute tubular necrosis

Pre-renal ARF is associated with reduced renal blood flow caused by hypotension or hypovolaemia. For a variable time this is reversible. Reversible oliguria (<500mls urine/24h) is characterised by low urinary sodium, and high urinary urea and osmolality, though these may be altered by diuretics, and are in any case an imperfect guide. When prolonged, acute tubular necrosis (ATN) may occur. On a renal biopsy, tubules are dilated and cells necrotic (mitotic figures can be seen as recovery occurs), but the physiological state also includes dramatic changes in renal blood flow.

In practice, ATN and pre-renal failure short of ATN are usually associated with other risk factors such as sepsis, or exposure to nephrotoxic drugs or other toxins (e.g. myoglobin in rhabdomyolysis). It is more likely in the presence of pre-existing renal disease and in the elderly, and usually occurs in the context of other severe illnesses. Mortality of over 50% for ATN occurring in hospital is usual, not because of renal failure directly, but mainly because of its association with failure of other organs and with severe sepsis.

Renal artery (or aortic) occlusion is true pre-renal failure, in the absence of signs of shock. There are usually other signs of vascular occlusion.

Approach to the patient with oliguria

Most of this also applies anyone with new renal failure, whether or not they are oliguric.

1. Is oliguria real – is output recorded and reliable? If complete anuria, obstruction (check for bladder) or vascular cause particularly likely.
2. Assess circulatory state – blood pressure (versus patient's normal), JVP, perfusion. Lying and standing BP can be informative.
3. Fluid balance – in and out over last 48h or longer. Extra losses? (vomiting, diarrhoea, fever, drains)
4. History or evidence suggestive of urinary tract obstruction?
5. Exposure to nephrotoxic drugs and other toxins (consider muscle lysis – rhabdomyolysis)
7. Regardless of cause, optimise circulation (fluid replacement; ?inotropic agents)

Important investigations in ARF

- Urinalysis - heavy proteinuria suggests glomerular disease. Haematuria may suggest kidney inflammation if taken before catheterisation. Urine infection can complicate the picture.
- Ultrasound - immediately diagnoses/excludes obstruction, identifies chronic scarring, missing kidneys etc.
- Chest X-ray
- Cultures of blood, urine, any wounds or drains. Infection is very common as cause and complication.
- In more detail - including additional tests if intrinsic renal disease seems likely - see Tests in acute renal failure (EdrenHandbook)

Management of established acute renal failure

1. Control intake of fluid (daily requirement if euvoalaemic = losses + 500mls ‘insensible’ loss if afebrile), sodium, potassium. Learn more about fluid prescribing.
2. Nutrition: low protein but high calories
3. Indications for dialysis or other renal replacement therapy:
   - Pulmonary oedema (urgent)
   - Severe hyperkalaemia despite medical management
   - Symptomatic, or very poor biochemical results, and unlikely to recover renal function quickly
   - Pericarditis
   - Need for high fluid intake (e.g. for nutrition) during oliguria

Dialysis: peritoneal dialysis is now rarely used in ARF. Haemodialysis may need to be given frequently (e.g. daily) in order to prevent large fluid swings and give enough biochemical clearance. Slow continuous treatments (haemodialysis or haemofiltration) are often used in an intensive care or high dependency setting. Prescribing dialysis in ARF from the EdRen Handbook.
**What do people with ARF die of?**

Without dialysis (or other type of RRT), the causes of death in acute renal failure are

1. Hyperkalaemia (info on acute management from Edren Handbook)
2. Pulmonary oedema
3. Infection - renal is an immunosuppressed state, and intravascular catheters, oedema etc put patients at great risk of bacterial infections
4. Uraemia - the malnutrition, coma, fits etc you read about in textbooks

Note that uraemia is fourth! Dialysis is a great treatment for 1 and 2 and prevents 4. Careful conservative management can prevent 1-3 and delay 4, allowing recovery to occur.

**Further info:**

- [Patient info on ATN](#)
- [Dialysis in 1959: early dialysis for acute renal failure](#)

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This page last modified 12.03.2010, 09:45 by Emma Farrell. www.edrep.org and www.edren.org are produced by the Renal Unit at the Royal Infirmary of Edinburgh. More about edrep. Please note that the information published here is primarily intended for education, not for clinical care, but it is relatively elementary, and we do make mistakes. More cautions. You might consider [making a donation](#) if you like what we do.

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Angiotensin is a short peptide hormone that causes constriction of the efferent arteriole at the glomerular leading to the increased glomerular filtration pressure. This can maintain glomerular filtration when renal blood flow drops (low blood pressure, renal artery stenosis) but drugs may paralyse this reflex. Angiotensin also has effects on many other cells and it is likely that its effects depend on these too.

### Angiotensin converting enzyme inhibitors (ACE inhibitors)

Excellent agents for hypertension in renal disease, and for proteinuria-associated renal disease:

- Effective with a low incidence of adverse symptoms
- Reduce proteinuria, regardless of cause
- Proven protective effect on renal function in renal disease with proteinuria
- Hypotensive effect potentiated by sodium restriction and diuretics

Most evidence for these benefits has come from trials in which ACE inhibitors were used at maximum or near-maximum doses.

### Problems

1. Cause a dry cough in some recipients
2. Can cause hyperkalaemia; especially
   - in combination with other drugs (e.g. potassium-sparing diuretics)
   - in patients with renal impairment
3. Can cause acute renal failure in presence of renal artery stenosis
   - if renal artery stenosis is bilateral or to a single kidney
   - more likely if combined with diuretic therapy
4. Predispose to acute renal failure if patient becomes dehydrated or infected or cardiac output or blood pressure drop.

### Choice of drug

Some are effective when given once daily. Some may be less likely to cause first-dose hypotension. However most effects are shared by all drugs in the class. Captopril was the prototype, but it needs to be given two or three times daily and has some additional side effects.

### Angiotensin II receptor type I antagonists (ARBs)

Angiotensin receptor blockers (ARBs) have similar effects and side-effects to ACE inhibitors, except that they do not cause cough. They are first-choice alternatives if ACE inhibitor-induced cough occurs, but are otherwise probably broadly comparable. They are usually more expensive. In trials in type II diabetes irbesartan and losartan were shown to be superior to other hypotensive agents, but ACE inhibitors were not directly compared.

### How to start an ACE inhibitor or ARB

- How to start an ACEI from Edren.org - GPinfo
- How to start an ACEI from the UK CKD eGuide

### Further info

- Hypertension and kidney disease
- Proteinuria
Biopsy of the kidney

This procedure is used to ascertain the nature and severity of renal disease, so that the prognosis and need for treatment may be assessed. The needle is guided by ultrasound into the renal pole. The acquired tissue is examined by microscopy and/or immunohistology.

Any pain associated with the procedure should usually be mild. There may be some bleeding around the kidney or into the urine, which in a small (<5%) proportion of patients can be severe and require observation, arteriography, and very rarely operation. For this reason 6-8h of observation post-procedure is essential and many centres require overnight admission.

Indications

- Unexplained acute renal failure (ARF)
- Chronic renal failure (CRF) with normal sized kidneys
- Nephrotic syndrome or heavy proteinuria in adults
- Nephrotic syndrome in children that is atypical or unresponsive to steroid therapy
- Haematuria with signs of renal disease

Contraindications

- Coagulation disorder or thrombocytopenia
- Uncontrolled hypertension
- Kidneys smaller than 60% of predicted size
- Solitary kidney

All of these are relative contraindications that should be balanced with possible benefits from the information that may be obtained.

Further info

Patient info about renal biopsy
Congenital disorders

Developmental disorders such as urethral valves obstructing outflow from the bladder, and congenital renal hypoplasia, are common renal disorders in infants. Reflux nephropathy is increasingly thought to be a developmental disorder and reflux is often associated with renal hypoplasia. Many of these conditions may not become apparent until later childhood or adult life, while at the other extreme some may be identified by antenatal ultrasound. The genetic and other causes of these conditions are increasingly well understood.

Urinary tract infections (UTIs)

UTIs are common in young boys as well as girls but may present in infancy with just fever. As in adults, infections may be associated with an abnormal urinary tract. Ureretic reflux is the most commonly identified phenomenon. Pyelonephritis in under-5s may lead to renal scarring, so should be investigated and prevented where possible. UTI in adults.

Minimal change nephrotic syndrome

This is such a common cause of nephrotic syndrome in childhood in western countries that usually treatment with steroids is given, and a renal biopsy only performed if there is not a typical response to treatment. In other regions, or if there are atypical features (e.g. haematuria, renal impairment), alternative diagnoses are more likely.

Acute renal failure associated with E.coli O157 infection

A minority of patients who develop haemorrhagic colitis with E.coli O157 infection go on to develop a thrombotic microangiopathy. The syndrome is caused by verotoxins released by certain enteropathogenic E.coli typically transferred by contaminated meat from infected cattle. Bloody diarrhoea with abdominal pain is followed a few days later by a fall in haemoglobin and platelet count, then hypertension, oliguria, and renal failure. This is the commonest cause of childhood acute renal failure in Western countries. In severely affected individuals, small vessel thrombosis may occur outside the kidney, particularly in the brain. The kidneys usually recover after a period of dialysis, but in some the residual damage leads to later ESRF. Patient info on HUS from Edren.

End stage renal failure

Peritoneal dialysis is generally the preferred mode of dialysis. Relatively high surface area:weight ratios make it more effective, and haemodialysis is less well tolerated, in small children. Vascular access is also more difficult to obtain in children. Transplantation is the best option, as it allows better growth and development, and dialysis is particularly difficult for most children.

Further info
Most early kidney disease is asymptomatic - people are unaware of it. It is usefully divided into stages. Symptoms are usually unimpressive before late stage 4.

The 5 K/DOQI CKD stages (KDOQI - Kidney Diseases Outcome Quality Initiative - more info from DOQI)

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR</th>
<th>Description</th>
<th>Management, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90+</td>
<td>Normal kidney function but urine or other abnormalities point to kidney disease</td>
<td>Stages 1-3 (5-10% of the population?) Need assessment, long term monitoring, control of blood pressure and CV risk factors</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mildly reduced kidney function; but must also have urine or other abnormalities (e.g. anatomical, genetic) to be classified as CKD</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>Moderately reduced kidney function</td>
<td>Few or no symptoms still</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severely reduced kidney function</td>
<td>0.2% Planning for endstage renal failure if progressive. Increasing symptoms.</td>
</tr>
<tr>
<td>5</td>
<td>14 or less</td>
<td>Very severe, or endstage kidney failure (ESRF or ESRD)</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Stage 3 CKD is common - estimates of incidence vary, but it may be round about 5% of the population, mostly elderly. Stages 1 and 2 could add nearly as many again, but this data is less reliably collected. Stage 4 is much less common, and stage 5 is uncommon.

The widespread adoption of eGFR reporting and in the UK, the QOF (quality outcomes framework) in general practice have led to many more people becoming aware that they have proteinuria or reduced kidney function. Most of these are elderly - the incidence of stage 3+ CKD rises very steeply over the age of 70 - and most never develop ESRF. The most important risk factors for developing ESRF are:

- Deteriorating function - unsurprisingly, if GFR falls with time, ESRF is more likely
- Severe of CKD - worse kidney function is more likely to deteriorate further
- Proteinuria is a strong risk factor, risk increasing with the severity of proteinuria.
- Haematuria can be an indicator of kidney inflammation
- High blood pressure - and blood pressure reduction reduces risk
- Young age - younger patients with CKD are more likely to reach ESRD

Most patients do not have these, and for them, increased cardiovascular risk is of greater immediate concern. CKD is associated with substantially increased risk of heart attacks and all kinds of cardiovascular disease, and if a patient with CKD has a cardiovascular event, or an operation, the risk of doing badly is substantially increased. Any patient with CKD should therefore have management of all risk factors attended to; this may involve blood pressure control, cholesterol/lipids, lifestyle alterations (smoking, weight, exercise), etc.

Assessment and referral guidelines use these factors to identify which patients should be referred for specialist assessment and how their risk might be assessed.

- Summary by urgency from EdREN
- The UK CKD eGuide

Preventing progression - see preventing progression in the next section on CKD 4-5 (CRF).

Early CKD is an invented disease?

Some have accused nephrologists and the renal community of scare mongering and inventing 'new diseases for healthy people' in publicity about early CKD. Average GFR falls with age, and the widespread use of the MDRD equation to report eGFR has led to many older people, especially women, being labelled CKD3. Are they abnormal? Probably most of them are (though the female preponderance has not yet been adequately explained). Imagine X-raying the hip of an 85 year old. It is quite likely to show some osteoarthritis. Is this normal, just because the hip is 85? No, it is abnormal, but if the patient is 85 it maybe isn't so surprising.

Seymour Jones and the Temple of CKD (YouTube) … misleading but entertaining. This video emphasises some of these issues - but the 'early warning' symptoms and signs it mentions are in fact late signs of CKD - late stage 4 and stage 5. Useful for students, but not useful for early detection by patients. Stages 1-3 are usually asymptomatic and often CKD 4 is too! The same applies to this great video from Taiwan (YouTube). But it's great, and it's very short too.
There are more resources on the Internet but beware lousy quality! Some resources, even paid resources, are quite poor. We can vouch for the UK CKD eGuide, you’ll learn a lot if you work through that. Kidney Research UK’s YouTube channel has some good videos on CKD. Our own additional learning resource on management of CKD in primary care is in preparation.

More pages like this
- CKD
- CRF (CKD 4-5)
- Hypertension
- Measuring renal function
- Old age
- eGFR

Childhood disease <<   >> CRF (CKD 4-5)
Chronic renal failure (CRF) implies that there is significant irreversible reduction in renal function; here we are using it to mean CKD stages 4-5 but that isn't a generally accepted convention. Common causes of CKD/CRF are:

- Circulatory problems such as renal artery stenosis
- Inflammation within the kidneys - interstitial nephritis or glomerulonephritis
- Diabetes is very important cause - diabetic kidney disease also affects glomeruli
- Urinary tract obstruction - in ureters, bladder, or below - more on obstruction
- Inherited diseases - more info on inherited/congenital diseases

Preventing progression of CKD

It is common for renal impairment to worsen slowly with time, even if the cause of damage is no longer present. There are various theories for this, including hyperfiltration stress on residual nephrons, and direct toxicity from proteinuria to the renal tubules. The following markers identify patients at greater risk of deterioration of renal function:

- Worse renal function - higher serum creatinine
- Proteinuria - the higher, the greater the risk of progression
- Hypertension - the higher, the greater the risk
- Renal biopsy shows fibrosis, or continuing inflammation
- Young age - they have longer for trouble to develop

However this process can be slowed in many cases by the following:

- Blood pressure control to stringent targets. More on BP control
- ACE inhibitors if there is proteinuria. More on ACEI
- Prevention of acidosis by treatment with bicarbonate may play a role
- Dietary restriction - the role of protein restriction is controversial. The gains is small if blood pressure control is good and ACE inhibitors are prescribed. Severe protein restriction does not retard progression in patients whose blood pressure is well controlled, but risks malnutrition. High protein intake is almost certainly a bad thing. Many nephrologists follow an intermediate course, recommending moderate protein restriction (0.6-0.8g/kg/day) but ensuring adequate calorie intake. Salt (sodium) restriction (<100mmol/d, maybe should be less) is indicated for most patients, but difficult to achieve with modern Western eating habits. Phosphate and potassium restriction may also be necessary. Further info for all on diet from Edren. Diet in the Edren Handbook

Complications of CRF

Become increasingly evident as renal function deteriorates.

- Hypertension is often an early feature. More on hypertension in renal disease
- Fluid retention commonly becomes a major problem in late renal failure, requiring large doses of diuretics.
- Anaemia can be treated by recombinant erythropoietin injections after other causes have been excluded and adequate iron stores demonstrated. This often requires intravenous iron therapy. This is not usually a serious problem until GFR falls below 20. More on anaemia.

Bone disease (renal osteodystrophy) is prevented by

- prescription of alfalcaldiol or calcitriol, vitamin D metabolites that do not require 1-alpha hydroxylation, a function normally carried out by the kidney. This controls hypocalcaemia (but may cause hypercalcaemia).
- prevention of high serum phosphate by dietary restriction and use of dietary phosphate binders such as calcium carbonate or acetate preparations, or aluminium hydroxide (risk of aluminium toxicity, now generally reserved for short-term use), or sevelamer ('Renagel'), or lanthanum carbonate. Phosphate retention is not usually a severe problem until GFR is less than 20-25.

Gastrointestinal symptoms - anorexia, progressing to nausea and ultimately vomiting - are usually late symptoms, GFR usually well below 20, and sometimes not becoming prominent until GFR <10. They may be helped by dietary modification but are often an indication that dialysis is required.

Other complications such as itching, neuropathy, pericarditis are usually late manifestations that are prevented or controlled by dialysis.

Further info

- Patient info about CKD 4/5 (EdREN)
- CKD eGuide - guidance on management of mostly stages 1-3 CKD in the community.
For some patients who are at a high risk of dying on dialysis, conservative management may provide a higher quality of life than renal replacement therapy, with little shortening of life.

Conservative management includes all usual measures to retard progression of renal disease and reduce symptoms, including particularly close attention to diet, and use of erythropoietin and other treatments to reduce symptoms.

Further info

- End stage renal failure (this textbook)
- Choice of RRT for patients
- About conservative management for patients

More about edrep. Please note that the information published here is primarily intended for education, not for clinical care, but it is relatively elementary, and we do make mistakes. More cautions. You might consider making a donation if you like what we do.

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This is a late microvascular complication of diabetes mellitus which typically appears after more than 20 years of type I diabetes. Most patients with diabetic nephropathy already have diabetic retinopathy, and many also have evidence of neuropathy. In type II diabetes it is common for subclinical diabetes to have been present for many years, so that complications may be identified at the time of diagnosis.

Patients move through characteristic phases:

- Hyperfiltration - elevated GFR (Phase 1 in diagram)
- Hypertension (still 1)
- Microalbuminuria, identified by sensitive immunoassays for albumin (dipstick tests for protein remain negative but albumin excretion >20mg/mmol creatinine) (still 1)
- Overt proteinuria (dipstick tests positive) = overt diabetic nephropathy (2)
- Nephrotic syndrome (2/3 junction)
- Progressive renal impairment. If unmodified by treatment, this can lead to ESRF over 1-2 years (3-4)

Risk factors

Not everyone gets diabetic nephropathy - about a third of patients do eventually, but there are risk factors

- Poor diabetic control
- Duration of diabetes
- Presence of retinopathy and other microvascular complications
- Race - some races have a markedly higher incidence of nephropathy
- Family history - perhaps segregating with susceptibility to hypertension and other renal diseases

Diagnosis

Other types of renal disease can occur in diabetes, but in the presence of other complications and with the characteristic progression, the etiology can usually be safely assumed. If there are atypical features then renal biopsy may be considered.

Preventing development and progression of diabetic nephropathy

Controlled trials have shown unequivocally that diabetic nephropathy can be prevented, or its progression arrested, at stages at least up to the development of abnormal renal function. Sometimes even abnormal renal function can be protected.

- Control of blood sugar reduces the risk of developing proteinuria, and stringent control can reverse microalbuminuria before overt proteinuria has developed.
- Blood pressure control reduces the rate of loss of renal function. More on hypertension.
- ACE inhibitors and ARBs reduce and in some instances abolish proteinuria. In individuals in whom proteinuria is reduced, the rate of loss of renal function is reduced, or abolished. This effect is not restricted to patients with hypertension, and exceeds the effect of blood pressure control alone. Hyperkalaemia may limit use in patients with renal impairment. Diabetics are also at increased risk of ACE inhibitor-induced deterioration of renal function in the presence of renal artery stenosis. More on ACE inhibitors
- Diet - the controversial role of protein restriction in controlling the progression of chronic renal failure is mentioned in the section on CRF - but dietary management is likely to be required. Patient info diet.

Renal replacement therapy in diabetes mellitus

The mortality of diabetics with ESRF is substantially higher than averages for other patients with ESRF, particularly because of the high incidence of other diabetic complications, notably accelerated atherosclerosis. Difficulties with fluid balance, and gastrointestinal symptoms aggravated by autonomic neuropathy, commonly lead to earlier institution of dialysis in diabetics than in other patients.

Systemic diseases such as diabetes were once considered to be contraindications to renal replacement therapies. Diabetics with many complications may still have a difficult time on dialysis, because of ischaemic limbs, ischaemic heart disease, or autonomic neuropathy, or a combination of these.
Renal transplantation leads to a much greater improvement in quality of life. The perioperative risk of transplantation is higher than for other patients, but in the medium and longer term, improved survival in transplant recipients outweighs the perioperative risks in patients considered fit for transplantation. Transplantation is not considered as an option in many type II diabetics with ESRF because of the risks associated with vascular disease and relatively short prognosis for many patients. Pancreatic transplantation carries additional risks, but also additional long term survival benefits. Many now regard combined kidney and pancreas transplantation as the treatment of choice in young type I diabetics with ESRF, although some are still excluded because of excessive risk.

Further info

Diabetic nephropathy - info for patients
A lecture on glomerulonephritis
As well as excreting the processed metabolites of the body, the kidneys also get rid of all excess fluid, salt etc that we take in over our daily requirements. Diet becomes increasingly important as renal function deteriorates, because the body becomes less able to deal with excessive intake first, and later, with the normal output of the body. Peter Quaife cartoon by kind permission of Jazz Communications, www.lightersideofdialysis.com

Deteriorating kidney function

Restrict salt; moderate protein; in late stages, phosphate and potassium often become important issues.

Where blood pressure control is possible, evidence no longer supports restricting protein below moderate levels. It does not seem to protect kidney function, and severe restriction of protein can be hazardous.

Dialysis

Salt, protein, fluid, potassium and phosphate are important to varying degrees depending on the type and frequency of dialysis, and on whether there is a little bit of residual renal function.

Transplantation

With good kidney function, it is important to eat a healthy diet to minimise cardiovascular risk.

Resources

- Patient info pages on diet on Edren - extensive and heavily used.
- Tutorial on diet in renal disease on this website
Diuretics are used in the treatment of hypertension, chronic renal failure, and the reduction of the extracellular fluid (ECF) volume in oedematous states. They act on particular segments of the renal tubule to decrease the reabsorption of sodium from the luminal fluid. Each inhibits a specific transporter in renal tubular cells.

Problems

Diuretics are usually well tolerated. However:

- Hypovolaemia is a predictable effect of over-treatment
- Hypopatraemia, hypokalaemia, metabolic alkalosis may occur.
- Hyperglycaemia, modest hyperlipidaemia, hyperuricaemia and gout may occur.
- Potassium-sparing diuretics may cause hyperkalaemia, especially in renal failure, or in combination with ACE inhibitors
- Hypersensitivity reactions, impotence, and other effects may be attributed to diuretics, but often these have other causes.
- Cramps may be a symptom of over-diuresis.

Choice and administration

Diuretics are usually given once daily, and the timing can be adjusted for social convenience. Intravenous administration is reserved for emergency treatment or diuretic resistance (see below). Thiazides are usually adequate in the treatment of mild oedema and hypertension. If hypokalaemia is a recurrent problem, a combination with a potassium-sparing diuretic may be better tolerated than continuous potassium supplementation.

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Drug</th>
<th>Major actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>THIAZIDES (Benzothiadiazines) including Metolazone, Indapamide, Chlortalidone</td>
<td>Inhibit reabsorption of NaCl in early distal tubule. Inhibit reabsorption of NaCl in proximal tubule. Inhibit some reabsorption of NaHCO₃ in proximal and distal tubules.</td>
</tr>
<tr>
<td>High</td>
<td>LOOP DIURETICS Furosemide (Frusemide) Bumetanide Torasemide</td>
<td>Inhibit reabsorption of NaCl in thick ascending limb of Loop of Henle. Increase renal perfusion.</td>
</tr>
<tr>
<td></td>
<td>K⁺-sparing Spironolactone</td>
<td>Aldosterone antagonist - inhibits Na⁺/K⁺ exchange in collecting tubule.</td>
</tr>
<tr>
<td></td>
<td>Triamterene Amiloride</td>
<td>Inhibit reabsorption of Na⁺ in collecting tubule.</td>
</tr>
</tbody>
</table>

Acetazolamide is a weakly effective diuretic that inhibits some reabsorption of NaHCO₃ in proximal and distal tubules. It is not clinically useful as a diuretic but can be used to reduce aqueous humour production (glaucoma) and to prevent mountain sickness (unlicensed indication). Thiazide-like drugs include chlortalidone (longer action), indapamide, and metolazone.

'Diuretic resistance'

In states of avid sodium retention (e.g. nephrotic syndrome or severe cardiac failure) and in some patients with renal failure, usual oral doses of loop diuretics may be ineffective.

- Check and restrict patient's intake of sodium and fluid.
- Using loop diuretics, double the dose every day or two until the maximum is reached.
- Intravenous loop diuretic may be more effective.
- Next consider adding an oral thiazide diuretic to produce 'sequential blockade', potentiating the effectiveness of the loop diuretic. There is a significant danger of over-diuresis with this combination: weigh daily, then reduce thiazide to alternate days or longer intervals until it can be stopped. Monitor electrolytes and renal function regularly.
- Monitoring of 24h urinary sodium and careful input/output charts are valuable if there is still difficulty. If high urinary sodium but no weight loss, sodium intake must be too high.

Further info

- Understanding fluid compartments of the body (tutorial)
- Fluid therapy
Glomerular filtration rate, GFR, is a measure of how fast the kidney is filtering through its 1 million glomeruli. GFR is the most useful test of overall kidney function and we have a separate section on measuring renal function. However because it is not straightforward to measure GFR directly, most of the time we use estimated GFR, eGFR, to give an approximate idea of how good kidney function is.

There are a number of ways of estimating GFR, but most of the time people mention eGFR they mean eGFR estimated using the MDRD equation, which is the best tested method. This uses age, sex, and creatinine level in a calculation. It is complex so it is usually calculated in the lab where creatinine is measured and the result returned along with the creatinine result. It can also be calculated (a little less accurately) using an online calculator, e.g. the RA eGFR calculator - but read the important info on that page, and linked from it. Here are some of the things to be aware of:

- It is an estimate not a precise measure. It is most accurate in people who are quite well and in reasonable health. People at extremes - amputees, body builders, people who have lost a lot of weight during an illness - are likely to get the least accurate results.
- It was worked out from results in white and black patients in the US. It may not be so accurate for other races.
- It's least accurate at good levels of kidney function, and gets better the worse kidney function is.
- It shouldn't be used in under-18s, in pregnancy, or relied on in acute illnesses.
- More information about eGFR from the UK CKD eGuide.

CKD stages: eGFR is used to categorise reduced kidney function into 5 CKD stages.

Prescribing: eGFR is very useful for identifying patients who might be at risk from drug overdoses because their kidneys don't get rid of the drug as fast as usual. However most drug datasheets only have instructions for adjusting dose according to creatinine clearance - so in some circumstances you may need to work that out before calculating the dose. More on measuring renal function

Improvements to come: research to identify more accurate equations, and to test MDRD and other methods with patients of different countries and races, is under way.
End-stage renal failure and renal replacement therapy

End stage renal failure (or disease; ESRF, ESRD) implies a level of renal function at which death is likely within weeks or months. Symptoms are those of severe chronic renal failure (see complications of CRF). It is not the same as CKD stage 5: the average GFR for commencing dialysis in the UK is below 10ml/min, but there is wide individual variation, and some may require renal replacement therapy (RRT) much earlier. There is no evidence of any benefit for starting dialysis earlier than currently. Treatment options include the three forms of renal replacement therapy, and conservative management:

- Haemodialysis
- Peritoneal dialysis
- Renal transplantation
- Conservative management

Transplantation tends to be limited to 'low risk' and younger patients. For some patients who are at a high risk of dying on dialysis, conservative management may provide a higher quality of life than renal replacement therapy, with little shortening of life.

Risk is related to both age and co-existing diseases. Prognosis with renal replacement therapy tends to be very good in younger patients with no other serious diseases, especially after transplantation. However even in this group, mortality from cardiovascular disease is many times higher that of the general population. Infectious causes of death are the second major problem in patients on renal replacement therapy.

High risk patients are the very elderly (over 80 years) or those of any age with two major comorbid conditions (clear evidence of coronary, cerebrovascular or peripheral vascular disease; diabetes; non-skin malignancy); or those aged 70-80y with one major comorbid disease. The median survival of the high risk group defined this way is generally under 18 months, although up to a quarter may survive >4y.

Conservative management includes all usual measures to retard progression of renal disease and reduce symptoms, including particularly close attention to diet, and use of erythropoietin and other treatments to reduce symptoms.

Further info

- Choice of RRT for patients
- About conservative management for patients

Up to top

eGFR <<

This page last modified 13.03.2010, 13:34 by Emma Farrell. www.edrep.org and www.edren.org are produced by the Renal Unit at the Royal Infirmary of Edinburgh. More about edrep. Please note that the information published here is primarily intended for education, not for clinical care, but it is relatively elementary, and we do make mistakes. More cautions. You might consider making a donation if you like what we do.

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A Quick Course on Fluid Balance and fluid prescribing

Concise revision and learning in three modules covering fluid compartments, losses-gains-requirements, and properties of solutions you can infuse

Followed by practical challenges - what should I prescribe? in clinical scenarios.

1. Learn about Body Fluid Compartments, Losses/Gains/Requirements, and What fluids can I give.

2. Then work through these cases: 'What fluids should I prescribe"

We like feedback. Send us an email

Daughter pages of this page

- Fluids basics
- Fluid cases
  - Fluid case 1
  - Fluid case 2
  - Fluid case 3
  - Fluid case 4

End-stage << Glomerulonephritis

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Glomerulonephritis implies inflammation of glomeruli but usually means just upset glomeruli. Many types are believed to be autoimmune in origin. Two ends of a spectrum:

1. Proteinuric diseases associated with damage to glomerular podocytes or mostly non-inflammatory architectural alterations to glomerular structure which upset podocytes. These cause proteinuria, which when severe causes nephrotic syndrome.
2. Diseases associated with inflammation and cell proliferation, and damage to glomerular cells and the GBM. Characterised by breaks in the GBM leading to haematuria as well as proteinuria. Severe disease may lead to rapid loss of renal function. Important examples:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy (Berger's disease)</td>
<td>Common disease with extremely varied presentation usually including haematuria and hypertension. Often slowly evolving over decades, may lead to ESRF. In young, often acute exacerbations with similarities to post-streptococcal glomerulonephritis; or occurs with Henoch-Schonlein purpura and vasculitic changes in glomeruli, skin and bowel (usually self-limiting). IgA is deposited in mesangium of glomeruli. More on IgA disease from Edren</td>
</tr>
<tr>
<td>Post-Streptococcal glomerulonephritis</td>
<td>10-14 days after Streptococcal or other infection; associated with fluid retention, hypertension and oedema, usually remits spontaneously. Diffuse proliferation of cells on renal biopsy, with immune deposits. This disorder is uncommon in prosperous countries, common elsewhere.</td>
</tr>
<tr>
<td>Small vessel vasculitis</td>
<td>Usually associated with antibodies to neutrophil granule enzymes (ANCA); may cause aggressive but treatable nephritis, can be associated with severe vasculitis affecting lungs and other organs. More info from Edren.</td>
</tr>
</tbody>
</table>

There are many other causes of glomerulonephritis. Many occupy the middle ground between the two presentations (nephrotic and nephritic) presented above.

Further info

- What I tell my patients about glomerulonephritis (pdf file from the British Journal of Renal Medicine)
- The spectrum of glomerulonephritis (tutorial/lecture)
- Glomerulonephritis for patients
- Crescentic nephritis from Edren

Up to top
Anaemia is almost universal in renal impairment – [renal anaemia page]

Microangiopathic Haemolytic anaemia blood films (diagrammatic): normal on left, and showing red cell fragments and reduced platelets on the right. See foot of the page for an illustration of how this occurs.

Thrombotic microangiopathy – these diseases are associated with platelet thromboses in small blood vessels and consequent thrombocytopenia. Damage to endothelium is a common factor. Other coagulation tests are not usually abnormal. Blood films show red cell fragments thought to be a consequence of damage in small vessels (microangiopathic haemolytic anaemia, MAHA; see diagram to the left). There is considerable overlap, but two major clinical patterns are recognised.

- In Thrombotic Thrombocytopaenic Purpura (TTP) haematological and central nervous system manifestations are prominent, renal disease not usually as severe. Deficiency of von Willebrand protease has been identified in some examples of TTP.
- In Haemolytic Uraemic Syndrome (HUS) renal disease is prominent. Most commonly occurs in association with bloody diarrhoea caused by verotoxin-producing E.coli (D+ HUS). Familial susceptibility may be associated with complement abnormalities (e.g. partial deficiency of Factor H): in familial cases, recurrence after renal transplantation is common.

Causes of HUS/TTP

- Pre-eclampsia/ post-partum
- Graft versus host disease after bone marrow transplantation
- Drugs – quinine, cytotoxic agents, others
- Verotoxins produced by some E.coli (e.g. O157)
- Inherited - complement abnormalities

Malignant hypertension may cause a clinically similar picture, and the appearance of glomerular capillaries on renal biopsy is also similar. However larger vessels often show hypertensive changes too. The renal lesion of systemic sclerosis is identical. [Patient info on systemic sclerosis (scleroderma)].

Disseminated intravascular coagulation (DIC) – consumption of coagulation factors leads to thrombosis and haemorrhage in microvasculature. Management involves maintaining haemostasis, replacing clotting factors if essential and treating the underlying condition

Myeloma and B cell dyscrasias (dysproteinemias) – may affect the kidney in several ways:

- Hypercalcaemia
- Cast nephropathy – ‘myeloma kidney’
- Amyloidosis (AL amyloidosis caused by deposition of free light chains, see below)
- Deposition diseases (rare, caused by deposition of immunoglobulin fragments)

Myeloma is a B cell neoplasm in which there is usually overproduction of a monoclonal immunoglobulin. It causes lytic bone deposits and hypercalcaemia, bone marrow suppression, and if free light chains are overproduced they can precipitate in tubules and be toxic to tubular cells (cast nephropathy). Renal failure may be the first manifestation. Characteristically it occurs after exposure to radiological contrast media, but more often renal impairment is identified during investigation of non-specific symptoms. As in other tubulointerstitial disorders, clinical findings are minimal. Urine analysis by immunoelectrophoresis or other tests for ‘Bence Jones’ protein are required.

Amyloidosis is caused by highly structured, fibrillar aggregation of certain proteins, either:

- normal proteins present in excess, or
- proteins of abnormal sequence, giving rise to uncommon genetic causes

This leads to deposition in various tissues according to the protein, but the kidney is affected by the common types. The deposits take up the histological staining reagent Congo Red, with a characteristic apple-green colour under polarised light. Three common types of amyloid in renal patients:

- AL amyloid, caused by excess production of some immunoglobulin light chains in myeloma or in a monoclonal B cell proliferation short of overt myeloma.
- AA amyloid, caused by excess production of serum amyloid A (SAA) protein in chronic infections or inflammation, such as long term arthritis. SAA is an ‘acute phase reactant’ like C-reactive protein (CRP) in inflammation.
- Dialysis amyloid, caused by reduced excretion of beta-2 microglobulin. Exclusive to dialysis patients, in whom it causes joint and musculoskeletal symptoms.
Microangiopathic Haemolytic Anaemia (Beth Shortt)
Haematuria may be caused by pathology of any part of the urinary tract. Blood may make the urine red or dark brown. Dipstick tests are very sensitive, identifying much smaller quantities of blood than can be seen with the naked eye.

Causes of haematuria

Not haematuria:
- menstruation
- dyes in food/medicines can cause red urine (dipstick testing negative)
- strenuous exercise may cause transient haematuria

Pathology:
- Urinary tract infections (UTI)
- Renal stones
- Tumours of the bladder or collecting system
- Kidney tumours and cysts
- Prostate gland disease
- Glomerulonephritis (proteinuria, hypertension and abnormal kidney function may also be present)

Investigation
- Dipstick test for urinary protein, consider testing for albumin
- Urine microscopy and culture (or FACS analysis)
- Blood pressure measurement
- Blood tests for renal function, blood count

Urological pathway (for stones, cancer) - favour if the patient is over 40, or has macroscopic haematuria, and lacks 'renal pathway' signs:
- Ultrasound scan of kidneys and urinary tract
- Cystoscopy
- Intravenous urogram if high risk of lesion in ureters/collecting system (e.g. macroscopic haematuria, or risk factors present)

Renal pathway (for glomerulonephritis etc) - favour in younger patients, and consider if there are any or many of:
- Hypertension
- Proteinuria
- Renal impairment (without urinary symptoms to suggest obstruction)

A past history or family history of renal disease may also influence you. Macroscopic haematuria may occur, almost always in the presence of one or more of the three features above, but in general is more likely from urological causes. Renal biopsy may be indicated. Microscopic haematuria alone carries a low but not zero risk of significant underlying renal disease and some may prefer a renal biopsy in these circumstances.

If all investigations are negative

If no cause is found and haematuria continues, regular monitoring (usually every 6 extending to 24 months) of urine protein, blood pressure and serum creatinine is all that is required. Reconsider if anything changes.

Further info

- EdRen patient info on haematuria
- GP info on microscopic and macroscopic haematuria

Up to top
Haemodialysis

Haemodialysis involves the blood of a patient being passed into a dialyser, where it interfaces with dialysate across a semi-permeable membrane. Dialysate has a similar content of salts (sodium, chloride, calcium, magnesium) to plasma, so most small molecules diffuse across the membrane into the dialysate. Fluid can be removed by applying a negative pressure on the dialysate side (ultrafiltration).

Anticoagulation with heparin prevents the extracorporeal blood from clotting. Good vascular access (best of all, a subcutaneous arteriovenous fistula involving no synthetic material) is necessary for effective and safe treatment.

Most patients with end stage renal failure (ESRF) require three sessions of haemodialysis per week, each lasting 3-5 hours, depending on the patient’s size, residual renal function, and the efficiency of the process. As this is an intermittent treatment, limitations on fluid, sodium, and potassium intake are often necessary. More frequent and/or longer treatments may be beneficial – though more laborious for the patient.

Methods for assessing the adequacy of haemodialysis have focused on small molecule clearance, which can be predicted and measured relatively easily. Urea Reduction Ratio (ratio of blood urea before and after dialysis) and a calculated parameter Kt/V are commonly used (K is a dialyser-specific figure for rate of urea clearance; t is duration of dialysis; V is the volume of distribution of urea in a patient). There is continuing controversy over the best way of assessing adequacy of treatment; duration of dialysis also appears to exert a significant effect. (Further information on measuring haemodialysis adequacy, but use also haemodialysis specialist pathway).

Patients on dialysis remain at risk of most of the complications of renal failure plus some additional ones.

Routine (e.g. monthly) monitoring of biochemical parameters before and after dialysis is usual. In addition there will be monitoring of blood count, and usually liver function tests. Less frequently virology samples will be sent to screen for infections that may be transmitted by blood (e.g. hepatitis).

Prognosis depends on age and comorbid diseases (further info).

Problems associated with intermittent haemodialysis

Haemodialysis requires complex machinery and skills that are usually only available in a hospital or similar specialist setting – although some relatively healthy patients are able to learn to dialyse themselves at home. The treatment is very time consuming, and travel is difficult. Post-dialysis symptoms, including fatigue, are common, sometimes leaving relatively few ‘good days’ each week. These symptoms tend to be worse in patients with serious comorbid conditions.

During treatment, hypotension is common because of the need to remove fluid at each treatment. Muscle cramps have similar etiology; both tend to be worse in patients who do not comply with fluid and sodium restrictions and in whom it is therefore necessary to remove more fluid in each treatment. Dialysis-related symptoms are also more likely in patients with cardiovascular disease.

The sick dialysis patient

This information is relevant to all but is particularly aimed at those who may see patients away from a renal unit.

Seek help. It is always appropriate to consult the patient’s renal unit about their management if you are at all uncertain about the relevance of their renal
failure. If it is a cardiovascular problem or possibly related to their dialysis treatment, emergency consultation is usually appropriate. All renal units will have a system for 24 hour availability of advice and assistance. Admission to hospital for non-renal indications should be immediately notified to their renal team.

**Potassium** and other electrolytes may be upset by coincident illnesses and should always be checked if a dialysis patient is unwell. Treat [K] > 7.0 medically (further info) and consult renal unit urgently.

**Fluid overload** closely resembles heart failure, but may also be easily confused with pulmonary disease. There is elevated jugular venous pressure and/or may be clinical or radiological signs of pulmonary oedema. Typically a crisis occurs just before dialysis is due, or at a weekend when there is a longer interval between dialyses, or when they have missed treatment. It cannot usually be effectively treated with diuretics as these require functioning kidneys: dialysis is usually necessary.

**Fluid management** is critical in dialysis patients in hospital. Remember that their normal daily fluid requirements are only output plus 500mls, and that 1 litre of isotonic saline far exceeds their normal daily sodium restriction, if there are no deficits or increased losses. A fluid restriction of 1 litre daily is common.

**Infection** is a leading cause of death in patients on dialysis. Bacterial infections of all types seem to be increased in incidence, but there is a particular risk of infections related to vascular access sites or devices in patients on haemodialysis. *Always send blood cultures from a sick dialysis patient.* Consult the renal unit before giving blind antibiotic therapy; but if patient has artificial vascular access device, include cover for organisms likely to be associated with indwelling catheters (particularly coagulase negative and positive Staphylococci). First doses of many antibiotics are unchanged for patients with renal failure, but dosage interval may be very substantially prolonged.

**Anticoagulation** - residual unfractionated heparin is likely to be present for a few hours after haemodialysis, but patients with renal failure also have a bleeding tendency. If low molecular weight heparins or other anticoagulants have been used, their half lives may be much longer. Do not use full-dose low molecular weight heparin or other new anticoagulants without seeking advice first.

**Further info:**

- Patient information about haemodialysis
- Patient info about ESRF treatment options
- Edrep Haemodialysis learning pathway

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**Haematuria** <<

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**Further info:**

- Patient information about haemodialysis
- Patient info about ESRF treatment options
- Edrep Haemodialysis learning pathway
HIV and the kidney

HIV may affect the kidney directly, as may other infections that people with HIV sustain, including Hepatitis viruses and bacterial and other infections. The components of anti-HIV therapy (HAART, Highly Active Anti-Retroviral Therapy) may be nephrotoxic. Reduced GFR is more common in patients with HIV infection, but this is may not be directly related to the HIV virus, but contributed to by the increased prevalence of features of the metabolic syndrome (diabetes, hypertension and dyslipidaemia) that is seen with HAART.

Classic HIV nephropathy is a 'collapsing' type of FSGS that occurs almost exclusively in those with black African ancestry. This susceptibility has been linked to the MYH9 gene. HIV-associated FSGS typically presents with proteinuria, nephrotic syndrome and progressive renal impairment. It is a feature of advanced HIV infection with high viral load and low CD4 count, but is is commonly a presenting feature of HIV infection. The nephropathy appears to respond to HAART if treated early, but may cause ESRF. ACE inhibitors and blood pressure control are as important as they are in all glomerular diseases.

Other glomerulopathies of diverse types have an increased in incidence in HIV infection, and are a more common diagnosis in non-black races. These are often associated with immune deposits and where they do not clearly fall into a clear other diagnostic category they may be termed HIV-ICK, HIV Immune Complex Kidney disease. This may be related to infection with HIV itself or to coinfection with other organisms, while some may be autoimmune in etiology. HAART is a logical response in addition to ACE inhibition and blood pressure control.

Drug effects - several anti-HIV drugs are known to be nephrotoxic. Indinavir is prone to form crystals, and acute crystalluria can cause acute renal failure. Tenofovir and others are associated with interstitial renal disease, and tefofivir may cause damage to proximal tubules leading to renal Fanconi syndrome (low phosphate caused by phosphaturia, along with glycosuria with normal blood sugar, and amino aciduria).

Other issues

Patients in low-resource environments with HIV often have reduced GFR and are at risk of incorrect dosing of all drugs, and of side effects with some anti-HIV drugs.

Renal replacement therapy by dialysis and/or transplantation can be successful in patients in whom HAART has successfully lowered viral titres and allowed recovery of CD4 counts.

Acknowledgements: The authors of this page were Neil Turner and Bryan Conway. It was first published in March 2010.
Hypertension and renal disease

Hypertension is important in renal disease for three reasons:

- Renal disease often causes hypertension
- Hypertension can cause further damage to impaired kidneys - it accelerates deterioration of renal function
- Hypertension with renal disease strongly predisposes to cardiovascular disease

Hypertension occurs in about 80% of patients with chronic renal failure, due to sodium (and therefore fluid) retention and often hypersecretion of renin. If there is renovascular disease, reduced renal perfusion may exacerbate the hypertension.

Management

Randomized controlled trials in patients with renal disease show that lowering blood pressure can protect renal function, especially in patients with proteinuria. Blood pressure targets are set lower than for many other patients, especially if there is proteinuria. The target should be individual to the patient depending on circumstance, but guideline levels are as follows:

- 140/90 max (130-139 systolic target) in patients with CKD, unless they justify lower targets:
- 130/80 max (120-129 target) if proteinuric: ACR>30 or PCR>50

(These targets are 2009 NICE/SIGN and other limits. The second blood pressure limit is slightly higher than previously, but the threshold for applying it has been lowered)

**ACE inhibitors** are more effective than other agents in patients with proteinuria. Angiotensin receptor blockers (ARBs) are probably equally effective. In diabetics (and arguably other patients with CKD) with increased albumin excretion, ACEI/ARB should be titrated up to maximal dose regardless of blood pressure.

Malignant hypertension

Presents with headache, impaired vision, and features of HUS. Very high blood pressure is associated with changes to small blood vessels in the retina causing haemorrhages and exudates, and with swelling of the optic disc. Similar changes in the kidney lead to glomerular capillary occlusion and thrombosis and rapid deterioration in renal function. Treatment of hypertension can reverse some of the damage. Malignant hypertension is more likely to occur in secondary hypertension than in primary, but primary hypertension is more common, so a cause may not be apparent.

Benign hypertensive nephrosclerosis

Although hypertension is often used as an explanation for renal disease, there is little evidence that it is often a primary cause. The histological changes labelled as benign hypertensive nephrosclerosis correlate poorly with blood pressure and may have other aetiologies.

Further info

- Patient info on high blood pressure and the kidney
- EdRen handbook on hypertension
- UK CKD eGuide on hypertension
Infection and renal disease

Infections causing renal disease

Post-infectious glomerulonephritis, classically occurring 10 days after a Streptococcal infection, is now uncommon in the developed world. More commonly glomerulonephritis is associated with current infection, notably bacterial endocarditis. Various infections (leptospirosis, viral infections) may cause a tubulointerstitial nephritis.

Infections in patients on dialysis

Infections are the second most common cause of death in patients on long-term dialysis, after cardiovascular disease. Some of these are related to dialysis access, but many are common bacterial pneumonias and other infections. Patients with ESRF have multiple defects in leukocyte and immune function, including responses to vaccines. Tuberculosis is increased in frequency in the dialysis as well as the transplant populations.

Infections in patients after renal transplantation and on treatment with immunosuppressive drugs

Early after renal transplantation there is a risk of Pneumocystis pneumonia, and various viral infections (notably the herpesviruses, including Epstein Barr virus and CMV) are both more frequent and more severe. Viral infections probably account for much of the increase in lymphoma and cervical malignancy, and perhaps some other tumours, in transplant patients.

Further info

Postinfectious glomerulonephritis in Glomerulonephritis tutorial
Polycystic kidney disease

Polycystic kidney disease (PKD) is the commonest inherited disease causing end stage renal failure (ESRF), and accounts for up to 8% of patients on RRT programmes. The major variety is an autosomal dominant disorder (ADPKD) said to affect 80/100,000 of the population. The kidneys become slowly enlarged and contain many fluid-filled cysts. There may be hypertension, haematuria, abdominal discomfort, or no symptoms at all.

Only about 50% of individuals with PKD1 mutations progress to ESRF, and those with mutations in PKD2 tend to have milder disease with less and later renal failure.

Cysts may not be detectable by ultrasound until affected individuals are in their 20s or even later. There may also be hepatic cysts, and there is also an increased incidence of subarachnoid haemorrhage and some other abnormalities. Cysts may bleed and become infected, and there is an increased incidence of renal stones and UTIs.

No management strategy has yet been shown to affect the rate of renal deterioration, though drug trials are commencing. Hypertension should be treated. Patients with PKD do well on dialysis and after renal transplantation, but if kidney enlargement is massive, nephrectomy is sometimes required to make space for transplantation.

Alport syndrome

The second most common inherited cause of kidney failure, usually X-linked and affecting young men. Autosomal recessive disease may also occur and is clinically indistinguishable. Caused by mutations in any of three tissue-specific basement membrane collagen genes. These collagens are an important part of glomerular basement membrane (GBM) and the cochlea. Their genes are called COL4A5 (X chromosome), COL4A3 and COL4A4.

Typically affected males develop progressive haematuria, proteinuria, then renal failure and deafness in their teens, and ESRF in their twenties. Carriers often have haematuria and the renal biopsy finding of a thin GBM. A proportion of carriers may develop serious renal disease in later life.

Renal hypoplasia

There are many other inherited renal disorders, but the largest group comprises conditions in which renal development is incomplete or imperfect. Unilateral renal agenesis (having a single normal kidney) is quite common and asymptomatic. If the kidney is normal, it will hypertrophy as you grow and provide adequate renal function. If it's damaged, it may not. Renal hypoplasia overlaps with other developmental or structural disorders, notably reflux nephropathy.

Further info

- Patient info on PKD
- Patient info on Alport syndrome
- Genetics from Medpedia. The videos are excellent, but the article is good too.
- A primer on genetics from the Wellcome Trust's human genome pages: see the individual links to dominant, recessive and X-linked diseases, and more.
Diuretics are used in the treatment of hypertension, chronic renal failure, and the reduction of the extracellular fluid (ECF) volume in oedematous states. They act on particular segments of the renal tubule to decrease the reabsorption of sodium from the luminal fluid. Each inhibits a specific transporter in renal tubular cells.

Problems

Diuretics are usually well tolerated. However:

- Hypovolaemia is a predictable effect of over-treatment
- Hyponatraemia, hypokalaemia, metabolic alkalosis may occur.
- Hyperglycaemia, modest hyperlipidaemia, hyperuricaemia and gout may occur.
- Potassium-sparing diuretics may cause hyperkalaemia, especially in renal failure, or in combination with ACE inhibitors
- Hypersensitivity reactions, impotence, and other effects may be attributed to diuretics, but often these have other causes
- Cramps may be a symptom of over-diuresis.

Choice and administration

Diuretics are usually given once daily, and the timing can be adjusted for social convenience. Intravenous administration is reserved for emergency treatment or diuretic resistance (see below). Thiazides are usually adequate in the treatment of mild oedema and hypertension. If hypokalaemia is a recurrent problem, a combination with a potassium-sparing diuretic may be better tolerated than continuous potassium supplementation.

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Drug</th>
<th>Major actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>THIAZIDES (Benzothiadiazines) including Metolazone, Indapamide, Chlortalidone</td>
<td>Inhibit reabsorption of NaCl in early distal tubule. Inhibit reabsorption of NaCl in proximal tubule. Inhibit some reabsorption of NaHCO3 in proximal and distal tubules.</td>
</tr>
<tr>
<td>High</td>
<td>LOOP DIURETICS Furosemide (Frusemide) Bumetanide Torasemide</td>
<td>Increase renal perfusion. Inhibit reabsorption of NaCl in thick ascending limb of Loop of Henle.</td>
</tr>
<tr>
<td></td>
<td>K+-sparing Spironolactone</td>
<td>Aldosterone antagonist - inhibits Na+/K+ exchange in collecting tubule.</td>
</tr>
<tr>
<td></td>
<td>Triamterene Amiloride</td>
<td>Inhibit reabsorption of Na+ in collecting tubule.</td>
</tr>
</tbody>
</table>

Acetazolamide is a weakly effective diuretic that inhibits some reabsorption of NaHCO3 in proximal and distal tubules. It is not clinically useful as a diuretic but can be used to reduce aqueous humour production (glaucoma) and to prevent mountain sickness (unlicensed indication). Thiazide-like drugs include chlortalidone (longer action), indapamide, and metolazone.

'Diuretic resistance'

In states of avid sodium retention (e.g. nephrotic syndrome or severe cardiac failure) and in some patients with renal failure, usual oral doses of loop diuretics may be ineffective.

- Check and restrict patient’s intake of sodium and fluid.
- Using loop diuretics, double the dose every day or two until the maximum is reached.
- Intravenous loop diuretic may be more effective.
- Next consider adding an oral thiazide diuretic to produce ‘sequential blockade’, potentiating the effectiveness of the loop diuretic. There is a significant danger of over-diuresis with this combination: weigh daily, then reduce thiazide to alternate days or longer intervals until it can be stopped. Monitor electrolytes and renal function regularly.
- Monitoring of 24h urinary sodium and careful input/output charts are valuable if there is still difficulty. If high urinary sodium but no weight loss, sodium intake must be too high.

Further info

- Understanding fluid compartments of the body (tutorial)
- Fluid therapy

Up to top
Inflammation within the kidney predominantly affecting tubules. Often seen in conjunction with glomerulonephritis, but then usually regarded as secondary to the glomerular disease. Acute interstitial nephritis is uncommon but important, as prompt therapy can save renal function.

**Recognition**

Often difficult as there may be minimal or no symptoms, and minor urine dipstick abnormalities. Urine often contains white blood cells. Blood tests show renal impairment.

**Causes**

- **Allergic** - the commonest cause is an allergic reaction to a drug, particularly non-steroidal anti-inflammatory drugs (NSAID) or antibiotics, or proton pump inhibitors (PPIs). Variable time after commencement. Usually responds to withdrawal of the drug and treatment with corticosteroids, which may need to be continued for some weeks.
- **Immune** - as a part of a multisystem autoimmune disease or alone. It is a major feature of renal transplant rejection.
- **Toxic** - a number of toxins can do this. The commonest is immunoglobulin light chains, produced in excess in myeloma. These are filtered freely at the glomerulus but may prove toxic to tubular cells which reabsorb them. Others include heavy metals and plant and fungal toxins.
- **Infective** - acute interstitial nephritis may be seen in a number of viral and other infections. The presence of large numbers of neutrophils in and around tubules suggests active bacterial infection - pyelonephritis.

**Further info**

Patient info on interstitial nephritis (Edren)
Measuring renal function

Normal value for glomerular filtration rate (GFR) = 120 +/- 25 ml/min (males 125, females 115)

**Urea** blood test measured in a ‘U+E’ or urea and electrolytes) is a poor indicator of GFR as it varies with protein intake, liver function (it is generated in the liver) and state of hydration. More is reabsorbed from the renal tubules when urine is highly concentrated, and less during polyuria.

Causes of high urea:
- Dehydration
- Renal failure
- GI bleeding (=large protein meal)

**Creatinine** is more reliable as it is produced by muscle at a constant rate (dependent on muscle mass) and is almost entirely filtered at the glomerulus. However its serum levels may not rise out of the normal range until substantial renal impairment exists – normal values can conceal a reduction of up to 50% in GFR.

**Creatinine clearance** (CrCl; from a 24h urine collection) measurement can circumvent this problem, but 24h urine collections are inconvenient and of variable reliability. CrCl tends to overestimate true GFR when renal function is poor. The Cockcroft-Gault formula estimates creatinine clearance from serum creatinine values (multiply by 0.85 for females because of relatively lower muscle mass):

\[
(140 - \text{age}) \times \text{weight} \times 1.23 \times (0.85 \text{ if female})
\]

Creat[micromol/l]

More info on Cockroft-Gault from the EdRen Handbook

**eGFR** More accurate predictors of GFR than this exist now. The best tested is the MDRD equation to calculate estimated GFR (eGFR) using serum creatinine, age, sex. It is very widely used and reported so we have a separate page on it. More info from the edrep page on eGFR

Direct measurement of GFR Isotope tests or compounds such as inulin are used to measure GFR more directly. Markers (e.g. 51Cr-EDTA, 99Tc-DTPA) that are cleared almost entirely by glomerular filtration are infused, and their rate of disappearance from the circulation measured.

Reciprocal of creatinine plots

Plots of the reciprocal of creatinine show how the plasma creatinine concentration changes with time. Declining renal function often follows a linear progression on these charts, but in fact a graph of eGFR will show just the same info if you have those values too. These are useful for predicting an approximate date of ESRF, and to identify changes in the rate of progression.

Blank charts for plotting creatinine changes can be downloaded from the Edren handbook page on measuring GFR

Further info

- Edren handbook page on measuring GFR
- edrep page on eGFR
Nephrotic syndrome

Usually defined as proteinuria >3.5g/day with hypoalbuminaemia and oedema. Some definitions vary a little around exact values. Serum albumin levels are low because of the urinary protein loss. This leads to avid sodium and fluid retention by the kidneys, seen symptomatically as oedema.

Causes

These are mostly conditions in which there is podocyte (glomerular epithelial cell) damage or non-inflammatory architectural alterations of the glomerulus, such as that caused by matrix expansion associated with diabetes, or by scarring. Subacute inflammatory (nephritic) types of glomerulonephritis may cause nephrotic syndrome through causing scarring in the glomerulus. Most important causes of nephrotic syndrome:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal segmental glomerular sclerosis (FSGS)</td>
<td>Focal scars in glomeruli. Variable response to steroids. May progress to renal failure.</td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>Usually idiopathic (autoimmune); sometimes due to drugs, rarely malignancy. May progress to renal failure in up to 30%; immunosuppression may halt progression if function deteriorating.</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>After long history of diabetes and with other microvascular complications.</td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Most types cause renal disease (usually nephrotic syndrome) as an early manifestation.</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Young women usually. May present in many ways but sometimes as renal disease alone.</td>
<td></td>
</tr>
</tbody>
</table>

Complications

- Susceptibility to infection
- Increased risk of venous thrombosis
- High cholesterol – often extreme (>10 mmol/L)

Investigation

Renal biopsy often required unless obvious (e.g. long history of diabetes with other complications and typical evolution and features). Minimal change disease usually assumed in children, unless fails to respond to steroids.

Management

- Diet - control salt intake
- Loop diuretics - to control salt and water retention
- ACE inhibitors - to control blood pressure, reduce proteinuria
- Anticoagulation - if immobilised, or thrombosis has occurred
- Lipid lowering - consider statin if syndrome persistent

Further info

- Patient info on Nephrotic syndrome
- Tutorial on glomerulonephritis
- Edren handbook on Nephrotic syndrome

Wordle
Measuring renal function <<

Obstruction >>

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Obstruction of the urinary tract causes urinary stasis and back pressure in the tract – this may lead to infection, calculus formation and renal failure. It is caused by an anatomical lesion or a neuromuscular defect. Obstruction may occur at any level:

Pre-bladder lesions present with renal colic if the onset is sudden, aching loin pain if gradual, or (commonly) with no symptoms. Infection is common and causes malaise, fever, dysuria and sometimes haematuria. Partial obstruction may result in paradoxical polyuria. Complete obstruction causes complete anuria.

**Investigation**

Renal function will only be severely altered if obstruction affects both kidneys (or a single functioning kidney). Rectal/vaginal examination may reveal enlarged prostate or pelvic tumour. Ultrasound detects dilatation of collecting system. Bladder, urethral and lower ureter lesions may be shown by cytoscopy, but CT scanning or MRI, and antegrade or retrograde pyelography, are often required if obstruction affects ureters. Urine cultures should always be performed.

**Management**

The aim is to remove the obstruction, but temporary relief by catheter drainage (e.g. nephrostomy) is often necessary first. Infection should be treated. Infection above an obstruction requires urgent drainage. Post-obstructive diuresis may require parenteral fluid replacement to prevent hypovolaemic renal failure.

**Further info**

- [Obstruction from Edren](http://www.edrep.org/pages/textbook/obstruction.php)
Old age and the kidney

Advancing age is often associated with a slow reduction in GFR (glomerular filtration rate), but also with a reduction in muscle mass, so that there is little change in serum creatinine. In the frail elderly, significant renal impairment can therefore be concealed by normal or slightly high serum creatinine levels. eGFR reporting has led to much greater recognition of subclinical CKD in the elderly. The fall in average GFR with age is probably not 'normal'; it probably reflects increasing incidence of diseases affecting the kidney. In developed societies, vascular disease is probably a major contributor.

Rise in incidence of ESRF

The rate of ESRF rises dramatically with age, mainly through an increase (in the developed world) in renovascular disease/atherosclerosis, and in 'etiology unknown'. However some important reversible causes of renal failure are particularly common in the elderly, including:

- Obstruction
- Drug-related
- Small vessel vasculitis

Treatment

Old age itself is not a bar to doing well on dialysis, though the very elderly are usually excluded from transplantation because of increased risk of the procedure and of immunosuppression. Survival on dialysis is adversely affected by age, and also by comorbid disease, so that the prognosis for elderly patients with two major comorbid conditions (e.g. diabetes and peripheral vascular disease) may be relatively short. Such patients often tolerate dialysis poorly and so may elect to have conservative care.
Oedema

Oedema can be local or general. Generalised oedema presents commonly in the ankles in adults, but may also be evident as ascites, pleural effusion, or as facial swelling. Diagnosis is from history and examination of the cardiovascular and gastrointestinal systems, and urine test for protein and blood for serum albumin. Generalised oedema implies expanded extracellular fluid volume and sodium retention.

Mechanisms

**Increased extracellular fluid**

Total extracellular fluid volume may be increased in a number of conditions. Sodium retention by the kidney is usually the major cause. Here are some examples:

- Heart failure
- Renal failure
- Low albumin conditions -
  - Nephrotic syndrome
  - Liver failure
  - Others
- Administration of too much salt in hospital - e.g. too much saline infusion. Usually in combination with one of the above causes of reduced excretion.

**Increased Hydrostatic Pressure**

Increased hydrostatic pressure in the veins or lymphatics reduces fluid return to the circulation. This is commonly local (e.g. after a venous occlusion by thrombus or lymphatic occlusion by tumour), but may be general (e.g. in heart failure).

**Generalised**: Venous pressure is generally high in heart failure or in volume (or sodium) overload.

**Local**: venous pressure will be raised by DVT or venous insufficiency, or by extrinsic obstruction such as pregnancy or tumour. Lymphatic obstruction may cause a non-pitting, localised oedema (known as lymphoedema when chronic). This occurs with some infections (e.g. filariasis), malignancy, radiation injury, or as a congenital abnormality.

**Increased Capillary Permeability**

Proteins leak into the interstitium, thus reducing the osmotic pressure gradient that draws fluid into the blood and lymphatics.

- Locally with infection or inflammation
- Systemically in severe sepsis

**Lowered Oncotic Pressure of Blood**

There is low serum albumin due to reduced synthesis or increased loss. Associated with avid sodium retention by the kidney - the problem is probably never purely a problem with oncotic pressure.

- Liver failure (prominent ascites); reduced synthesis of albumin
- **Nephrotic syndrome** (heavy proteinuria); increased loss of serum proteins
- Malnutrition/malabsorption; reduced synthesis

All cause generalised oedema which tends to be worse in dependent regions. In children, and those with liver disease, ascites tend to occur early.

Management
Management of generalised oedema is by use of diuretics, along with salt (and fluid) restriction. However if the cause is local, this will lead to hypovolaemia.

Compression devices (e.g. stockings) are used for local relief.

**Common errors**

- Oedema with hyponatraemia - whole body sodium is increased, treatment with saline is not usually appropriate.
- Ankle oedema may not be due to a generalised problem. Check JVP if you suspect heart failure. Diuretics in the absence of generalised fluid retention causes dehydration (desalination, really).
- Excessive sodium administration - where is it coming from? Look out for hidden and unexpected sources such as high salt snacks, effervescent drug preparations.

**Cases to test your knowledge**

- (Malawi) A 2 year old girl with generalised oedema
- (Malawi) A 30 year old man with a swollen leg (in preparation)

These cases are from the Medical Education Malawi-Edinburgh project. They should open in a new window/tab. More cases like this (link to follow, Moodle site or similar).

Up to top
Renal osteodystrophy refers to the complex combination of skeletal abnormalities that develops in patients with longstanding chronic renal failure, with the potential to cause fractures and deformities. Management seeks to prevent these from occurring. Contributing elements include:

**Osteomalacia**

Osteomalacia - incomplete bone calcification caused by vitamin D deficiency. Rickets in children.

Caused by failure of the 1α-hydroxylation of vitamin D to form 1,25 dihydroxycholecalciferol, a step that usually occurs in renal tubular cells. Prevented by administration 1α-hydroxylated derivatives of vitamin D, (alfacalcidol or calcitriol). This raises serum calcium and also directly suppresses PTH secretion.

**Hyperparathyroidism**

Increased secretion of parathyroid hormone (PTH) is driven by hypocalcaemia (in part due to effective vitamin D deficiency) and high serum phosphate (as renal excretion is reduced). After some years, responsiveness of PTH to lowered phosphate and raised calcium levels is lost (tertiary hyperparathyroidism). Prevention is through control of calcium (see below) and phosphate levels (dietary modification and ingestion of phosphate binders such as calcium carbonate or acetate with food). Calciumsensor agonists are a more recent innovation.

**Adynamic bone disease**

Recognised more recently. Thought to be at least partially due to over-suppression of PTH by excessive use of vitamin D therapy. In the past aluminium toxicity (from dialysis and use of aluminium hydroxide as a phosphate binder) may have contributed to this.

This unusual combination of features makes standard methods for assessing bone density of very uncertain value in patients with chronic renal failure.

**Further info**

- Renal bone disease - info for patients
- Renal osteodystrophy in the Edren handbook

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Peritoneal dialysis (PD) uses the peritoneum as the semi-permeable membrane for dialysing the blood. A catheter is used for peritoneal access. (Illustration by Jan Smith from a leaflet produced by the Nottingham Childrens Renal Unit.) Solutes pass from the blood into the dialysate along their concentration gradient, and water by an osmotic gradient created by adding glucose or a polymer to the dialysate. Watch an animation

Continuous ambulatory peritoneal dialysis (CAPD) typically involves 4 two-litre fluid exchanges daily, with fluid left in constantly. They are usually 4-6 hours apart with a longer gap overnight. Each bag change takes 30-40 minutes. Automated peritoneal dialysis (APD) occurs for 8-9 hours overnight whilst the patient sleeps.

The peritoneal dialysis catheter (Tenckhoff catheter) is usually placed under general anaesthetic. After an interval the patient begins training to undertake dialysis at home. Laparoscopy can be used. Local anaesthetic insertion is possible.

Techniques for assessing the adequacy of peritoneal dialysis are controversial. Survival appears to be most strongly correlated with residual native renal function, which is better preserved in patients on peritoneal dialysis than with haemodialysis. It is difficult to provide adequate dialysis by PD for some adults with little or no residual renal function. Properties of the peritoneal membrane differ between patients, and over time in individual patients. Episodes of peritoneal infection and responses to dialysate may damage the membrane. This may lead to deterioration of control of biochemistry and fluid balance, and over a long period many patients who start treatment on peritoneal dialysis transfer to haemodialysis.

Peritoneal dialysis may be preferred to haemodialysis in the following circumstances:

- Children
- Adults who value greater independence and freedom to travel
- Patients with cardiovascular instability or risk factors

Contra-indications:

- Major abdominal surgery or peritoneal adhesions
- Inguinal hernias (unless repaired)
- Severe respiratory compromise
- Inability to perform the technique safely and hygienically

The sick PD patient

For general issues concerning sick dialysis patients (fluid management, potassium, infections etc.) see 'The sick dialysis patient'.

Peritonitis is the major complication of PD, usually caused by Staph. epidermidis or bowel organisms. Patients often present with abdominal pain, pyrexia, cloudy PD effluent – but may have only one of these at first. Investigations reveal a raised white cell count in fluid. Treatment is urgent in these circumstances and all units will have a regimen for blind antibiotic therapy after cultures have been sent. Antibiotics are usually added to dialysate and/or given systemically.

Blood glucose testing: Patients using dialysate containing the glucose polymer icodextrin may have high levels of other circulating sugars that lead to misleadingly high values on some commonly used glucose testing kits. This could lead to dangerously inappropriate management and hypoglycaemia.

Further info

- Patient info about PD (Edren)
- Edren handbook on PD

Up to top
Potassium

The usual dietary intake of K+ is about 80 mmol/day. 85% of normal potassium excretion is in urine. Potassium balance depends on regulation of urinary excretion. Endogenous potassium is largely intracellular, hence changes in K+ distribution between ECF and ICF may greatly affect plasma K+ concentration.

Hyperkalaemia

Caused by:-

- Increased intake (food, IV fluids, potassium supplements) (unlikely to be sole cause)
- Tissue breakdown (e.g. tissue damage, bleeding, haemolysis, rhabdomyolysis)
- K+ release from cells (e.g. in hyperglycaemia, acidosis)
- Endocrine – Addison’s disease; drugs – spironolactone (aldosterone antagonist)
- Impaired excretion in urine (e.g. in renal failure, and with drugs – ACE inhibitors, potassium-sparing diuretics)

Clinical signs are rare. An ECG may show tall T waves, increased PR interval and widened QRS complexes. In severe cases, the P and T waves are absent. A plasma K+ of over 7 mmol/l may lead to cardiac arrest.

Treatment of acute hyperkalaemia

**Intravenous calcium** is necessary only if there is dysrhythmia or severe ECG changes
10% gluconate or chloride, 10mls over 5 minutes (maximum 2mls/min)
- Give if ECG changes – peaked T-waves, prolonged PR
- Check in 15 minutes and if still abnormal, repeat once or twice
- Does not change [K+]; reduces excitability of membranes

**Intravenous glucose** (dextrose)
50ml 50% (25g) + 5u Actrapid over 20 minutes (i.e., maximum ratio of 5g:1 unit)
- Acts in 30 minutes, peak effect 90 minutes, lasts up to 6 hours
- Lowers [K+] by 0.7-1.6mmol/l
- Can be followed by slow infusion of 10-50% dextrose (give insulin only if glucose high)
- Monitor blood sugar after administration

**Salbutamol**
5mg nebulised
- Acts in 60 minutes, peaks 90 minutes, lasts up to 6 hours
- Similar to dextrose in efficacy

**Sodium bicarbonate**
50 mmol, usually as 330mls 1.26% (isotonic) (50ml of 8.4%, but this is irritant)
- The least effective intervention and involves sodium load; consider if acidic and extra sodium tolerable
- Can reduce [K+] by 0.2-0.3mmol/l
- Not routine but may be useful in emergency

**Dialysis**
Only necessary if renal function very poor - working kidneys excrete potassium!
- Note that above treatments do not remove, they only redistribute [K+]
- A standard haemodialysis removes 40-60mmol [K+]
- Haemodialysis lowers [K+] faster than haemofiltration or peritoneal dialysis

**Calcium resonium**
Not useful in acute setting but may be short/medium term option if dialysis not desirable or possible. Unpleasant to take, causes constipation, limited effectiveness.

**Diet**
May explain acute hyperkalaemia usually only if there are other risk factors such as drugs, reduced renal function. In the presence of risk factors and an episode of hyperkalaemia, important for prevention.

Hypokalaemia

A decrease in plasma K+ is commonly caused by:-
- Loss of K+ from GI tract (e.g. vomiting, diarrhoea, intestinal obstruction)
- Shift into cells (e.g. insulin treatment of hyperglycaemia)
- Endocrine – hyperaldosteronism, primary or secondary
- Drug treatment (e.g. most diuretics)

The clinical features include lethargy and muscle weakness. Tingling in fingers, paralysis and coma are present in more severe cases. In chronic hypokalaemia there may be nocturia, polyuria or polydipsia.

There is commonly divergence between serum [K] and whole body stores - e.g. depletion yet normal plasma [K] in diabetic ketoacidosis; low plasma [K] despite normal total body potassium in metabolic alkalosis.

Hypokalaemia is treated by giving KCl, intravenously in severe cases, and correcting any associated salt and water imbalance. Recurrence is prevented by encouraging a K+ rich diet, but K+ supplementation or a K+-sparing diuretic is advisable if the patient requires diuretics, and supplementation if receiving intravenous fluid treatment.

**Further info**

- Diet and potassium
- Hyperkalaemia management from Edren handbook
- Fluid spaces and requirements

**Peritoneal dialysis**

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Pregnancy and renal disease

During pregnancy, physiological changes occur which are important in the assessment of medical problems. These include:

- Reduced peripheral vascular resistance
- Lowered blood pressure
- Increased cardiac output
- Increased GFR
- Reduced plasma creatinine, urea, uric acid

Some renal problems become more severe:

- UTI and pyelonephritis are more common in those with and without prior history – asymptomatic bacteriuria should be treated
- Proteinuria becomes more severe – and hence nephrotic syndrome (this increases the risk of venous thromboembolism)
- Hypertension – usually improves in early pregnancy but blood pressure rises later

Some diseases are unique to pregnant women. These include hyperemesis gravidarum, post-partum HUS, amniotic fluid embolism, but most commonly pre-eclampsia.

Pre-eclampsia

A third-trimester systemic disorder usually. More prevalent in first-time mothers, very young or old mothers, multiple pregnancies, previous history, or in those with pre-existing hypertension or renal disease. It is characterised by the triad of oedema, proteinuria and hypertension, but may occur with just one or even none of these typical features.

Blood tests typically show falling platelets and increasing uric acid levels. Defective placentation leads to retarded foetal growth. Acute renal failure, more severe haematological disease, and hepatic dysfunction may develop. Acute fatty liver of pregnancy and 'HELLP' syndrome are probably variants of pre-eclampsia. Convulsions (eclampsia) are a late development usually associated with hypertension. Magnesium sulphate is the most effective therapy for eclampsia and may be given prophylactically.

The only effective management is delivery. Anti-hypertensive drugs can be used to protect the mother from extreme hypertension but do not alter the course of the condition.

Patients with pre-existing renal disease

The presence of proteinuria or high blood pressure in the first trimester suggest pre-existing renal disease.

Blood pressure may improve and serum creatinine fall in early pregnancy, and these are good prognostic signs. In a few patients (typically with more severe renal impairment and/or hypertension) renal function may be permanently lost during pregnancy.

Worsening renal function, blood pressure and proteinuria in late pregnancy closely resemble the development of pre-eclampsia.

Drug therapy during pregnancy should be changed to agents of known safety so far as possible, and risks versus benefits need to be carefully discussed.

Further info

Patient info on pregnancy and contraception in renal disease (see links to drug info at the foot of that page)
Prescribing in renal disease

Drugs that are predominantly renally excreted require lengthening of dose intervals or reduced maintenance doses – see datasheets or specialist resources for information on individual drugs.

Drugs requiring dose reductions

Examples only! - not a complete list.

<table>
<thead>
<tr>
<th>Mild renal failure</th>
<th>Moderate renal failure</th>
<th>Severe renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
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<tr>
<td>Vancomycin</td>
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<tr>
<td>Aciclovir</td>
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<td>Digoxin</td>
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<tr>
<td>Zidovudine</td>
<td></td>
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<tr>
<td></td>
<td>Opiates (except fentanyl)</td>
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<tr>
<td></td>
<td></td>
<td>Cephalosporins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penicillins</td>
</tr>
</tbody>
</table>

Drugs to be avoided

Sometimes the drug must be entirely avoided. Again note that these are examples, and mostly refer to moderate to advanced renal failure.

- NSAIDs in advanced renal failure (except when on dialysis; balance risk at intermediate GFR)
- Tetracyclines (except doxycycline and minocycline)
- Compounds containing aluminium, bismuth or lithium, except with cautious monitoring
- Nitrofurantoin
- Fibrates
- Chloramphenicol
- Chloroquine
- Methotrexate

Other prescribing notes

ACE inhibitors and ARBs cause potassium retention and may cause hyperkalaemia.

Diuretics are less effective in severe renal failure – thiazides are less effective, loop diuretic doses often need to be increased. Potassium-sparing diuretics should be used with caution.

Further info

- Notes on prescribing in renal disease from the Edren handbook
Protein in the urine always comes from the kidney and in general it implies significant kidney disease. Any renal disease or injury may cause proteinuria. Glomerular disease may cause heavy proteinuria, but in many patients it is initially detected at lower levels. The level of proteinuria is a prognostic factor for most diseases – the higher, the poorer the renal prognosis.

Proteinuria may be caused by almost any renal lesion, but higher levels (>2g/d) are always caused by glomerular disease; some key causes are listed at nephrotic syndrome.

**Diagnosis**

Usually asymptomatic, identified on dipstick test of urine

Protein/creatinine ratio, or 24h urine collection, to quantitate.

Proteinuria is probably not important if it:

- Only occurs following strenuous exercise
- Only occurs during a fever
- Only occurs during a UTI
- Is absent in the morning but occurs later in the day (orthostatic proteinuria) (controversial)

**Quantification:** Ratios of protein or albumin to Creatinine (PCR, ACR) have largely replaced 24h collections for quantitating proteinuria. Albumin is about 70% of glomerular proteinuria at levels >1g/d. So very approximately:

\[ \text{Proteinuria 1g/day} = \text{PCR 100 mg/mmol} = \text{ACR 70 mg/mmol} \]

**Further investigation**

Is there:

- Proteinuria >100mg/mmol creatinine (lower in young; maybe higher in old)?
- Haematuria also present?
- Raised serum creatinine (urgent if function deteriorating)?
- Hypertension? (less suggestive with increasing age)
- Previous or family history suggest significant renal disease?

If so:

- Quantitate proteinuria and get previous creatinine values
- Ultrasound scan of kidneys may be valuable
- Consider referral (renal biopsy may be justified)

**Management of low level proteinuria**

In the absence of haematuria, hypertension or impaired renal function, or other symptoms, history or abnormalities, it is usually reasonable to monitor urine tests, blood pressure and renal function at 6 months, extending the interval to annually, indefinitely.

**Further info**

- Patient info about proteinuria
- Edren handbook on proteinuria
- Referral guidelines - Edren - GPinfo
- Proteinuria in the UK CKD eGuide
Reflux nephropathy and chronic pyelonephritis

This is a chronic interstitial nephritis associated with vesico-ureteric reflux (VUR, usually congenital) in early life. There is also a close association with recurrent urinary tract infections, and sometimes there are other urinary tract or other congenital abnormalities such as incomplete growth of the kidney - renal hypoplasia.

Pathogenesis

Normally the oblique entrance of the ureter through the bladder wall causes ureteric occlusion during bladder contraction. In VUR there is a structural abnormality of the intra-mural ureter allowing reflux of urine from the bladder to the kidney. CIN becomes established leading to further renal deterioration. By an uncertain mechanism, interstitial nephritis may cause focal scars and initiate a slowly progressive renal deterioration.

Clinical features

Often asymptomatic. May present with hypertension, proteinuria reflecting renal damage; or with associated UTIs. Reflux itself sometimes causes loin pain during micturition but this is rarely a significant problem.

Investigation

Diagnosis is confirmed by demonstration of focal renal scars (IVU or isotope renogram; ultrasound less reliable for this); will also reveal other abnormalities, e.g. obstruction. Urine culture necessary to show infection. Assess renal function, proteinuria etc. in usual way.

Management

Associated UTIs should be managed in the usual way. Correct obstruction. There is no consistent benefit from procedures to correct reflux. If there is significant renal damage (proteinuria, hypertension, renal function), aggressive control of blood pressure is important. Other aspects as for CRF of other causes.

Further info

- Reflux nephropathy from Edren
- UTI and reflux - tutorial
Renal artery stenosis and renovascular disease

Renal artery stenosis (RAS) may cause an ischaemic nephropathy, potentially leading to acute or chronic renal failure, or secondary hypertension. Stenosis of over 70% may have haemodynamically significant effects. Hypertension is a usual consequence of RAS, unless cardiac disease prevents it from developing. A classic but rare presentation is with recurrent episodes of sudden ('flash') pulmonary oedema associated with hypertension and with reasonably good cardiac function and good or only moderately impaired renal function.

If there is bilateral renal artery stenosis (or stenosis of the artery to a single functioning kidney), worsened renal function (>20% rise in creatinine) after starting an ACE inhibitor is characteristic. However this is not reliable as a diagnostic test.

Causes

In over-50s it is usually caused by atheroma at the orifice of the renal artery, and is almost always accompanied by disease of other branches of the aorta, particularly peripheral vascular disease. Up to 15% of cases lead to complete occlusion with loss of renal function. If progression is gradual, collaterals may form, restoring some function.

RAS occurs rarely in the young (<30 years), where it is more likely to be caused by fibromuscular dysplasia, which causes an irregular beading pattern on arteriography.

Investigation

Chronic RAS is difficult to diagnose clinically as there are no specific signs. Hypertension is usual. Urinary dipstick testing is normal or mildly abnormal. Hypokalaemia may occur because of secondary hyperaldosteronism. Non-invasive tests have been greatly improved by gadolinium-enhanced magnetic resonance angiography and CT angiography. Ultrasound: if a small kidney is due to RAS, it is too late to save substantial renal function. Doppler signals are an insensitive guide to RAS.

Management

Young patients with fibromuscular dysplasia in the proximal renal artery often respond to balloon dilatation.

Atheromatous lesions are typically close to the aorta and respond less well to angioplasty, but stenting can improve patency. However this treatment is risky and may not offer substantial benefits except after an acute occlusion. Randomised controlled trials (ASTRAL) have not shown any benefit from stenting in chronic or slowly progressive RAS. This should maybe not be such a surprise, because

- In atherosclerotic RAS there is a poor correlation between the severity of the renal artery lesion and the renal function on that side.
- Even when the anatomical result is good, the response (blood pressure and protection/ improvement of renal function) is uncertain. This may be because of pathology distal to the stenosis, caused by atheroembolism (cholesterol embolisation) or ischaemia. A small kidney or one with abnormal peripheral vessels is unlikely to be improved by revascularisation, but a ‘normal’ kidney may not be improved either.
- There is a significant risk of renal artery occlusion as a result of the procedure, and because atherosclerosis is often severe and widespread, of atheroembolism affecting kidneys, lower limbs, gut and elsewhere. This can occasionally be fatal.

Alternative medical management involves giving low-dose aspirin and lipid-lowering therapy, treat hypertension and monitor function. Where the benefit from revascularisation is uncertain (most cases), this therapy may be prescribed without angiography when the diagnosis is thought likely or possible.

Small vessel diseases

Thrombotic microangiopathy, disseminated intravascular coagulation – see Haematology.

Malignant hypertension – see Hypertension.

Systemic sclerosis (scleroderma renal crisis) – very similar to malignant hypertension; prompt treatment with ACE inhibitors may arrest the disease. More on systemic sclerosis

Further info

- Patient info about Renal artery stenosis
- Radiology and complications of radiological procedures
- Info for patients about angiography and angioplasty

Up to top
Rhabdomyolysis is muscle damage caused by:

- Pressure or crush injury (e.g., prolonged unconsciousness)
- Ischaemic injury when blood supply is cut off
- Chemical injury (e.g., sometimes in those taking cholesterol-lowering statins)

It was first described in the Second World War (1939-45) in people trapped beneath bombed buildings. Huge numbers of cases may occur after earthquakes. The damaged muscle releases a number of things as perfusion is restored:

- **Myoglobin** - this small haem-containing protein is filtered at the glomerulus because of its small size, but is toxic to renal tubular cells. Its toxicity may be reduced by alkalinising the urine by giving sodium bicarbonate. Urine containing a lot of myoglobin is dark brown to black.
- **Potassium** - the levels may rise very rapidly and dangerously in ARF caused by rhabdomyolysis, requiring frequent and intensive dialysis.
- **Phosphate** - Levels rise very high, causing calcium phosphate to precipitate and leading to low calcium levels.
- **Muscle enzymes** - Creatine Phosphokinase (CPK) levels rise very high (to values of tens of thousands), a useful diagnostic test. LDH and some other enzymes will be elevated too; so will uric acid.

### Management

- **Emergency treatment for hyperkalaemia.** [More about potassium](#)
- Preventive treatment - fluid resuscitation to restore circulation and urine output. Include sodium bicarbonate in large quantities to alkalinise the urine.
- Dialysis if urine output not restored and biochemical changes dangerous
- Muscle compartment pressure may rise very high after muscle damage, cutting off blood supply. Compartment pressures can be measured, and operations to cut open the affected compartments can save further muscle damage, and may be needed urgently.

Recovery follows the standard pattern for ARF.

### Further info

- Edrep page on ARF
- EdRen handbook on management of ARF
- *Bombs, earthquakes and rhabdomyolysis* - how natural and human disasters led to the discovery of this condition.

Up to top
The plasma sodium concentration is a good indication of the water content of body fluids. It is not usually a guide to sodium or salt loading.

Hypernatraemia

Although it is possible to administer too much sodium and cause this, water depletion is a much more common cause. The main causes of water depletion are:

- reduced water intake (e.g. coma, dysphagia, extreme depression). Because hypernatraemia is an extremely strong stimulus to thirst, reduced water intake is almost always involuntary.

And increased losses of hypotonic fluid. Usually both are present, though either alone can be sufficient.

- increased loss via gut, skin or respiratory tract. Cholera syndromes (likely to be sodium depleted too); severe sweating, etc
- increased loss in urine caused by impaired ability to concentrate urine (diabetes insipidus, central, nephrogenic or drug-induced)

If circulating volume is reduced hypernatraemia is exacerbated by reabsorption of sodium due to aldosterone secretion.

Clinical features include thirst, oliguria and concentrated urine. More severe cases may result in confusion and weakness, and possibly tachycardia, and finally hypotension and coma. Plasma urea is usually increased. These findings, along with a urine osmolality of over 600 mosm/kg confirm water depletion.

Treatment is by oral replacement of water in mild cases; 5% dextrose (i.v.) in moderate cases; and a combination of 5% dextrose and 0.9% (150mmol/l) saline (i.v.) if dehydration is severe, as volume expansion requires salt as well as water.

Hyponatraemia

This usually indicates an increase in the relative proportion of water to sodium in plasma, rather than a reduced sodium content. The main causes of hyponatraemia are:-

- Increased total body water alone (e.g. due to the syndrome of inappropriate antidiuretic hormone secretion, SIADH; though secretion of ADH is also triggered by understandable physiological stimuli)
- Increased body water and sodium; excess water exceeds excess sodium. Often seen in cardiac, liver or renal failure.
- Reduced body sodium: water depletion accompanied by excessive Na+ depletion – e.g. large electrolyte losses replaced largely by water drinking. Seen in Addison's disease, for example, when kidneys fail to retain sodium.

Confusion, drowsiness and sometimes seizures are features of hyponatraemia. Other manifestations depend on cause; increased body fluid, or dehydration.

It is dangerous to correct [Na] too quickly. Central pontine myelinolysis can be a consequence, causing severe permanent brain damage. Hypertonic saline solutions should not be used, and the maximum rate of correction should be less than 10mmol/l per 24h. For dehydrated patients, administer 0.9% (isotonic) saline (150 mmol/l NaCl) to replenish volume.

Management of fluid overloaded patients involves restricting water and fluid intake. ADH receptor antagonists are becoming available as an alternative approach.

Further info

- Learn about fluid compartments and IV fluid prescribing
- Hypernatraemia at ganfyd.org
Stones

Kidney stones are common. They can form anywhere in the urinary tract, but usually in the kidney. Stone constituents become concentrated in the urine due to increased excretion or reduced urine volume, and begin to crystallize and grow. 80% of all stones contain calcium (as oxalate, sometimes as phosphate). Struvite stones, containing calcium, ammonia and phosphate, can form in presence of urine infections. Uric acid stones form from the substance which causes gout. Cystine stones occur in the inherited condition cystinuria and are rare. Occasionally some drugs can form crystals and stones.

Presentation

- Severe loin pain, travelling anteriorly and into testis/ labium, sometimes in colicky waves
- Haematuria
- With complications – urinary tract obstruction or infection

Risk factors

- Male sex (3 times as likely as females)
- Age 30-60 years
- Hot climate
- Caucasian race
- Family history of stones
- Abnormal urinary tract – infection, scars or cysts

Causes

- Low urine flow (hot climates, low fluid intake)
- High urinary calcium, oxalate, urate - genetic, dietary, etc
- Inherited disorders (e.g. medullary sponge kidney, cystinuria, renal tubular acidosis)
- Urinary tract obstruction/infection

Management

- Analgesia – opiates often required
- Hydration to ensure adequate urine flow
- Anti-emetics
- Investigation – Stones may be visible on plain X-ray but intravenous urography (IVU) or (better) CT scanning will show both stones and obstruction.
- Stones of <4mm usually pass spontaneously. Stones >6mm usually require intervention.
- Lithotripsy and percutaneous techniques have revolutionised management of larger stones and of obstruction.

General measures for recurrent calcium stones

- Increase fluid intake as much as possible, particularly at night.
- Moderate (not high) protein intake
- Low salt intake
- Increase dietary calcium (binds oxalate in gut) but avoid calcium supplements (dietetic advice valuable)
- Thiazide diuretics reduce urine calcium

Further info

- Patient info on renal stones
- Edren handbook on renal stones
Systemic lupus erythematosus (SLE)

A multi-system autoimmune disease predominantly affecting young women. Typically presents with joint pains and malaise, quite often with fever, and a characteristic erythematous facial ‘butterfly’ rash. Pleurisy is another common early symptom. However the range of possible manifestations is very large. Antinuclear antibodies and antibodies to double-stranded DNA are typical. Serum complement levels may be low.

Renal involvement may occur in 50% but is often minor. Major renal disease indicates serious disease. Patients typically present with the inflammatory signs of haematuria, proteinuria, high blood pressure. Nephrotic syndrome is also a very common presentation. SLE is an important cause of serious renal disease in young women. It is more common in black and particularly some East Asian races.

The most common histological pattern is an inflammatory, diffusely proliferative glomerulonephritis. Appearances are highly variable but prognostically important.

Corticosteroids are required for most types of lupus affecting the kidneys. For aggressive disease, treatment with cyclophosphamide (usually in regular pulses) reduces the risk of progression to ESRF. Mycophenolate mofetil (MMF) may be a less toxic alternative for some patients. Cyclophosphamide is usually stepped down to azathioprine or other cytotoxic agent after a variable period.

If ESRF is reached despite treatment, SLE tends to become relatively quiescent. Dialysis and transplantation are successful.

Further info

- Patient info on SLE
- Patient info on immunosuppressive drugs
- SLE in the Edren handbook
Transplantation

Quick link - The sick transplant patient

Dialysis merely improves the symptoms of chronic renal failure; renal transplantation can cure them. Successful transplantation also extends the life expectancy of patients with end stage renal failure.

Improvements in immunosuppression and technique have improved graft survival to >85% at 1 year, and the ‘half-life’ of successful grafts to over 10 years, with longer survival expected for well-matched or live donor grafts. In all countries shortage of donors is a problem. Cadaver organ transplantation is usually restricted to relatively low risk patients. Live donor transplantation is associated with excellent results and low risk to (health-screened) donors and is increasingly relied on in many nations.

The operation

The allograft may be kept on ice for 24 hours or longer, but extended ‘cold ischaemia’ time is associated with poorer outcomes. The donor renal vessels are most commonly anastomosed to recipient iliac vessels and the donor ureter tunneled into the bladder. The kidney lies in the iliac fossa; native kidneys are untouched.

Matching

Blood group: Donor must be ABO compatible (Rhesus type not important). For cadaver organ transplantation a ‘same blood group’ rule is usually maintained, to prevent disadvantaging group O recipients.

Tissue type: Matching for HLA types HLA-DR, HLA-A and HLA-B have been shown to affect graft survival. HLA-DR has the strongest effect, but ‘6-antigen matches’, i.e. with no mismatching for HLA-DR, A or B, have much improved survival. National organ sharing protocols aim to achieve this as often as possible.

Age, size, quality: These and other non-immune factors also have powerful effects on graft survival.

Immunosuppression

A widely used triple therapy comprises

- tacrolimus or cyclosporine
- azathioprine or mycophenolate mofetil
- relatively low-dose prednisolone.

Some centres also use anti-lymphocyte antibodies (e.g. anti-IL2 receptor, or anti-CD52, or anti-T cell) or newer agents in attempt to reduce the rate of acute rejection still further. Rejection is most likely to occur in the first few weeks after transplantation, but can occur after months or years, for example if immunosuppression is interrupted. Early rejection can usually be reversed by high-dose steroids or by anti-lymphocyte antibodies but may leave the graft damaged. With modern immunosuppression, signs of rejection may be minimal and suspicion may only be aroused by changes in renal function.

As the risk of acute rejection falls, levels of immunosuppression are reduced.

Complications

Delayed graft function is common after cadaveric organ transplantation and dialysis may need to continue for days to weeks. This makes it difficult to assess rejection and protocol biopsies may be undertaken. Tacrolimus and cyclosporine are nephrotoxic and this complicates assessment of renal function; in the long term, they may cause renal failure. Short term (and dose-related) toxicity is mostly reversible.

Technical problems usually become apparent within days, though delayed obstruction or vascular occlusion are sometimes a problem. A ureteric stent is commonly left in situ for several weeks to reduce early urine leaks.

Acute rejection is usually signalled by a rise in serum creatinine. Doppler ultrasound is a useful investigation to exclude major vascular mishap or ureteric obstruction. Biopsy confirms the diagnosis, there are still no reliable non-invasive tests. Risk is highest in the first weeks and months but can occur at any time if immunosuppression is interrupted.

Infections Immunosuppression is at its most intense in the first few weeks, which is therefore the period of greatest risk of serious viral or other opportunistic infection. Those given additional treatment for acute rejection are at greatest risk. CMV is a particular problem; prophylactic ganciclovir or other therapies are commonly used for CMV seronegative patients exposed to a CMV positive graft. Primary EBV infection may cause the pre-malignant condition post-transplant lymphoproliferative disorder (PTLD), and sometimes overt lymphomas. Serious renal infections with polyoma virus may occur after about 3 months and closely resemble rejection, but their management is the opposite.

Long term risks In the long term there is a substantially increased risk of skin tumours and patients should avoid exposure to much direct sunlight. Lymphomas and some other cancers (especially virally mediated) are increased.
The sick transplant patient

Patients are immunosuppressed and need to continue immunosuppression for ever. They are therefore at risk of opportunistic infections. Immunosuppression (especially corticosteroids) may mask the development of acute infections, including graft pyelonephritis, and other pathology. Acute rejection or technical problems (notably obstruction) associated with the allograft are always a possible explanation for illness; serum creatinine is a useful guide.

Malignancies, particularly those thought to have a viral etiology (lymphoma, carcinoma of the cervix), are increased from the early post-transplant period. Women should have regular cervical cytology.

Most patients are hypertensive. Many have some degree of continuing renal impairment, and therefore are at risk of all the problems associated with renal failure. At least in part because of their history, transplant patients continue to have a high incidence of cardiovascular and other vascular disease.

If a transplant patient is admitted to hospital for any reason, their transplant team should be notified and advice sought if necessary.

Further info

- Patient info on Transplantation
- Edinburgh transplant protocols (see right of page)

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Urinary tract infections

Simple urinary tract infections (UTIs) such as cystitis are extremely common. Infants, girls and young women, and elderly men and women are most commonly affected. There is often a sudden onset of dysuria and increased frequency. Suprapubic pain, haematuria and odorous or cloudy urine may also occur. Youngest and oldest patients, and the immunosuppressed, may not complain of all these symptoms. Malaise, pyrexia, loin pain and nausea and vomiting, suggest upper tract infection and pyelonephritis.

Urine contains white blood cells and organisms (dipstick tests may show temporary blood and protein). E.coli and other bowel organisms are the most common pathogens.

Predisposing factors

- Age, sex
- Abnormal urinary tract – especially incomplete bladder emptying (e.g. in prostatic hypertrophy)
- Vesicoureteric reflux
- Diabetes mellitus

Management

All patients should have urine examined for blood cells and culture, and a dipstick examination for blood, protein and glucose. Severe upper tract infections require blood cultures, blood count, renal function tests.

Antibiotics should be based on likely pathogens and local resistance patterns. Treatment for 3 days gives higher success rate for cystitis than shorter courses. Oral antibiotics should be combined with advice to take plenty of fluid. Injected antibiotics may be required for pyelonephritis, and treatment is longer. Asymptomatic bacteriuria should not usually be treated, except in pregnancy or if there are other risk factors for complicated infection.

Further investigations are indicated in infants, children, men with a single UTI, and women with pyelonephritis or frequent recurrences. Ultrasound is usually adequate and can assess completeness of bladder emptying, but IVU gives better delineation of collecting system if required. Isotope renogram may show scars of reflux nephropathy and can identify continuing reflux.

Further info

- Patient info on urinary tract infections
- Tutorial on UTI and reflux from Edren

Up to top
Urine volume

Urine volume is a poor guide to renal function as it is physiologically variable and 24-hour collections are often erroneous. However severe oliguria or polyuria imply pathology and require further investigation.

Too much

Difficult to set an upper limit of normal, but 4 litres is a lot. Causes:

- Osmotic diuresis – diabetes mellitus
- Loss of antidiuretic hormone (ADH) – cranial diabetes insipidus (head injury, etc)
- Failure to respond to ADH – nephrogenic diabetes insipidus
- Excessive intake – psychogenic polydipsia

Too little

300-500 mls of urine is needed to excrete adequate amounts of solute each day. Less than this is therefore oliguria.

- Physiological response to severe dehydration
- Hypoperfusion of the kidneys – hypotension or damage/occlusion to renal artery/aorta
- Acute Renal Failure (see Approach to the patient with oliguria)
The term vasculitis covers a number of probably autoimmune conditions in which there is inflammation of blood vessels. Small-vessel vasculitis (SVV) commonly affects glomeruli. Medium or large-vessel vasculitis alone will only cause renal disease if arterial involvement leads to hypertension or renal infarction.

ANCA are antibodies to neutrophil cytoplasmic antigens, granule enzymes such as myeloperoxidase and proteinase 3. They are useful but not completely reliable guides to the diagnosis of systemic vasculitis.

The glomerulonephritis of SVV may be accompanied by involvement of other organs. In severe disease crescentic nephritis (rapidly progressive glomerulonephritis, RPGN; see glomerulonephritis) may occur in combination with lung haemorrhage. Any other organ may be involved; skin and gastrointestinal involvement are perhaps the most common. However in a significant proportion of patients the kidneys seem to be the only major organ affected at the time of diagnosis. Although most patients have acute disease, the diagnosis is sometimes picked up unexpectedly in patients with slowly progressive kidney disease.

SVV is a serious diagnosis. Without treatment it is usually progressive, and it may be fatal through causing renal failure, gastrointestinal haemorrhage, stroke, or other involvement. Involvement of other organs may indicate the underlying subtype of vasculitis, e.g. ENT and lung complications in Wegener’s disease.

Treatment of SVV with cyclophosphamide, corticosteroids and plasma exchange can salvage renal function even if the patient is oliguric, and this is usually the favoured treatment in anyone with aggressive disease. Other cytotoxics (MMF; methotrexate in non-renal disease) may be used in some circumstances.

**Case history:** A 73 year old woman became non-specifically unwell over a period of several weeks. She then developed arthralgias without visible joint swelling. 7kg weight loss was noted. 3 weeks before admission blood tests showed a mild anaemia, moderately elevated erythrocyte sedimentation rate, mild renal failure (urea 7 mmol/l, creatinine 138 micromol/l), and she was referred to a rheumatologist.

Before attending that appointment she became increasingly breathless over 24h. On admission she had bilateral lung shadowing and crackles without evidence of heart failure, fluid retention or infection, though she had a mild pyrexia. Urea had risen to 20 mmol/l and creatinine to 420 micromol/l. Urine testing showed blood ++++, protein ++. Fresh haemoptysis developed and oxygenation worsened. She became oliguric and soon required dialysis and assisted ventilation. In the absence of evidence of infection or other cause, a suspicion of systemic small vessel vasculitis was supported by positive ANCA (anti-myeloperoxidase specificity). A later renal biopsy showed crescentic nephritis. Treatment with cyclophosphamide, prednisolone and plasma exchange led to rapid improvement in lung pathology and slower improvement in renal function. Dialysis was discontinued after two weeks. One year later she was taking azathioprine 100mg, prednisolone 10mg daily, had a creatinine of 160 micromol/l, and was well.

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**Further info**

- Patient info vasculitis
- Patient info immunosuppressive drugs
- Edren handbook on systemic vasculitis

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Vascular access for haemodialysis

Since the earliest days, the 'Achilles heel' of haemodialysis.

In acute renal failure, temporary access to the circulation for dialysis is achieved by inserting a wide-bore dual lumen catheter into a major vein, usually the femoral or internal jugular vein. For patients awaiting AV fistula development or with no possibility of fistula formation, soft tunneled central catheters are used.

Risks for all catheter devices:

- Infection, especially by Staphylococci, which may be life-threatening. May be difficult to eradicate without removal of catheter. Severe secondary infections (endocarditis, discitis, osteomyelitis) may occur.
- Thrombosis/stenosis. Thrombosis within the catheter can often be cleared by instillation of urokinase or tissue plasminogen activator (tPA). Thrombosis around the catheter can alternatively be cleared by 'stripping' with a snare, often inserted via the femoral vein. Occlusion of vessels is a major problem in some patients.

Catheter care programmes and recurrent cycles of audit are being increasingly used to minimise these risks.

Temporary (non-tunelled) and femoral vein catheters are most likely to become infected. However the femoral veins are often favoured for emergency access as there is no risk of pneumothorax, insertion can be undertaken in a semi-erect patient, and it preserves central veins.

Further info

- See Haemodialysis pathway
- Edren handbook on vascular access
- YouTube videos of fistula cannulation etc;
  - We need a modern one …
  - 40 years ago - just the same! (not for the squeamish)

Up to top
Websites

www.edren.org our own site, has information about individual diseases for patients and medical staff, protocols for immediate in-hospital management.

www.nephron.com The links under 'professional resources' are particularly good, and include good Urology links.

The UK CKD eGuide is worth working through to gain an understanding of current primary care management of CKD.

History and other blogs History is incredibly informative as well as interesting. The History of Nephrology Blog is our own, but there is a rapidly increasing list of blogs on other topics, some excellent. Look at the links in the right hand sidebar at the History of Nephrology blog.

Books and equivalent

Davidson's Textbook of Medicine (Churchill Livingstone). Frequent new editions. We are biased about this one, as we write it. There is a lot of detailed nephrology info in this book and links to online MCQs and other resources.

Forrest's Principles and Practice of Surgery (Churchill Livingstone). Urology chapter by our own Lawrence Stewart, and Transplantation chapter by John Forsythe.


UpToDate in Medicine. This frequently updated online text is detailed, very good, and (unusually) works well online. However it is expensive unless you can gain access through your work, or qualify for a reduced subscription.

Afterword

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