Renal disease

Edited by **Dr C G Winearls** DPhil, FRCP, *Churchill Hospital, Oxford*

Starting with this issue, the Journal will have a systematic CME section. It is our response to the readership survey (*JRCPL* 1996;30:246–251). The first topic is **renal disease** which we will continue in the March issue. It draws heavily on the topics and speakers of the CME day at the College on 30 September 1996, which was also organised by Dr Winearls. *We acknowledge with thanks an educational grant from Janssen-Cilag Ltd.*

The acute uraemic emergency

CRV Tomson, DM, FRCP, *Consultant Renal Physician, The Richard Bright Renal Unit, Southmead General Hospital, Bristol*

Most physicians have a sense of impending doom when faced with a patient presenting in severe renal failure. They must distinguish between acute renal failure (often reversible), acute on chronic, and chronic renal failure, seek a primary diagnosis, detect complications and decide whether and when to refer for specialist care. Often there is little time to spare.

Prevalence and incidence

Acute and chronic renal failure present with roughly equal frequency; both are much commoner in the elderly.

Chronic renal failure

In a predominantly Caucasian community the prevalence of a serum creatinine of above 300 μmol/l was 450 patients per million population (pmp); above 500 μmol/l it was 132 patients pmp[1]. The annual incidence of end-stage renal failure is around 80–120 patients pmp, with much higher rates in ethnic minority populations[2].

Acute renal failure

A community-based study in Devon showed an incidence of acute renal failure (ARF) of 172 patients pmp; incidence rose with age, from 17 in the 16–49 age group to 949 pmp in those aged 80–89[3].

Causes

Important causes of renal disease presenting as an acute uraemic emergency include:

- urinary tract obstruction
- sepsis, hypovolaemia and hypotension (sometimes following surgery or trauma)
- medical conditions:
  - renal vascular disease, including embolism and atheromatous embolism
  - drug-induced, particularly ACE inhibitors, non-steroidal anti-inflammatory drugs, and aminoglycosides
  - haemolytic uraemic syndrome
  - acute glomerulonephritis, including rapidly progressive glomerulonephritis in association with systemic vasculitis
  - rhabdomyolysis
- obstetric accidents
- previously undetected chronic renal failure, major causes of which include:
  - diabetic nephropathy

Key Points

RECOMMENDED PROCEDURES:

- **Make a diagnosis – the starting points are:**
  - **clinical examination**
  - **urine examination**
  - **renal ultrasound**
- **Correct fluid balance**
- **Monitor and treat hyperkalaemia**
- **Consult renal unit early – late transfer costs lives**

UNPROVEN VALUE:

- **Dopamine**
- **Loop diuretics**

- chronic glomerulonephritis
- obstruction
- reflux nephropathy
- renal vascular disease, including renal artery stenosis and small vessel disease
- polycystic kidney disease
- myeloma kidney.

As shown in Fig 1, the relative proportions of cases of acute renal failure due to obstetric accidents has decreased, with an increasing proportion of cases due to medical causes. Most of this increase in medical acute renal failure is in the context of severe multi-system illness; only a very small proportion of all acute renal failure in the UK is due to glomerulonephritis, although recognition of the latter is important because it is potentially reversible.

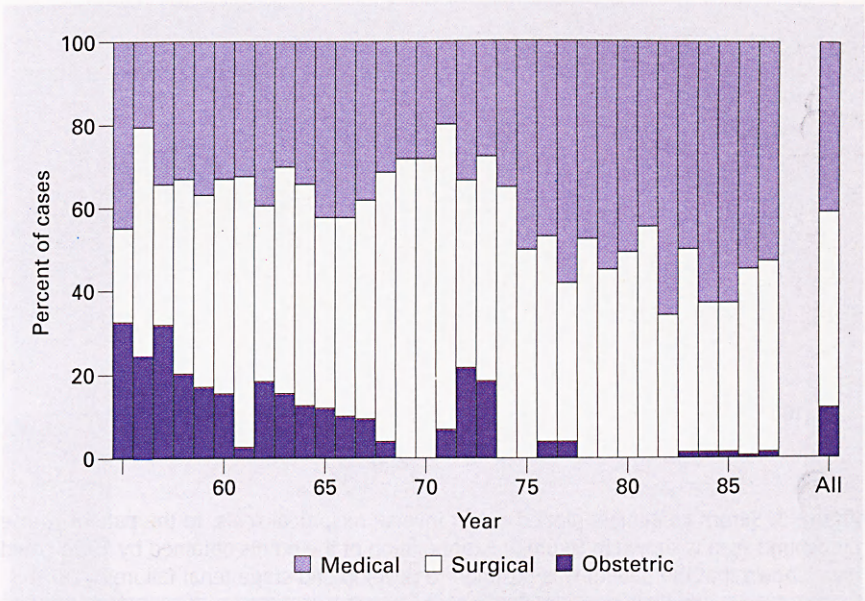

Figure 1. Proportion of diagnostic categories in patients admitted to the Leeds General Infirmary with acute renal failure between 1956 and 1988[12].
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Distinction between acute and chronic renal failure

The distinction between acute and chronic renal failure is important because of the very different prognosis of the two conditions; in particular, it is important to recognise a potentially treatable cause of renal disease before its effects become irreversible.

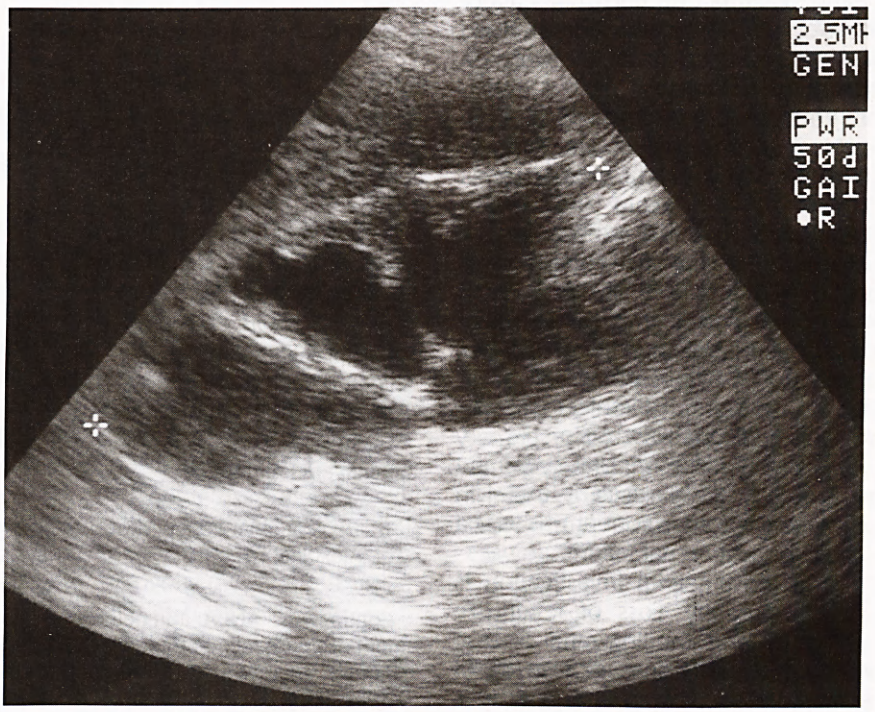
Long-standing renal impairment is suggested by a history of

- growth retardation during childhood
- polyuria and nocturia
- anorexia, nausea and vomiting
- itching
- possible causes of chronic renal impairment, such as:
  - bladder outflow obstruction
  - coronary or peripheral vascular disease (suggesting co-existing renal atheromatous disease)
  - diabetes
  - multiple myeloma.

Clues to possible causes of acute renal failure should be sought, in particular recent drug ingestion, infections (most topically, food poisoning) and exposure to toxins.

On examination, clues that suggest chronic renal failure include scratch marks, uraemic pigmentation, brown

Figure 2. Ultrasound of the kidney of a patient with a 6-year history of bladder outflow symptoms whose renal impairment had been attributed to diuretics used for treatment of cor pulmonale associated with emphysema. He presented as an acute uraemic emergency with severe acidosis and hyperkalaemia. Following bladder catheterisation, serum creatinine stabilised at around 250 μmol/l. Severe parenchymal thinning is shown, together with marked hydronephrosis.



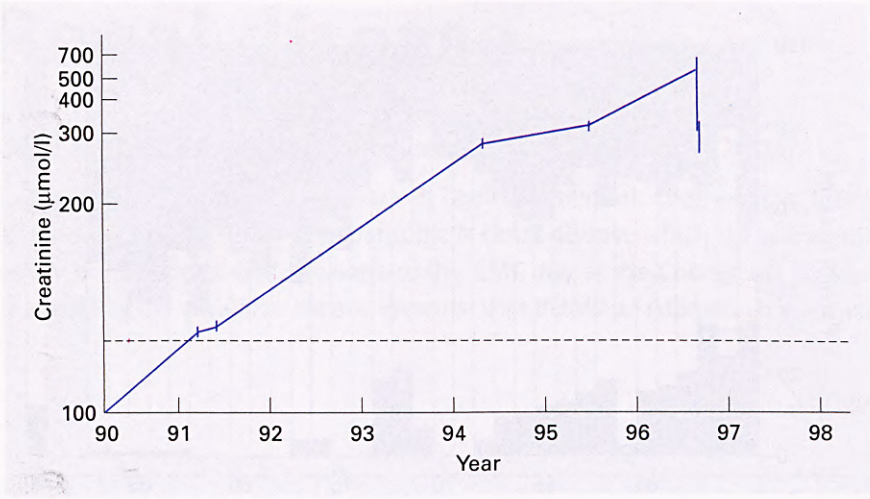


Figure 3. Serum creatinine, plotted on an inverse reciprocal scale, in the patient whose ultrasound scan is shown in Figure 2. Extrapolation of the points obtained by 1994 could have shown that the patient was destined to develop end stage renal failure by 1996.

nail arcs (uncommon), corneal calcification or hypertensive retinopathy (though similar retinopathy may accompany acute renal failure, eg in systemic vasculitis). Hypertension without retinopathy may be the cause (rare) or effect (common) of renal impairment; its presence favours a diagnosis of chronic renal failure. Large palpable kidneys (± liver) suggest polycystic disease. Signs of hypovolaemia, in particular hypotension and a postural drop in blood pressure, suggest acute, or acute on chronic, renal failure.

Routine laboratory investigation seldom shows whether renal impairment is acute or chronic. Anaemia occurs in both acute and chronic renal disease, but a normal haemoglobin argues against chronic renal failure. Disturbances of calcium and phosphate occur rapidly in acute renal failure so are seldom of help. Evidence of hyperparathyroidism on bone radiographs indicates long-established renal disease or primary hyperparathyroidism. Urinalysis and microscopy are particularly useful in detecting glomerulonephritis as a cause of acute renal failure.

The most helpful investigation is ultrasonography. Loss of renal size indicates long-standing renal disease but not all renal diseases cause loss of renal mass. Increased echogenicity is also highly suggestive of chronic disease. Renal swelling may occur in some acute renal diseases. Hydronephrosis is a very sensitive sign of obstructive nephropathy; parenchymal loss suggests that this is long-standing (Fig 2).

Previous measurements of serum creatinine should be obtained from hospital notes, including those from other hospitals, from laboratory records, and from the GP's files. This information, particularly when plotted graphically, is of great value in assessing the time course of renal impairment (Fig 3).

Investigation

The history and examination, urinalysis, microscopy and ultrasound should inform the choice of further tests (Table 1).

Reversible causes of acute uraemic emergencies

Obstructive nephropathy

Delayed diagnosis of obstruction to the upper urinary tract is an important avoidable cause of chronic renal impairment; the longer obstruction is left untreated, the less recovery of renal function can be expected after relief of obstruction[4] (Figs 2 and 3). Because patients may tolerate bladder outflow symptoms for many years, and because obstructive nephropathy seldom causes oliguria until very late in the course of the disease, such patients may present with extremely advanced uraemia,

Table 1. Further investigations: some common examples.

Suspected diagnosis	Test	Confirmatory findings
Haemolytic uraemic syndrome	Full blood count	Fragmented red cells Thrombocytopenia
Rapidly progressive nephritis	ANCA, Anti-GBM	
Systemic lupus	ANF, Anti-DNA	
Rhabdomyolysis Serum CK	Very high level	
Renal infarction Serum LDH		
Unexplained CRF (age>40) (for myelomatosis)	Serum electrophoresis Urinary light chains	
Pyonephrosis } in doubt after Obstruction } ultrasound	Retrograde pyelography Antegrade pyelography	
Renal arterial disease	Doppler ultrasound Angiography	
Treatable glomerulonephritis or interstitial nephritis	Renal biopsy	

Contractions: ANCA: anti-neutrophil cytoplasmic antibodies. Anti-GBM: anti-glomerular basement membrane antibodies. ANF: anti-nuclear factor. Anti-DNA: antibodies to double stranded DNA. CK: creatinine kinase. LDH: lactic dehydrogenase.

sometimes with serum creatinine levels in excess of 2000 μmol/l.

Angiotensin converting enzyme (ACE) inhibitor-induced renal failure

ACE inhibitors are an increasingly important contributory cause of acute renal failure, particularly in the elderly. The renal impairment they cause in the presence of renal vascular disease may be irreversible[5]. Risk factors include:

- renal artery stenosis (see Fig 4)
- hypovolaemia – an important precipitant in the presence of otherwise haemodynamically insignificant renal artery disease
- small vessel renal disease
- concurrent use of non-steroidal anti-inflammatory drugs.

Non-steroidal anti-inflammatory drug (NSAID) induced renal failure

NSAIDs cause a variety of renal diseases, including nephrotic syndrome, interstitial nephritis, hyporeninaemic hypoaldosteronism, and fluid retention. However their commonest adverse effect on the kidneys is inhibition of prostaglandin production in response to reduced perfusion. The unopposed renal vasoconstriction causes renal impairment. Situations in which this may occur include:

- concurrent use of ACE inhibitors
- hypovolaemia (eg after diarrhoea and vomiting)
- pre-existing chronic renal disease
- acute pyelonephritis[6].

Acute and rapidly progressive glomerulonephritis

These are rare causes of acute uraemic emergencies and are discussed in an accompanying paper by Dr Gill Gaskin. They are important because delay in instituting specific treatment (eg plasmapheresis, cyclophosphamide, and high dose corticosteroids) may result in irreversible loss of renal function, so condemning the patient unnecessarily to life-long renal replacement therapy, whereas early treatment is usually effective (Fig 5).

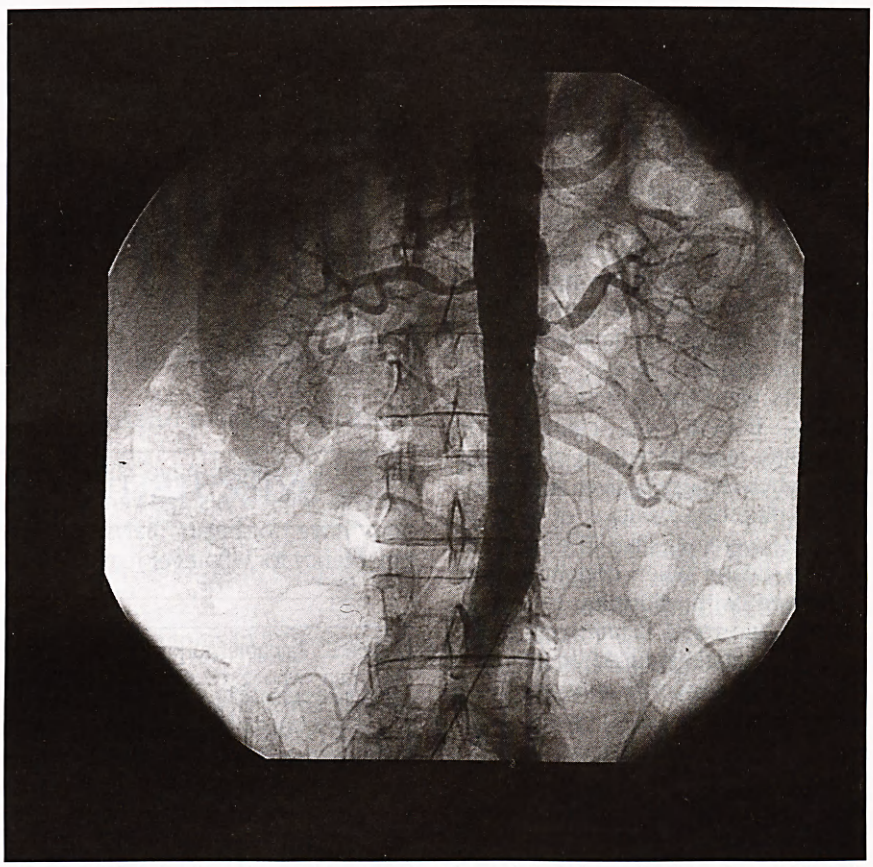


Figure 4. Digital subtraction angiogram showing a tight left renal artery stenosis. Renal impairment is often undetected in these unilateral lesions since creatinine may remain in the normal range after 50% loss of touch.

Initial management

Correction of hypovolaemia and hypotension are the first priorities. This requires replacement of crystalloid, colloid, or blood (depending on, among other factors, what has been lost), and may also require inotropic support. Fluid resuscitation requires frequent reassessment of volume status, sometimes aided by measurements of central venous pressure. There is no place for fluid challenges in an already fluid-overloaded patient with oliguria; the frequent result is pulmonary oedema. Conversely, severe hypovolaemia is often undertreated with fluid replacement.

Serum potassium must be measured daily or more often, and hyperkalaemia treated (with dextrose and insulin, salbutamol, correction of acidosis, and oral or rectal resonium resin) and the myocardium protected with intravenous calcium (unless the patient is on digoxin); refractory hyperkalaemia is an indication for dialysis.

Further renal insults must be avoided if possible: in particular non-steroidal anti-inflammatory drugs should be eschewed and aminoglycosides used only when there is no good alternative and with careful monitoring of blood levels. The outcome is often determined by whether or not secondary infection occurs.

Most importantly, advice from a renal unit should always be sought in case of doubt.

Dopamine

Dopamine increases renal blood flow in normal subjects, and acts as a

potent diuretic and natriuretic. Whether such actions are preserved in acute tubular necrosis is uncertain. Recently, doubt has been cast on the efficacy of renal-dose dopamine in human acute renal failure, particularly because it may cause ischaemia of the gut mucosa[7]. A recent survey of the published literature on the use of renal dose dopamine revealed a paucity of controlled studies. The available studies, in the main, failed to demonstrate benefit, although numbers were small in most of the studies. Benefit was claimed for dopamine over placebo in one study of prophylactic use in liver transplantation; nine other studies of prophylactic use were negative. The situation was no clearer when dopamine was combined with diuretics in established acute renal failure; one small study in malaria-induced acute renal failure was the only one to show benefit[8].

Diuretics

Loop diuretics have theoretical advantages in acute renal failure: by inhibiting energy-dependent ion exchange in the tubule, they should protect against ischaemic damage. However, loop diuretics have never been shown to accelerate recovery of glomerular filtration in human acute renal failure. What they do, sometimes very effectively, is to convert renal failure from oliguric to polyuric in some patients. This increase in urine flow has putative advantages in that it makes space for drugs and nutrition but no study has demonstrated a mortality advantage for diuretics in acute renal failure, and a recent, randomised comparison of frusemide, torasemide, and placebo showed a higher incidence of fits in the diuretic-treated groups[9].

Dialysis

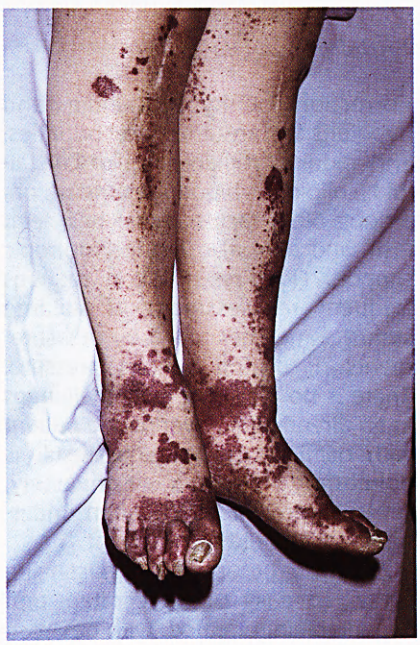
The anticipated need for dialysis is one of the major reasons for transfer of an acute uraemic emergency to a renal unit, although the increasing availability of continuous haemofiltration techniques on intensive care units allows avoidance of transfer of many patients with multiple organ failure. Age *per se* is no barrier to acceptance for dialysis. Indications for dialysis include:

- rapidly rising blood urea
- hyperkalaemia
- severe acidosis
- pulmonary oedema
- pericarditis
- symptomatic uraemia.

The impact of late referral

Numerous studies have shown that patients with end-stage renal failure who have to begin dialysis as an emergency for whatever reason, have a poorer prognosis than those in whom the need for renal replacement therapy has been anticipated and planned for[10]. In some, who present as uraemic emergencies without any prior history, this is unavoidable. However, one of the major reasons for emergency dialysis is late referral of patients with severe uraemia, often despite a well documented history of slowly worsening renal function. In particular, elderly patients, about whose suitability for long-term renal replacement therapy there may be some doubt, are often referred as uraemic emergencies, despite the fact that these are the very patients for whom earlier referral would allow counselling and careful assessment of the advantages and disadvantages of dialysis.

Figure 5. Palpable purpura in a 73-year old man who presented as an acute uraemic emergency having been admitted 5 days earlier to a rehabilitation ward 'off legs'. The rash was present on admission, as were haematuria and proteinuria on dipstick urinalysis. Serum creatinine was 159 µmol/l on admission, rising to 743 µmol/l prior to transfer. Renal biopsy the morning after transfer showed vasculitis affecting arterioles and venules. Renal function improved, and the rash faded, following treatment with methylprednisolone and cyclophosphamide.



Outcome

The outcome of the acute uraemic emergency clearly depends on the cause, and on whether renal failure is found to be acute or chronic. In acute renal failure, recovery of renal function is expected in 90% of uncomplicated cases, 40–50% in cases with combined renal and respiratory failure, and 5–10% in those with multiple organ failure. The prognosis for recovery of renal function is poorer in the elderly, in whom the entity of acute irreversible renal failure is increasingly recognised[11].

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Management of rapidly progressive glomerulonephritis

Gill Gaskin MA, PhD, MRCP *Senior Lecturer, Royal Postgraduate Medical School and Honorary Consultant in Renal Medicine, Hammersmith Hospital, London*

Rapidly progressive glomerulonephritis (RPGN) causes the loss of renal function in a matter of weeks or months. Early recognition is important as treatment may prevent the development of end-stage renal failure.

Causes of RPGN

The glomerular and systemic diseases which may present with RPGN are listed in Table 1. Small vessel vasculitis, usually associated with anti-neutrophil cytoplasmic antibodies (ANCA), is the most common diagnosis[1]. Anti-glomerular basement membrane antibody-mediated nephritis (anti-GBM disease), is much rarer, but is notable as the most rapidly progressive of all.

Clinical picture and investigations

The diagnosis of RPGN should be suspected in the presence of a rapidly rising creatinine with blood and protein in the urine, and is supported by the finding of urinary red cell casts. Until significant uraemia is present, it is rare for symptoms to arise from the nephritis itself.

Characteristic clinical features may reveal the underlying diagnosis – for example the granulomas in the upper and lower respiratory tract of Wegener's granulomatosis. However, certain illnesses may look superficially similar: microscopic polyangiitis, mixed essential cryoglobulinaemia and infectious endocarditis may all cause a febrile illness with vasculitic skin lesions and RPGN. Both vasculitis and anti-GBM disease may present with pulmonary haemorrhage and RPGN, and both may present without extrarenal disease.

Further investigations are aimed at confirming a severe glomerulonephritis, and making a specific diagnosis. Serological tests should include assays for ANCA, anti-GBM and lupus autoantibodies, and assays for cryoglobulins should be considered. Measurements of serum complement components can help distinguish between RPGN due to lupus, cryoglobulinaemia, or infection (certain components reduced) – and vasculitis-associated RPGN and anti-GBM disease (complement levels normal or increased).

These serological markers do not have 100% sensitivity and specificity, and unless the risks are unusually high, a renal biopsy should be performed and examined by light microscopy and for immune

Table 1. Causes of RPGN.

ANCA-associated systemic vasculitis	With extrarenal vasculitis Wegener's granulomatosis Microscopic polyangiitis Without extrarenal vasculitis Idiopathic RPGN
Anti-GBM disease (Goodpasture's disease)	
Crescentic phase of primary glomerulonephritis	For example IgA nephropathy Mesangiocapillary glomerulonephritis
Post-infectious glomerulonephritis	
Other systemic diseases	SLE Mixed essential cryoglobulinaemia Relapsing polychondritis Chronic infection Malignancy