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Management of Acute Renal Failure in the Elderly Patient

A Clinician's Guide

Ching M. Cheung, *Arvind Ponnusamy* and *John G. Anderton*

Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Preston, UK

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Abstract

Numerous anatomical and functional changes occurring in the aging kidney lead to reduced glomerular filtration rate, lower renal blood flow and impaired renal autoregulation. The elderly are especially vulnerable to the development of renal dysfunction and in this population acute renal failure (ARF) is a common problem. ARF is often iatrogenic and multifactorial; common iatrogenic combinations include pre-existing renal dysfunction and exposure to nephrotoxins such as radiocontrast agents or aminoglycosides, use of NSAIDs in patients with congestive cardiac failure and use of ACE inhibitors and diuretics in patients with underlying atherosclerotic renal artery stenosis.

The aetiology of ARF is classically grouped into three categories: prerenal, intrinsic and postrenal. Prerenal ARF is the second most common cause of ARF in the elderly, accounting for nearly one-third of all hospitalized cases. Common causes can be grouped into true volume depletion (e.g. decreased fluid intake), decreased effective blood volume (e.g. systemic vasodilation) and haemodynamic (e.g. renal artery stenosis, NSAID use). Acute tubular necrosis (ATN) is the most common cause of intrinsic ARF and is responsible for over 50% of ARF in hospitalized patients, and up to 76% of cases in patients in intensive care units. ATN usually occurs after an acute ischaemic or toxic event. The pathogenesis of ATN involves an interplay of processes that include endothelial injury, microvascular flow disruption, tubular hypoxia, dysfunction and apoptosis, tubular obstruction and trans-tubular back-leak. Vasculitis causing ARF should not be missed as this condition is potentially life threatening. The likelihood of a postrenal cause for ARF increases with age. Benign prostatic hypertrophy, prostatic carcinoma and pelvic malignancies are all important causes. Early identification of ARF secondary to obstruction with renal imaging is essential, and complete or partial renal recovery usually ensues following relief of the obstruction.

A comprehensive medical and drug history and physical examination are all invaluable. Particular attention should be paid to the fluid status of the patient (skin turgor, jugular venous pressure, lying and standing blood pressure, urine output). Urinalysis should be performed to detect evidence of proteinuria and haematuria, which will aid diagnosis. Fractional excretion of sodium and urine osmolality may be measured but the widespread use of diuretics in the elderly gives rise to unreliable results. Renal imaging, usually ultrasound scanning, is routinely performed for assessment of renal size and to exclude urinary obstruc-

tion. In some cases, renal biopsy is necessary to provide specific diagnostic information.

The general principles of managing ARF include treatment of life-threatening features such as shock, respiratory failure, hyperkalaemia, pulmonary oedema, metabolic acidosis and sepsis; stopping and avoiding administration of nephrotoxins; optimization of haemodynamic and fluid status; adjustment of drug dosage appropriate to glomerular filtration rate; early nutritional support; and early referral to nephrologists for diagnosis of ARF cause, timely initiation of dialysis and initiation of specific treatment. The treatment of prerenal and ATN ARF is largely supportive with little evidence of benefit from current pharmacological therapies.

Despite advances in critical care medicine and renal replacement therapy, the mortality of ARF has not changed significantly over the last 40 years, with current mortality rates being up to 75%.

1. Definition of Acute Renal Failure (ARF)

Acute renal failure (ARF) is common and in one large American study was found to complicate 5% of all medical and surgical admissions.[1] The definition of ARF varies widely in published studies, ranging from severe (e.g. ARF requiring dialysis) to relatively modest observable increases in serum creatinine level (e.g. increase in serum creatinine of 50 μmol/L [0.6 mg/dL] above baseline).[2] In the absence of a universal definition, ARF is generally defined as an abrupt or rapid decline in renal function that results in a rise in blood urea nitrogen or serum creatinine levels, with or without a decrease in urine output occurring over hours or days.

In the absence of a specific definition of ARF, the Acute Dialysis Quality Initiative has recently formulated the Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE) classification, which aims to standardize the various definitions of ARF based on a combination of serum creatinine level and urine output criteria (table I).[3] More recently, the term 'acute kidney injury' has been proposed to encompass the entire spectrum of ARF with the aim of improving patient outcomes.[4]

Conventionally, the 'elderly' population has been defined as those aged ≥65 years. However, with improvements in life expectancy, health and functional ability, some suggest that the 'elderly' in today's world should be regarded as those aged ≥75 years.[5] The incidence of ARF increases with age, being 3.5 times more prevalent in those aged ≥70 years than in younger individuals.[6] In one British community-based study, the overall incidence of severe ARF (defined as serum creatinine >500 μmol/L for the first time in the past 2 years) in the adult population was 172 cases per million per year.[7] A significant increase in incidence with age was observed with 17 cases per million per year documented in those aged 16–50 years compared with 949 per million per year in those aged 80–89

Table I. Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE) classification[3]

Class	Glomerular filtration rate criteria	Urine output criteria
Risk	Serum creatinine × 1.5	<0.5 mL/kg/h × 6 h
Injury	Serum creatinine × 2	<0.5 mL/kg/h × 12 h
Failure	Serum creatinine × 3, or serum creatinine ≥4 mg/dL with an acute rise >0.5 mg/dL[a]	<0.3 mL/kg/h × 24 h, or anuria × 12 h
Loss	Persistent acute renal failure = complete loss of kidney function >4 wk	
End-stage kidney disease	End-stage kidney disease >3 mo	

a For conversion to SI units (μmol/L), multiply by 88.4.

years; 72% of patients with ARF were aged >70 years.

2. Anatomical and Functional Changes in the Aging Kidney

The higher incidence of ARF in the elderly can in part be explained by changes in morphology and function that occur in the aging kidney.

The kidney shrinks with age and by the eighth decade is 2 cm shorter in length with an estimated 40% loss of parenchymal volume.[8] Age-related anatomical changes include: cortical atrophy with relative medullary preservation, decreased glomeruli and proximal tubule numbers, increased glomerulosclerosis and tubulointerstitial fibrosis, increased glomerular volume and intimal thickening of arteries and arterioles.[9-11]

Functional changes in the aging kidney include progressive decreases in renal blood flow (RBF) and glomerular filtration rate (GFR). RBF progressively decreases by up to 50% from age 20 to 80 years.[12] This decline in RBF is thought to be related to an increase in renal vascular resistance resulting from intimal thickening of arteries and arterioles, from a heightened responsiveness to angiotensin II and endothelin[13,14] and from decreased production of vasodilatory prostaglandins and nitric oxide.[15]

The decrease in GFR is the most important functional defect caused by aging. Normal GFR in young adults is approximately 120–130 mL/min/1.73 m^2 and remains fairly constant until the age of 30 years, after which it declines at a rate of 1 mL/min/1.73 m^2 per year.[16] Other factors such as hypertension, diabetes mellitus and hyperlipidaemia, which are all more prevalent in the elderly, have significant influence in increasing the risk for age-related decline in renal function.[17] Serum creatinine levels are often observed to be within 'normal limits' despite significant reductions in GFR relating to progressive loss of muscle mass with aging.

Other changes include the impaired ability of the kidney to concentrate urine, particularly after water deprivation, which increases the elderly person's vulnerability to hypovolaemia.[18]

3. Causes of ARF in the Elderly

The aetiology of ARF is classically grouped into three categories: prerenal, intrinsic and postrenal (figure 1).

ARF is often iatrogenic and multi-factorial in the elderly.[19,20] Examples of common iatrogenic combinations include: pre-existing renal dysfunction and exposure to nephrotoxins such as radiocontrast agents or aminoglycosides; use of NSAIDs by patients with congestive cardiac failure; and use of ACE inhibitors and diuretics in patients with atherosclerotic renal artery stenosis. In one large multicentre prospective trial, 48% of elderly patients (aged ≥80 years) with prior normal renal function developed ARF (defined as an acute rise in serum creatinine level to >177 μmol/L [2 mg/dL] or by ≥50%) during in-hospital stay.[21]

3.1 Prerenal ARF

Prerenal azotaemia is the second most common cause of ARF in the elderly population, accounting for 21–30% of all hospitalized cases.[21,22] The integrity of the renal parenchyma is generally preserved. Common underlying causes are gastrointestinal fluid losses, decreased fluid intake and diuretic treatment (figure 1). Other causes include a reduction in effective circulating volume because of poor cardiac output, systemic vasodilatation and haemodynamic reasons relating to use of NSAIDs (renal vasoconstriction), ACE inhibitor or angiotensin II type 1 receptor antagonist (angiotensin receptor blocker [ARB]) and underlying renal artery stenosis.

The elderly are particularly vulnerable to prerenal ARF due to their impaired mechanisms of renal autoregulation and increased risk of developing hypovolaemia. Reduced thirst sensation,[23] reduced renal ability to conserve sodium and hence water, decreased urine concentrating ability[18] and frequent diuretic usage (25–40% of those aged ≥65 years[24]) are all contributing factors to development of hypovolaemia.

Elderly individuals receive 30% of all prescribed drugs and 40% of all drugs bought over the counter.[25] Consideration of age-related declines in

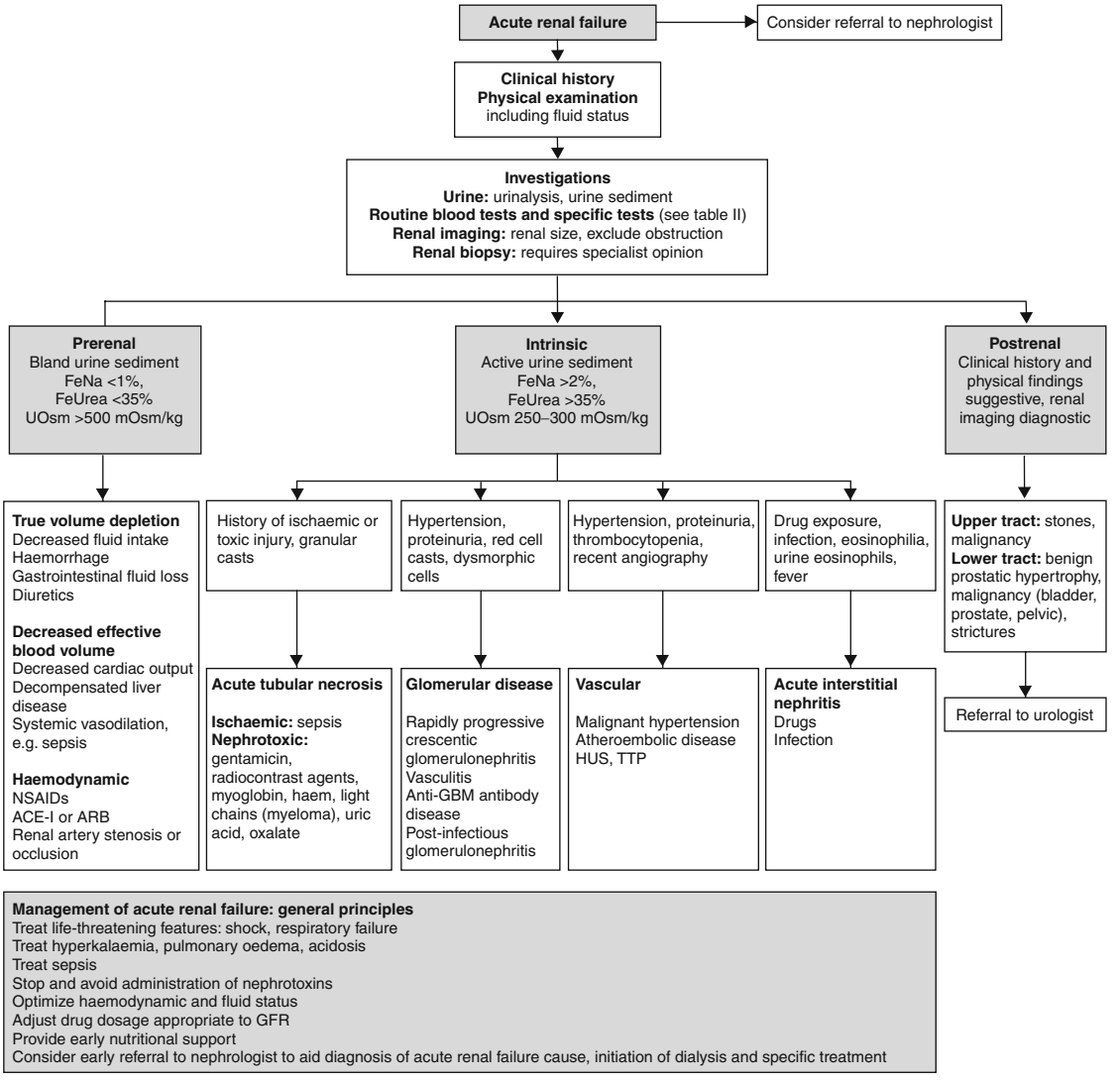

Fig. 1. Algorithm for the management of acute renal failure. **ACE-I** = ACE inhibitor; **ARB** = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker); **FeNa** = fractional excretion of sodium; **FeUrea** = fractional excretion of urea; **GBM** = glomerular basement membrane; **GFR** = glomerular filtration rate; **HUS** = haemolytic-uraemic syndrome; **TTP** = thrombotic thrombocytopenic purpura; **UOsm** = urine osmolality.

GFR, RBF and autoregulation is absolutely essential when prescribing drugs in this patient population.

The elderly are susceptible to ARF induced by nephrotoxic drugs, particularly those that interfere with renal haemodynamics.[26] Frequently prescribed drugs that commonly precipitate haemodynamically related ARF are discussed below.

Because nitric oxide and prostaglandin production are reduced as part of the aging process,[15] inhibition of prostaglandin synthesis in the elderly can precipitate a haemodynamically related ARF.[27] The most common class of drugs to induce ARF via this pathway is NSAIDs. NSAIDs induce renal vasoconstriction through inhibition of cyclo-oxygenase. Most epidemiological studies evaluating the

association between NSAIDs and ARF have shown a 3-fold increased risk for developing ARF whilst taking NSAIDs compared with non-NSAID users.[28] NSAIDs are widely prescribed in the older population with reported usage ranging from 13% to 26%.[29-32] Patients are often unaware of the potential adverse effects of NSAIDs and, when informed of these, the majority would prefer to opt for a safer, albeit less effective, analgesic.[33]

ACE inhibitors and ARBs are increasingly used in the elderly to treat hypertension and heart failure. Use of these agents is frequently associated with renal functional deterioration, especially in elderly patients and those with co-morbidities, but in the majority of patients these agents can be continued without risk of progressive decline.[34] The general consensus is that ACE inhibitors or ARBs should be continued unless there is a >30% rise in baseline serum creatinine after initiation of therapy.[35] However, there should be a high index of clinical suspicion for underlying atherosclerotic renal artery stenosis in patients who exhibit a significant deterioration in renal function with use of these drugs. Cases of ACE inhibitor-related uraemia have been reported since the introduction of these agents in the early 1980s, and they are responsible for at least 3% of all acute uraemic admissions.[36] ARF occurs with renal artery stenosis when glomerular perfusion is critically dependent upon the action of angiotensin II on efferent arteriolar tone. However, the large majority of patients with ACE inhibitor-related ARF have coexisting heart failure and normal renal vasculature.[37] Late detection of ACE inhibitor-associated ARF, usually in vulnerable elderly patients, is commonly the result of poor monitoring following initiation of the drug.[38] Renal function should be checked 1–2 weeks post-initiation to ensure there is no significant rise (>30%) from baseline in serum creatinine. Reversal of renal failure should be expected if these agents are withdrawn in a timely fashion; however, if diminished renal perfusion is prolonged, acute tubular necrosis (ATN) may ensue.

3.2 Intrinsic Renal Disease

Renal parenchymal injury, whether glomerular, tubular or vascular, is the defining feature of intrinsic renal disease. ATN is by far the most common cause of ARF in any age group and is discussed in more detail in section 3.2.1.

Acute glomerulonephritis is the least common cause of ARF. However, the physician should be vigilant for rapidly progressive glomerulonephritis, for example, related to vasculitis, which is potentially life threatening and requires urgent treatment. Acute interstitial nephritis (AIN) accounts for approximately 2–3% of ARF, and in such cases, exposure to certain drugs, for example, NSAIDs and antibacterials, is usually implicated. Infection is the second most common cause of AIN. Vascular causes include vasculitis, scleroderma, atheroembolic renal disease, malignant hypertension and thrombotic microangiopathy.

3.2.1 Acute Tubular Necrosis (ATN)

ATN is responsible for 39–55% of all cases of ARF in hospitalized patients,[21,22] and for up to 76% of cases in intensive care units.[39] Sepsis is the leading cause of ischaemic ATN, occurring in up to 50% of critically ill patients.[40,41] Toxic ATN results from direct tubular damage from nephrotoxins such as aminoglycosides, radiocontrast agents, haem pigments and myeloma light chains.

Pathogenesis

ATN usually occurs after an acute ischaemic or toxic event. Ischaemic ATN can often be the result of prolonged prerenal azotaemia or sepsis; nephrotoxic ATN occurs following exposure to drugs that induce direct tubular damage.

The pathogenesis of ATN involves an interplay between a number of processes that include endothelial injury, disruption of microvascular flow, tubular hypoxia, dysfunction and apoptosis, tubular obstruction and trans-tubular back-leak.[42] Although an in-depth discussion of each of these components is beyond the scope of this review, an excellent detailed review article on this subject is provided elsewhere.[42]

The clinical progression of ATN often, but not always, follows a well defined sequence of three events: initiation, maintenance and recovery.

The initiation phase is characterized by an acute increase in serum creatinine and blood urea nitrogen levels, and a decline in urine output (oliguria or anuria). Hypoperfusion initiates cellular hypoxic injury, mainly affecting the proximal tubules and the thick ascending loop of Henle. The ensuing necrosis of tubular epithelial cells causes tubular obstruction and back-leak of filtrate through the damaged epithelium, through which 50% of the filtrate may be lost.[43] At this stage, the histological appearance is characterized by necrosis of individual tubular epithelial cells, loss of the brush border in proximal tubules, sloughing of necrotic cells leading to tubular obstruction, congestion of peritubular capillaries and extensive inflammatory cell infiltration.[44]

A sustained period of ARF with oliguria or anuria characterizes the maintenance phase, which often lasts for 7–21 days. This is a period when renal support with dialysis may be required pending renal recovery.

The recovery phase is heralded by a dramatic increase in urine output and a subsequent decline in serum creatinine and blood urea nitrogen to baseline or near baseline levels. Polyuria can occur during recovery of ATN despite a normalizing GFR and this is related to delayed recovery of tubular function. Careful monitoring of fluid status and maintenance of adequate hydration is essential. Histologically, the recovery phase is characterized by regeneration of tubular epithelial cells.

Oliguric versus Non-Oliguric

Urine output in ATN can vary from anuria or oliguria to relatively normal values.[45,46] The variation in urine output in ATN is thought to be related to two factors:[47] (i) patients with non-oliguric ATN have a higher GFR than patients with oliguric ATN; and (ii) GFR is the same in both non-oliguric and oliguric ATN but re-absorption at the tubules is less in the non-oliguric state. Non-oliguric ATN does not necessarily have a better prognosis than oliguric ATN. One observational study has shown an increased mortality associated with non-oliguric ATN, a finding which is thought to be related to the delay in starting renal replacement therapy whilst anticipating renal recovery with a relatively preserved urine output.[48]

3.3 Postrenal ARF

The incidence of postrenal ARF increases with age. In one prospective study, incidences of 11% between the ages of 65 and 79 years, and 20% in patients aged ≥80 years compared with 7% in patients aged <65 years were reported.[22] Benign prostatic hypertrophy, prostatic carcinoma and pelvic malignancies are all important causes. Early identification of ARF secondary to obstruction is essential; relief of the obstruction usually results in recovery of renal function. Post-obstructive diuresis frequently occurs following removal of the obstruction. Osmotic or urea diuresis is the most common type and usually resolves within 24–48 hours. Sodium diuresis is the second most common cause and is self-limiting but can last for more than 72 hours. Careful monitoring is required to prevent prerenal ARF through volume depletion or overzealous fluid resuscitation that drives further diuresis.

The diagnosis of postrenal ARF is usually made with ultrasonography, and further imaging to confirm or refute the diagnosis is generally not required. The reported sensitivity and specificity of ultrasound to diagnose obstruction are 98% and 78%, respectively.[49] However, it is important to note that urinary obstruction can still be present even without ultrasound evidence of calyceal dilatation or dilatation of the renal pelvis or the ureter that is proximal to the obstruction.[50] Occasionally, a trial of percutaneous nephrostomy might be required.

4. Diagnostic Approach in ARF

4.1 Assessment of Renal Function

4.1.1 Serum Creatinine

Serum creatinine level is the most widely used marker of renal function in clinical practice. However, it is important to note that in the non-steady state setting of ARF, serum creatinine will not pro-

vide an accurate reflection of GFR because it is influenced by several other factors that include muscle mass, hypercatabolic states and drugs that inhibit tubular excretion of creatinine, such as trimethoprim. Nonetheless, monitoring variations in serum creatinine is generally sufficient to monitor the progress of ARF.

Recent guidelines recommend estimating GFR using prediction equations based on serum creatinine, age, sex, race and body size. The two most commonly used equations in adults include the Cockcroft-Gault equation:[51]

$$\text{Creatinine clearance (mL/min)} = \frac{[140 - \text{age (y)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times (0.85 \text{ if female})$$

and the simplified MDRD (Modification of Diet in Renal Disease) Study equation:[52]

$$\text{GFR (mL/min/1.73 m}^2) = 186 \times (\text{serum creatinine [mg/dL*]})^{-1.154} \times (\text{age [y]})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African race})$$

* SI conversion 1 mg/dL = 88.4 μmol/L

Although the Cockcroft-Gault equation and abbreviated MDRD study equation have good general agreement they cannot be used interchangeably.[53]

4.1.2 Serum Cystatin C

A promising alternative marker of GFR is serum cystatin C. Cystatin C is a non-glycosylated protein that belongs to the cysteine protease inhibitor group of the cystatin superfamily. Cystatin is produced at a constant rate by nucleated cells and is found in relatively high levels in blood and other extracellular fluids. Use of serum cystatin C as a marker of GFR has been widely reported. Several studies have documented greater sensitivity and accuracy of serum cystatin C compared with serum creatinine for detecting mild renal insufficiency.[54] Serum levels of cystatin C are unaffected by age, lean body mass, infection or inflammatory conditions. Hence, cystatin C may be a better marker of GFR in the elderly. However, serum cystatin C assays are not yet widely available.

4.2 Assessment of ARF Cause

4.2.1 Clinical History and Examination

Distinguishing between ARF and chronic renal failure or acute on chronic renal failure without prior serum creatinine results may be difficult. Renal imaging showing kidneys of reduced size with cortical atrophy or cyst formation may provide a clue to the chronicity of renal dysfunction. Medical history and physical examination, including urinalysis, may be helpful in providing further diagnostic clues. Biochemical markers of anaemia, hypocalcaemia and hyperphosphataemia are generally not helpful because ARF can also present with similar biochemical findings.

The list of differential diagnoses of ARF is extensive and the clinical history and examination should therefore be targeted in terms of prerenal, intrinsic and postrenal causes.

4.2.2 Prerenal ARF

Clues to prerenal ARF include symptoms relating to hypovolaemia (increased thirst, decreased urine output, postural hypotension) and causes of hypovolaemia (increased fluid loss – haemorrhage, gastrointestinal or renal losses – or decreased fluid intake); history of decreased effective circulating volume such as congestive cardiac failure; and exposure to NSAIDs, ACE inhibitors, ARBs and diuretics.

4.2.3 Intrinsic ARF

ATN

ATN is suggested by a history consistent with prolonged prerenal ARF and hypotension; evidence of sepsis; exposure to nephrotoxins (drugs, radiocontrast agents, drug overdose); and a history of trauma, muscle tenderness, seizures, drug abuse, alcohol, excessive exercise and limb ischaemia in the case of suspected rhabdomyolysis.

Acute Interstitial Nephritis

AIN is suggested by recent drug ingestion, fevers, rash and arthralgia.

Glomerular Disease

Glomerular disease is suggested by upper respiratory tract symptoms, rash, fever suggestive of vasculitis; recent throat infection suggestive of post-

streptococcal glomerulonephritis; systemic diseases such as systemic lupus erythematosus; and suggestive urinalysis with significant proteinuria and haematuria, urine sediment with red cell casts and dysmorphic red cells.

Vascular Disease

Clues to vascular disease include a recent angiography suggestive of atheroembolism; malignant hypertension; and suspected haemolytic-uraemic syndrome or thrombotic thrombocytopenic purpura with recent diarrhoeal illness, drug ingestion or infection.

4.2.4 Postrenal ARF

Postrenal ARF is suggested by symptoms of prostatism, urgency, increased frequency of micturition, hesitancy and incontinence suggestive of lower tract obstruction, together with flank pain and haematuria relating to upper tract obstruction such as renal stones.

4.3 Investigations

4.3.1 Urinalysis and Urine Sediment

Urinalysis should be performed in all patients with ARF. Detection of urinary blood, protein and leukocytes is helpful for providing diagnostic clues to the cause of renal dysfunction.

Detection of urinary albumin can be easily achieved using a urine dipstick but only if the albumin excretion exceeds 300–500 mg/day. Urine dipstick is only semi-quantitative for protein excretion due to variations in urine concentrations and the inability to detect other proteins. A more reliable method for measuring protein excretion is through a 24-hour collection of urine. However, these collections are frequently cumbersome, time consuming and can be problematic for elderly patients, potentially leading to collection errors and poor compliance. A more simple approach is to calculate the urine protein-creatinine ratio from a single random urine sample;[55,56] this method of quantifying urinary protein excretion is reliable and becoming increasingly favoured in the clinical setting.

Microscopic evaluation of the urine sediment is essential. Red cell casts, dysmorphic red cells and significant proteinuria are generally diagnostic of glomerulonephritis or vasculitis; granular casts or epithelial cells are suggestive of ATN; and pyuria, white cell or granular casts are suggestive of tubulointerstitial nephritis or urinary tract infection.

4.3.2 Urinary Electrolytes and Osmolality

Measurements of fractional excretion of sodium, calculated as follows:

$$\text{FeNa}\ (\%) = \frac{\text{urine}_{\text{Na}} \times \text{plasma}_{\text{creatinine}}}{\text{plasma}_{\text{Na}} \times \text{urine}_{\text{creatinine}}} \times 100$$

may be helpful for distinguishing between prerenal (FeNa <1%) and intrinsic (FeNa >2%) ARF. The value of performing the test decreases if the patient is taking diuretic treatment, which is frequently the case in elderly patients. The resulting natriuresis from diuretics increases FeNa, even in patients with prerenal ARF. In patients receiving concurrent diuretic therapy, measurement of fractional excretion of urea might potentially be more useful as a diagnostic aid than FeNa.[57]

A hallmark of intrinsic ARF is the failure to maximally concentrate urine. Thus, measurement of urine osmolality is often a helpful diagnostic aid with values >500 mOsm/kg being obtained in prerenal ARF, compared with <300 mOsm/kg typically in patients with intrinsic causes.

4.3.3 Other Serum Tests

Table II lists other diagnostic markers for specific renal diseases.

4.3.4 Renal Imaging

Renal imaging is routinely performed for assessment of urinary tract obstruction, urinary stones, renal cyst or mass, disorders with characteristic radiographic findings, renal vascular diseases and vesicoureteral reflux. Ultrasonography is widely available, safe and is the most commonly used radiological technique for evaluating the patient with ARF. Other imaging techniques include CT and magnetic resonance imaging (MRI). Administration of radiocontrast agents with CT should be avoided if at all possible to prevent further renal insult. Use of gadolinium with MRI is associated with life-threatening nephrogenic systemic fibrosis primarily in

Table II. Specific tests in acute renal failure

Disease	Test
Rapidly progressive glomerulonephritis	Anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibody, anti-nuclear antibody, C3/C4 levels, cryoglobulins
Acute interstitial nephritis	Blood eosinophils, urine eosinophils
Multiple myeloma	Serum immunoglobulins and electrophoresis, urinary Bence-Jones protein
Atheroembolic disease	Blood eosinophils, urinary eosinophils, C3/C4
Rhabdomyolysis	Serum creatine kinase, urinary myoglobin
Post-streptococcal glomerulonephritis	Anti-streptolysin O titre

patients with moderate-to-advanced renal impairment (i.e. GFR <30 mL/min).[58] Administration of gadolinium in patients with GFR <30 mL/min is currently not recommended.

4.3.5 Renal Biopsy

The underlying cause of ARF in the elderly can often be difficult to ascertain. Histological findings on renal biopsy commonly do not correlate with pre-biopsy clinical diagnosis.[59-61] In a retrospective evaluation of 259 renal biopsies in older patients (>60 years of age) with ARF, renal histology was in disagreement with the pre-biopsy clinical diagnosis (or differential diagnosis) in one-third of cases.[59] Nevertheless, the procedure is generally safe and well tolerated, and can provide vital diagnostic information that guides specific therapies in ARF.

5. Management of ARF

Figure 1 summarizes the general principles of managing ARF. Regardless of age, initial immediate management is directed at treating life-threatening complications, i.e. hypotension, shock, respiratory failure, hyperkalaemia, pulmonary oedema and severe metabolic acidosis. Providing supportive therapy to optimize renal recovery and preventing further renal insults are mandatory even before a definite cause for ARF has been established.

5.1 Treat Immediate Life-Threatening Complications

5.1.1 Hyperkalaemia

Hyperkalaemia where serum potassium is >6.5 mmol/L is a medical emergency because of an increased risk of cardiac arrhythmias. The medical treatment of hyperkalaemia is summarized in table III. If hyperkalaemia is refractory to medical treatment or ECG changes, the patient should be referred for urgent haemodialysis.

5.1.2 Pulmonary Oedema

Pulmonary oedema is often the result of overzealous fluid resuscitation, particularly in the elderly patient with known cardiac disease. The patient should be initially assessed for the need for immedi-

Table III. Treatment of hyperkalaemia

Treatment	Action	Time to onset of action	Duration of action
Stabilization of myocardium			
Calcium gluconate or chloride	Stabilizes myocardium; prevents K^+-related arrhythmias	1–3 min	30–60 min
Reduction in plasma K^+			
Insulin plus dextrose	Drives K^+ into cells	15–30 min	4–6 h
Salbutamol (albuterol) [usually nebulized]	Drives K^+ into cells	30 min	2–4 h
Removal of K^+			
Calcium resonium	Binds K^+ in gastrointestinal tract and prevents absorption	2–3 h	4–6 h
Haemodialysis or haemofiltration		Immediate	
Decreased K^+ intake			
Low K^+ diet			

ate respiratory support (supplemental oxygen and assisted ventilation). Pharmacological therapy involves diuretics, e.g. furosemide, opioids and nitrates. Higher than usual doses of diuretics are often required in ARF. Within 1–2 hours, the effect of reducing intravascular volume will eventually lower the pulmonary capillary wedge pressure. Furosemide, and possibly other loop diuretics, has an immediate venodilatory effect that decreases pulmonary congestion prior to the onset of diuresis. Opioids such as morphine sulphate have a role to play in reducing patient anxiety and reducing the work of breathing but care should be taken in those with impending airway compromise. Patients who are refractory to such treatments or those unlikely to respond (particularly oligo-/anuric individuals) should be referred for haemodialysis or haemofiltration.

5.1.3 Metabolic Acidosis

Severe metabolic acidosis (pH <7.2) produces systemic vasodilatation, increases the risk of hyperkalaemia and arrhythmias and impairs cardiac function. Intravenous sodium bicarbonate solutions (1.26% or 1.4%) are frequently used to correct acidosis and lower serum potassium levels in patients requiring fluid replacement. Haemodialysis or haemofiltration is usually required in those who are oligo-/anuric or fluid overloaded.

5.2 Stop and Avoid Nephrotoxins

Cessation and avoidance of nephrotoxic agents (e.g. NSAIDs, radiocontrast media, aminoglycosides) are mandatory to prevent perpetuation of ischaemic or toxic injury and to encourage tubular regeneration.[62]

5.3 Optimize Haemodynamics and Fluid Status

Optimization of renal haemodynamics (i.e. adequate intravascular volume, blood pressure and cardiac output) and treatment of the underlying cause of ATN (e.g. sepsis) are essential. Assessment of fluid status through physical examination, i.e. jugular venous pressure, measurements of blood pressure (lying and upright), daily weighings and fluid input and output, provides invaluable information. Invasive haemodynamic monitoring may be needed if physical assessment of fluid status is difficult. Once euvolaemia is achieved, maintenance fluid delivery should generally aim for a positive balance of 500 mL/day. Inotropic support may be required when adequate fluid resuscitation fails to maintain cardiac output or correct hypotension.

5.4 Nutritional Support

Nutrition is an important part of the supportive care of the patient with ARF. Patients are often hypercatabolic and nutritional requirements are high; enteral or even parenteral administration of nutrition may be needed. Elderly patients are at particular risk of malnutrition. It is reported that 1% of elderly individuals in the community are undernourished, increasing to 20% in hospitals and up to 37% in institutions.[63] Nutritional status in ARF is a significant prognostic factor[64] and feeding should be instituted early when nutritional requirements are not being met.

5.5 Dopamine

Dopamine has actions on renal haemodynamics through the activation of dopamine D_1 and D_2 receptors. At low doses, dopamine (0.5–3 μg/kg/min) dilates both the afferent and efferent glomerular arterioles and increases RBF but with little net gain in GFR. This 'renal dose' of dopamine is frequently administered to patients with ARF with the aim of limiting renal injury. However, the frequent use of dopamine for renoprotection is not supported by current published evidence.[65,66] In a multicentre trial by Bellomo and colleagues,[66] 328 patients admitted to intensive care with early renal dysfunction were randomly assigned to low-dose dopamine (2 μg/kg/min) or placebo. No differences were found between groups with respect to renal functional outcome in terms of renal replacement therapy, deterioration of renal failure, length of intensive care or hospital stay and death. A recent meta-analysis of 61 randomized trials incorporating 3359 patients also showed no significant clinical benefit

for low-dose dopamine in patients with or at risk of renal failure.[67] Furthermore, administration of dopamine can be harmful; a recent study has reported that dopamine can induce renal vasoconstriction in older patients (aged >55 years) with ARF, thereby potentially worsening renal perfusion.[68] Additionally, low-dose dopamine is associated with serious cardiac complications such as tachycardia, cardiac arrhythmia, myocardial ischaemia and possibly intestinal ischaemia.[69] The available evidence thus indicates that low-dose dopamine should no longer be used routinely purely for purposes of renoprotection.

5.6 Diuretics

Furosemide is a loop diuretic with vasodilatory properties. It acts on the Na-K-2Cl co-transporter at the thick ascending loop of Henle. High-dose furosemide is often used in patients with oliguric ARF with the aim of improving urine output. Non-oliguric ARF has generally been thought to be associated with a better prognosis than its oliguric counterpart but this has been a largely speculative notion and is not supported by current evidence, as discussed in section 3.2.1. Several prospective trials have consistently failed to show a renal or survival benefit with use of furosemide in patients with ARF.[70-73] The largest prospective, randomized, placebo-controlled study was conducted by Cantarovich et al.[71] In this study, high-dose furosemide (25 mg/kg/day intravenously or 35 mg/kg/day orally) improved urine output in 338 critically ill patients requiring dialysis but did not affect survival or time to renal recovery. Observational data have suggested that use of diuretics in ARF is associated with increased risk of mortality, risk of non-recovery of renal function[72] and permanent hearing loss.[73] Thus, administration of diuretics purely to maintain urine output in ARF has no prognostic benefit and use of this class of agents is no longer recommended except when the aim is to maintain optimal fluid balance.

Mannitol has not been shown to be effective in humans as a means of protecting the kidney from ischaemic or toxic injury despite evidence in support of this from animal studies.

5.7 Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) preferentially vasodilates the afferent arteriole and constricts the efferent arteriole, thus increasing GFR. In animal studies, ANP has been shown to improve glomerular filtration and urinary output.[74] In humans, an early randomized study of 53 patients showed potential benefit for ANP in improving GFR and reducing the risk of progression to dialysis dependence.[75] More recently, the renoprotective effects of ANP were investigated in 61 patients with normal preoperative renal function who underwent cardiac surgery.[76] In this randomized, double-blinded, placebo-controlled study, ANP decreased the risk of need for dialysis. However, a more recent larger randomized, placebo-controlled, multicentre trial of 504 critically ill patients found no overall differences between groups randomized to receive ANP or placebo in terms of mortality, dialysis-free survival or dialysis.[77,78] In the absence of convincing prognostic clinical data, ANP is largely confined to investigational use.

5.8 Fenoldopam

Fenoldopam is a selective $D_{\alpha 1}$ receptor agonist that specifically mediates vasodilatation in the renal and splanchnic circulation. In the normotensive human kidney, fenoldopam has been shown to reduce renal vascular resistance and increase RBF.[79] A potential beneficial role of fenoldopam in ARF has been suggested in several randomized controlled studies of patients undergoing various cardiovascular procedures[80,81] but these studies were small. The most recent and largest randomized controlled trial involved 315 patients from several centres undergoing invasive cardiovascular procedures.[82] This study compared intravenous fenoldopam (0.05 μg/kg/min titrated to 0.10 μg/kg/min) versus placebo. All patients underwent hydration prior to angiography and continued to received fenoldopam for 12 hours. This trial found no significant difference between fenoldopam and placebo in

terms of contrast nephropathy or 30-day rates of death, dialysis or readmission to hospital. Fenoldopam is not routinely used in the setting of ARF.

5.9 Other Pharmacological Therapies

Pentoxifylline, an inhibitor of tumour necrosis factor-α production, has shown promising results in animal studies in preventing progressive renal tubular damage as a result of ischaemic and reperfusion injury,[83] and nephrotoxicity associated with cisplatin[84] and ciclosporin.[85] Data on the role of pentoxifylline in ARF in human are limited.

Several growth factors such as insulin-like growth factor-1, transforming growth factor-α and epidermal growth factor have been shown in animal models to promote renal tubular proliferation following ischaemic renal injury. These findings have not been replicated in humans.

5.10 Future Non-Pharmacological Therapeutic Options

As discussed so far, pharmacological therapy to aid the repair and recovery of ARF in humans has been largely unsuccessful. The kidney has a wonderful ability to regenerate after acute injury but a prerequisite for such regeneration is that a critical number of surviving cells be preserved. An exciting area of research is the use of mesenchymal and haemopoeitic stem cells in acute renal repair. Experimental and animal studies have shown promising results[86,87] with reports of mesenchymal and haemopoeitic stem cells differentiating into tubular epithelial cells and enhancing tubular proliferation. With more evidence supporting the role of stem cells in humans, this unique therapy could potentially improve mortality and morbidity associated with ARF.

5.11 Renal Replacement Therapy

Renal replacement therapy is required in about 85% of patients with oliguric ARF and in about 30% of patients with non-oliguric ARF.[88] ARF in the context of multi-organ failure is increasingly recognized and management of such cases is usually in the setting of the intensive care unit. There are some guidelines for initiating renal replacement therapy (table IV); however, whether renal replacement therapy should be initiated early or whether it should be initiated at all should be assessed on an individual basis and usually requires specialist opinion. Factors such as dialysis modality (intermittent haemodialysis, continuous renal replacement therapies), dialyzer membrane characteristics and dosing strategies might affect clinical outcome in terms of renal recovery and patient survival;[89-92] however, the results of clinical trials have been conflicting.

6. Prognosis of ARF in the Elderly

6.1 Renal Survival

In general, with optimum supportive treatment, the majority of patients with ATN have significant renal recovery even after a prolonged period of dialysis. Renal recovery usually occurs 1–3 weeks after the initial insult. The recovery phase is usually reflected by an increase in urine output followed by a progressive fall in serum creatinine back to baseline levels in the majority. Results from early studies have shown that 43–67% of elderly patients recover renal function completely, with 2.7–6% requiring long-term maintenance dialysis.[93,94] A more recent prospective study of 433 critically ill patients with ATN receiving renal replacement therapy reported that none of the 226 survivors required renal replacement support on discharge.[95] These investigators reported that, on discharge, 57% had normal renal function, 33% had mild-to-moderate renal failure (serum creatinine: 1.3–3 mg/dL [115–265 μmol/L]) and 10% had severe renal failure (serum creati-

Table IV. Guidelines for initiation of renal replacement therapy

Severe hyperkalaemia: >6.5 mmol/L, unresponsive to medical treatment or with ECG changes
Severe acidosis: pH <7.2
Blood urea level >30–50 mmol/L
Uraemic encephalopathy
Uraemic pericarditis
Drug overdose with a dialyzable toxin

nine: 3–6 mg/dL [265–530 μmol/L]). Cause of ARF,[96] pre-existing chronic renal dysfunction[97] and severity of illness[98] are all independent risk factors for non-recovery of renal function. The influence of age on renal and patient survival in ARF is debated. Many studies of ARF have failed to show any relationship between increased age and prognosis,[95,96] but conflicting results have been reported in other studies.[99,100] In general, age alone should not be a barrier to therapeutic decisions relating to ARF.

There are concerns that dialysis itself might delay renal recovery through perpetuation of renal injury during episodes of hypotension occurring while the patient is on haemodialysis, and through activation of various inflammatory pathways due to membrane bioincompatibility.[89-91] Changes to biocompatible membranes have been shown to improve patient mortality and renal functional recovery.[89,91]

6.2 Patient Survival

Despite advances in critical care medicine and renal replacement therapy, the mortality of ATN necessitating dialysis remains 45–75% in critical care units.[95] Several factors that have significantly impacted on mortality in ATN have been defined in a number of multicentre prospective trials.[101-104] One large multicentre trial of 256 critically ill patients defined several characteristics that are predictive of mortality at 60 days: male sex (relative risk [RR] 2.01), oliguria (RR 2.25), intubation or mechanical ventilation (RR 1.86), acute myocardial infarction (RR 3.14), acute stroke or seizure (RR 3.08) and hypoalbuminaemia (RR 0.56 per 1 g/dL increase in serum albumin concentration).[101] Patient age was not predictive of mortality or dialysis. ARF itself is an independent risk factor for mortality.[102]

As noted in section 5.4, malnutrition is found in 20% of hospitalized elderly patients.[63] Poor nutritional status in the context of ARF is predictive of mortality. A large prospective study of 309 patients with ARF has shown that pre-existing or hospital-acquired nutritional status was significantly predictive of death.[105] Severe malnutrition was common and was found in 42% of patients with ARF. Severe malnutrition was also significantly associated with a 7-fold increased risk of in-hospital mortality compared with those with normal nutritional status.

There is a tendency to treat elderly patients with ARF less aggressively than younger individuals. However, prospective and retrospective studies have not shown that age alone is a poor prognostic maker in ARF in terms of renal functional recovery and mortality. Indeed, mortality and renal functional recovery are similar in older and younger patients when ATN is present.[22,101,106,107] Age alone should therefore not be used as a discriminating factor when making therapeutic decisions; dialysis should not be withheld from patients solely based on their age.

Delayed nephrology consultation has been associated with increased morbidity and mortality. Mehta and colleagues[108] found that a delayed nephrology consultation occurred in 28% of critically ill patients with ARF and resulted in increased duration of stay in the intensive care unit and higher mortality. Delayed consultation was more likely to occur if urine output was maintained or in the presence of lower serum creatinine levels. Interestingly, consultation with nephrologists was less likely to occur with increasing age. In a retrospective UK-based study of 311 patients with ARF, 100% of patients aged between 0 and 19 years were referred for a nephrology opinion compared with only 5% of those aged ≥80 years.[109] As discussed in section 4.3.5, diagnosing the underlying cause of renal insufficiency can be difficult in the elderly and often the clinical diagnosis does not correlate with the tissue diagnosis.[59,60] Early nephrology referral is recommended to aid accurate diagnosis and to guide specific treatments with the aim of improving patient outcome in ARF. Age alone should not be a barrier to specialist consultation.

7. Other Specific Renal Diseases

The incidence of certain renal diseases is higher in elderly individuals than in younger adults. Among such diseases are contrast-induced nephropathy (CIN), rapidly progressive (crescentic) glomer-

ulonephritis, atherosclerotic renovascular disease, atheroembolic disease and multiple myeloma.

7.1 Contrast-Induced Nephropathy

CIN is a significant common cause of ATN and is characterized by an increase in serum creatinine that usually occurs 12–24 hours after the radiocontrast procedure. CIN is an important cause of ARF in elderly patients, accounting for up to 17% of cases.[20,110] The incidence of CIN can vary from 0% to 50% depending upon: the patients studied, the presence of pre-existing risk factors (chronic kidney disease, diabetic nephropathy, reduced circulating volume, use of ACE inhibitors or ARBs)[111-113] and the type and amount of radiocontrast used (the risk is highest with high-volume and non-ionic contrast).[112,114,115]

Prevention of CIN is essential. To this end, use of low-volume non-ionic contrast agents,[115] avoidance of repetitive closely-spaced studies and adequate hydration with intravenous normal saline[116,117] or sodium bicarbonate[118] prior to the procedure are all effective measures for preventing contrast-induced ARF.

Use of N-acetylcysteine (NAC) on a prophylactic basis is of debatable value. NAC has antioxidant and vasodilatory properties and could potentially prevent CIN. However, several prospective studies examining the use of NAC have reported conflicting results, mainly because of the heterogeneity across trials of the study population, the definition of CIN, the amount and type of contrast used and the differences in NAC dosing and administration of intravenous fluids.[116,119-127] NAC appears to affect tubular handling of creatinine and therefore may lead to a falsely lower serum creatinine level with no effect on GFR.[128] Numerous meta-analyses have been published, the findings of which have again varied widely from no significant benefit to risk reductions of CIN by as much as 56%.[129-134] Some argue that given the increased mortality of contrast-induced ARF,[135] the evidence for a potential benefit of NAC and the fact that oral NAC has few adverse effects, is generally well tolerated and inexpensive means that high-risk patients should be considered for prophylactic NAC (600–1200 mg twice daily, administered the day before and on the day of the procedure).

There is some evidence to suggest a role for HMG-CoA reductase inhibitors (statins) in reducing the risk of CIN through their anti-oxidative and anti-inflammatory properties. One observational study of 29 409 patients undergoing percutaneous coronary intervention reported a significantly lower incidence of CIN (defined as an increase in serum creatinine by ≥0.5 mg/dL and/or >25%) in patients receiving pre-procedural statin therapy (8.8%, compared with 11.9% in patients not taking statins).[136]

There is currently no proven role for prophylactic dialysis or haemofiltration in CIN.[137,138]

7.2 Rapidly Progressive (Crescentic) Glomerulonephritis and Vasculitis

ARF relating to systemic vasculitis warrants further discussion as diagnosis of this condition is often difficult and late management can result in life-threatening complications. Early diagnosis and treatment are therefore essential.

There have been few epidemiological studies of primary systemic vasculitides (including Wegener's granulomatosis, microscopic polyangitis, polyarteritis nodosa, Churg-Strauss syndrome) in the elderly. One prospective study from 1988 over a 10-year period in the UK showed an overall annual incidence of 20 per million (diagnosis based on the classification criteria of the American College of Rheumatology and definitions by the Chapel Hill Consensus Conference).[139] In this study, primary systemic vasculitis was found to be more common in the elderly, with an age-specific peak incidence at 65–74 years of age (60 per million per year).

The most common clinical manifestation of systemic vasculitis is ARF with hypertension. Haematuria and proteinuria on urinalysis are frequently observed and urine microscopy reveals red cell and granular casts. Histology characteristically shows focal necrotizing glomerulonephritis with crescent formation. Individuals with renal involvement usually have circulating antibodies directed at neutrophil cytoplasmic antigens,[140] making testing for

anti-neutrophil cytoplasmic antibodies essential in the diagnosis of vasculitis-associated ARF. Immunofluorescence should always be followed by ELISA testing; when these two assays are combined, a sensitivity of up to 82% and a specificity of 99% have been achieved.[141,142] It is important to note, however, that a negative anti-neutrophil cytoplasmic antibody test cannot exclude systemic vasculitis. This emphasizes the importance of renal biopsy in making the diagnosis and guiding treatment.[59,60,143,144]

The prognosis of rapidly progressive glomerulonephritis due to underlying systemic vasculitis is extremely poor in the absence of treatment. Aggressive initial therapy with intravenous high-dose methylprednisolone and oral or intravenous cyclophosphamide has resulted in impressive renal recovery and remission rates of nearly 90%[145-147] with renal survival maintained at 75% at 5 years.[148] Serious treatment-related morbidity such as sepsis and malignancy can be as high as 42% with immunosuppressive treatment.[149] It is frequently thought that older patients are more likely to experience therapy-related serious adverse events but there are few data to support this. Alternative induction regimens include use of methotrexate. Methotrexate has been reported to be as effective as cyclophosphamide in inducing remission but relapse rates are higher and, because of increased toxicity in renal insufficiency, its use is limited to those with near-normal renal function.[150]

Remission is usually achieved in 3–6 months following induction therapy.[151] Azathioprine, administered at a dose of 2 mg/kg/day in most patients, is the drug of choice for maintaining remission. The CYCAZAREM (Cyclophosphamide versus Azathioprine during Remission for Generalised Vasculitis) trial reported similar efficacy of azathioprine to cyclophosphamide in maintaining remission, allowing the safe withdrawal of cyclophosphamide after 3 months.[151]

Pulmonary haemorrhage is a definite indication for plasma exchange. It is also generally recommended that patients who are dialysis-dependent at diagnosis should be offered plasmapheresis. Several small trials and data from the MEPEX (Methylprednisolone versus Plasma Exchange) trial have shown significant benefits for plasma exchange in improving renal functional outcome in dialysis-dependent patients.[152-154] To date, no benefit has been shown for non-dialysis-dependent individuals.[146]

Left untreated, primary systemic vasculitis has a mortality rate of 90% within 2 years. Increasing age, severity of renal disease and sepsis are adverse prognostic indicators of renal functional recovery and mortality.[153,155,156] The introduction of cyclophosphamide regimens has dramatically reduced mortality rates, with more than 75% of patients now surviving 5 years.[155] Some investigators have reported better survival rates of 80%[149] and 88%[157] at 8 years and 12 years, respectively. Newer agents, including therapeutic recombinant proteins aimed at cytokine blockade or lymphocyte depletion, are emerging and there is hope that they can reduce toxicity and improve renal and patient survival.[158]

7.3 Atherosclerotic Renovascular Disease and Atheroembolism

Underlying atherosclerotic renal artery disease is present in 42% over the age of 75 years.[159] It is commonly associated with chronic kidney disease and end-stage renal failure. ARF or deterioration on a background of chronic kidney disease in an individual with underlying renal artery stenosis usually occurs in the context of hypovolaemia, hypotension, cardiac failure, use of ACE inhibitors or ARBs or cholesterol embolization.[160] Although infrequent, presentation of anuric ARF in a patient with underlying renal artery stenosis should alert the physician to the possibility of acute renal artery occlusion (bilateral or unilateral in a patient with a single kidney).[160]

Cholesterol embolization is mainly a disease of the elderly with the mean age of affected patients being 71 years in one prospective study.[161] Cholesterol embolization is a common cause of ARF in the older population. In an analysis of 259 renal biopsies from patients aged ≥60 years with ARF, atheroembolic disease accounted for 7.1% of all cases of ARF.[59] Atheroembolic disease should be suspected

when acute renal insufficiency develops in patients with atheromatous disease who undergo aortic surgical or angiographic procedures,[162,163] thrombolysis[164] or anticoagulation.[165] The incidence of atheroembolic disease following angiographic procedures has been quoted to be 1.4–2%.[162,166] The associated clinical features of cholesterol embolization include purpuric rash or livedo reticularis, focal digital ischaemia, proteinuria and eosinophilia. Demonstration of characteristic clefts left by cholesterol crystals in tissue biopsy specimens is a pathognomonic finding. Cholesterol embolization may be responsible for a spectrum of renal impairment: some patients manifest only a moderate loss of renal function with subsequent improvement, whereas in others, progressive renal failure occurs. An eventual return of kidney function can occur even after a prolonged period of renal insufficiency.[163]

There is currently no proven effective medical treatment that will affect outcome in patients with renal atheroembolic disease, and treatment is primarily supportive. Nevertheless, treatment should be given for vascular protection, which includes aspirin (acetylsalicylic acid), statins, glycaemic control and blood pressure control. The prognosis remains poor, with nearly 40% of patients dying within 5 years.[161]

7.4 Acute Interstitial Nephritis

AIN accounts for approximately 2–3% of ARF. However, in a retrospective analysis of 259 renal biopsies for investigation of ARF in older patients, AIN accounted for nearly one-fifth of causes.[59] Drugs are the most common cause of AIN, accounting for 71% of all cases, with one-third of these being attributed to antibacterial therapy.[167] Infection is the second most common aetiological cause.

AIN is thought to be more common in the elderly because of the increased exposure to prescribed and over-the-counter drugs, particularly NSAIDs. Table V lists the most common drugs that can cause AIN; however, this list is not exhaustive. Timely withdrawal of the offending agent usually results in renal recovery. In the absence of renal recovery, immunosuppressive therapy with corticosteroids is usually given based on the results of a small series of uncontrolled studies.[168-170] To date, no large randomized controlled trial has been performed to assess the efficacy of corticosteroids in AIN.

Table V. Drugs commonly implicated in acute interstitial nephritis

NSAIDs, including cyclo-oxygenase-2 inhibitors
Antibacterials: penicillins and cephalosporins, rifampicin (rifampin), ciprofloxacin, cotrimoxazole
Proton pump inhibitors: omeprazole, lansoprazole
Cimetidine
Allopurinol
5-Aminosalicylates

8. Prescribing in the Elderly

Age-related changes in GFR, RBF and autoregulation must be considered when prescribing drugs to elderly patients. Since GFR may be significantly impaired despite an apparently normal serum creatinine level, calculation of GFR (Cockcroft-Gault or MDRD equations) is essential when estimating renal function. This is particularly important with drugs that are both dependent on renal excretion and have a narrow therapeutic index or are nephrotoxic. Dosages of renally excreted drugs should be adjusted according to estimated GFR. Failure to account for impaired renal function in the elderly is in part responsible for the increased incidence of iatrogenic drug-related ARF.

9. Conclusions

ARF is a common problem in the elderly population. Regardless of advances in critical care medicine and renal replacement therapy, the mortality of this condition in this age group remains extremely high. As with any age group, prerenal and ATN combined account for the majority of ARF. The treatment of prerenal and ATN ARF is largely supportive with little evidence of benefit from current pharmacological therapies. Early recognition is essential to avoid further insults and to initiate treatment aimed at optimizing renal recovery. Even with optimal care, non-recovery of renal function with residual mild-to-moderate renal dysfunction occurs in 33% of patients, and severe renal dysfunction in 10%, most commonly in patients with pre-existing

renal impairment and those who are older.[171] A specific diagnosis of the cause of ARF should be sought with consideration for the need for nephrology referral to aid diagnosis and ensure timely initiation of renal replacement therapy. Early diagnosis of specific acute glomerulonephritis, particularly when related to vasculitis, is essential to allow urgent treatment. Whether or not age is an independent prognostic marker for renal and patient survival remains unanswered; the evidence on this point is conflicting. Nonetheless, age alone should not influence therapeutic strategies or be a barrier to specialist consultation.

The elderly are especially vulnerable to development of ARF because of various changes to renal physiology and increased co-morbidity in this age group. ARF in the elderly is often iatrogenic and multi-factorial. It is essential that physicians recognize the increased susceptibility of elderly patients to ARF and aim to prevent development of the disorder by avoiding prescriptions of nephrotoxic drugs and interventions that increase this risk.

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Correspondence: Dr *Ching M. Cheung*, Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Preston, PR2 9HT, UK.
E-mail: Ching-Mei.Cheung@cmmc.nhs.uk