Q J Med 2001; **94**:533–540

Non-specialist management of acute renal failure

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Received 29 December 2000 and in revised form 1 August 2001

Summary

In a 12-month prospective study of the initial management of patients with acute renal failure (ARF) in East Kent (population 593 000), we evaluated the initial management of ARF and assessed what proportion of ARF may have been preventable. Patients were seen and assessed on a daily basis, and were followed until discharge from hospital or death; survivors were subsequently followed for 3 years. Overall, 288 patients developed ARF (486 per million population/year). Mean age at presentation was 73 years (range 14–96). Initial assessment was often suboptimal, and key features in investigation and initial management were often lacking. In 108 cases, ARF was iatrogenic and/or potentially preventable (53 preventable, 99 iatrogenic, 44 both). Overall survival was 56% at discharge from hospital, 35% at 1-year follow-up, 31% at 2 years, and 28% at 3 years. In discharged patients, recovery of function was complete in 69%. A significant proportion of ARF is preventable. Clear guidelines, easily accessible at the point of care, could aid the diagnostic evaluation of the patient with ARF and indicate where referral for a specialist opinion is appropriate.

Introduction

ARF is characterized by a rapid, potentially reversible, decline in renal excretory function occurring over a period of hours or days. Prompt recognition and appropriate early management can prove crucial in terms of outcome. The majority of ARF is first subject to initial management by non-specialist clinicians, generally at a comparatively junior level. The model core curriculum in adult renal medicine suggests that a qualified doctor should be able to recognize the symptoms and signs of ARF, request and interpret appropriate initial investigations, initiate appropriate therapy, and know when and how urgently to refer the patient to a more experienced colleague or specialist.[1] In a community-based study of ARF (defined as a serum creatinine >500 μmol/l) Feest *et al.* found that 51 cases per million population (pmp) per year were referred for specialist opinion.[2] The overall incidence was 140 episodes pmp/year and after scrutinizing the notes of those not referred, they estimated an appropriate referral rate would have been 70 pmp/year. More recently a retrospective study looked at the incidence, factors affecting referral, and outcome of ARF in an unselected population in the Grampian region of Scotland.[3] ARF was defined as a temporary rise in serum creatinine to $\geqslant 300$ μmol/l, or clinical features indicating an acute deterioration of previously normal renal function. Advanced ARF was defined as a first measured serum creatinine $\geqslant 500$ μmol/l. The incidence of ARF was 620 pmp/year and that of advanced ARF 102 pmp/year. A nephrology opinion was sought in 22% of patients overall, and in 35% of those with advanced ARF. The design

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of both of these studies precluded assessment of patients and their management at the time of presentation with ARF.

This current study prospectively addressed the initial management of ARF in all patients admitted to hospitals in the East Kent Health Authority area over the course of 12 months from March 1997 to February 1998. Survivors were then followed-up for a minimum of 3 years to assess long-term outcome. The aims of the study were to determine the epidemiology of ARF in East Kent, to evaluate the initial management of ARF by non-specialists, and to determine what proportion of ARF was iatrogenic and/or potentially preventable. This paper describes the initial management and long-term outcome of ARF, and considers those cases of ARF that were iatrogenic and potentially preventable. We also investigated whether the age of a patient at presentation appeared to influence the subsequent management.

Methods

The study was done in the East Kent Health Authority area, comprising a population of 593 000 (1996 mid-year population statistics) served by three district general hospital Trusts at the time of the study. Before commencing, we sought permission from all consultants in the Trusts for a member of the renal team (PES, NAT, MKA-H, AIM, DIP or PC) to come and assess patients admitted under their care without prior referral. Throughout the study period, all in-patient serum creatinine and urea values $\geqslant 300$ μmol/l and $\geqslant 40$ μmol/l, respectively, were extracted by computer from all results issued by each laboratory that day and brought to the attention of the renal team. These levels were chosen in accordance with the Renal Association biochemical definition of ARF.[4] The patients were clinically assessed within 24 h of notification and their management was reviewed. Case notes, drug charts and nursing notes were also reviewed. Only patients with ARF were included in the analysis. ARF was defined as a temporary rise in serum creatinine to $\geqslant 300$ μmol/l (and/or a rise in urea to above 40 μmol/l), or clinical features indicating an acute deterioration of previously normal renal function. Patients with previously-known impaired renal function who had a serum creatinine of <250 μmol/l and had a rise of at least 50% above their initial presenting value were included as acute on chronic renal failure (after the methods of Liaño *et al.*[5]). Patients with chronic renal failure (serum creatinine >250 μmol/l), patients with myeloma and previously deteriorating renal function, and patients with hydronephrosis and cortical atrophy were all excluded. Patients in whom the renal failure was considered to have occurred in the context of an untreatable terminal illness (such as metastatic disease) were also excluded from analysis. Patients who were visiting the area and developed ARF were also excluded from the study.

The information collected at the time of assessment is shown in Table 1. Any clinical interventions relevant to underlying renal function, either beneficial or detrimental, were also recorded. After assessment of the initial management, the reviewing member of the nephrology team gave appropriate advice with respect to further investigation and management, or suggested transfer to the renal ward where clinically indicated. Key assessments were those helping to distinguish prerenal, renal, and postrenal ARF. These included assessment of fluid status, urinalysis, and renal tract imaging. Additional desirable assessments included measurement of respiratory rate and/or oxygen status, search for underlying sepsis (blood cultures and C-reactive protein estimation), assessment of acid/base status and measurement of calcium/phosphate levels. The assessment of ARF was judged to have been complete in patients receiving all of these assessments. Patients who had none of the three key assessments had no useful assessment of their ARF.

Preventable ARF was defined as the development or failure of resolution of ARF directly related to an intervention, or lack of intervention; for example, the introduction of ACE inhibition leading directly to ARF, or the failure to recognize the introduction of ACE inhibition as the cause of ARF. Iatrogenic ARF was defined as the development of ARF that related directly or indirectly to a

Table 1 Information collected at time of initial assessment and subsequent follow-up

Reason for admission: acute/elective, ward of origin
Coexisting medical disorders and treatment regimen
Presence of other system failure, inotrope or ventilator dependency
Vital signs, CVP, other invasive cardiovascular monitoring, oxygen saturation
Presence of urethral catheter, record of urine output
Serum and urine biochemistry, arterial blood gas analysis
Haematology including clotting studies
Microbiology
Radiological assessment
Aetiology of ARF and whether sepsis-associated
Type and duration of renal replacement therapy
Outcome: renal functional recovery and patient survival
Follow-up at 3 months, 1 year, 2 years and 3 years post-presentation

therapeutic intervention, which may not necessarily have been preventable (for example, an episode of fluid depletion in a patient already undergoing treatment with ACEIs and NSAIDs).

Survival outcome was assessed at time of discharge from hospital, and at 3 months, 12 months, 24 months, and 36 months post-presentation with ARF. In survivors, renal function was judged to have recovered completely if the serum creatinine level returned to the normal range in patients with established ARF on admission to hospital, or to known premorbid levels in those who had developed ARF during the course of their hospital admission.

Results were expressed as percentages. Ages were expressed as means $\pm$ SD. Statistical significance was assessed by Student's *t*-test and χ^2 analysis using SPSS statistical software. A p value <0.05 was considered significant.

Results

During the study, 323 patients with ARF were identified (545 pmp per year), of whom 35 were excluded from analysis because their ARF occurred in the context of untreatable terminal illness. The mean age at presentation for the remaining 288 patients was 73.03 ± 13.43 years (range 14–96 years); 195 patients (68%) were aged 70 years or over. There were 185 males and 103 females. Forty-two (14.6%) fulfilled the criteria for acute on chronic renal failure. Forty-eight patients received renal replacement therapy (17%). Survival to discharge from hospital was 56% (161/288), and was higher in those aged <70 years (65%) compared with those aged 70 and above (53%). At 3 months following discharge, overall survival had fallen to 47%, falling further to 35% at 12 months, 31% at 24 months, and 28% at 36 months.

Table 2 summarizes the initial assessments and investigations carried out in all 288 patients, together with a comparison of the elderly vs. younger age groups, and with a subgroup of patients with sepsis-associated ARF. Overall, in 78/288 there was no record of urine output. Only seven of these 78 patients had any assessment of fluid status (by CVP measurement). Urinalysis was recorded in 164/288. Information about renal size and shape and presence or absence of obstruction was sought in 137/288. In total, 81 patients had all three of these key assessments, 100 patients had 2/3, 75 patients had only one, and 32 patients did not have any (Figure 1). Only 21 patients had all of the key and desirable assessments performed. Long-term outcome appeared significantly better in patients receiving more key assessments; at 36 months of follow-up, 36 (44%) of the 81 receiving all three key assessments were still alive, compared with 27/100 (27%) receiving two key assessments, 14/75 (19%) receiving only one, and 5/32 (16%) who had none ($p=0.001$).

Although patients under the age of 70 had a greater percentage of investigations performed compared with those aged $\geqslant 70$ years, a greater proportion of those under 70 were in a critical care area (33% vs. 9% of those aged $\geqslant 70$ years) where a significantly greater percentage of assessments and investigations were performed in comparison with medical and surgical wards (Table 3).

Table 2 Assessment and investigation: All cases of ARF compared with elderly vs. younger age groups and with sepsis associated ARF

Assessment/investigation	All ($n=288$)	Age <70 ($n=93$)	Age $\geqslant 70$ ($n=195$)	Sepsis-associated ($n=73$)
Record of urine output	73	81	69	79
Record of respiratory rate	29	39	25	38
Bladder catheterization	68	63	71	49
Central venous pressure	32	46	26	47
Renal tract imaging	48	54	45	45
Chest radiography	71	82	66	86
Urinalysis	57	63	54	73
Blood cultures	42	56	35	67
C-reactive protein	18	18	18	32
Assessment of acid-base status	60	75	53	78
Assessment of oxygen status	30	45	23	49
Clotting studies	42	55	36	56
Calcium and phosphate studies	66	81	59	75

All data are percentages of cases.

Correcting for the ward of origin revealed higher rates of bladder catheterization in the elderly on medical wards ($p<0.01$); significantly less renal tract imaging ($p<0.05$), assessment of acid-base status ($p<0.05$), and oxygen status ($p<0.05$) in the elderly on surgical wards; and significantly less calcium and phosphate studies in the elderly on both medical and surgical wards ($p<0.05$). All three key assessments were undertaken in 47/195 patients aged $\geqslant 70$ years (24%) compared with 34/93 patients aged <70 years (37%).

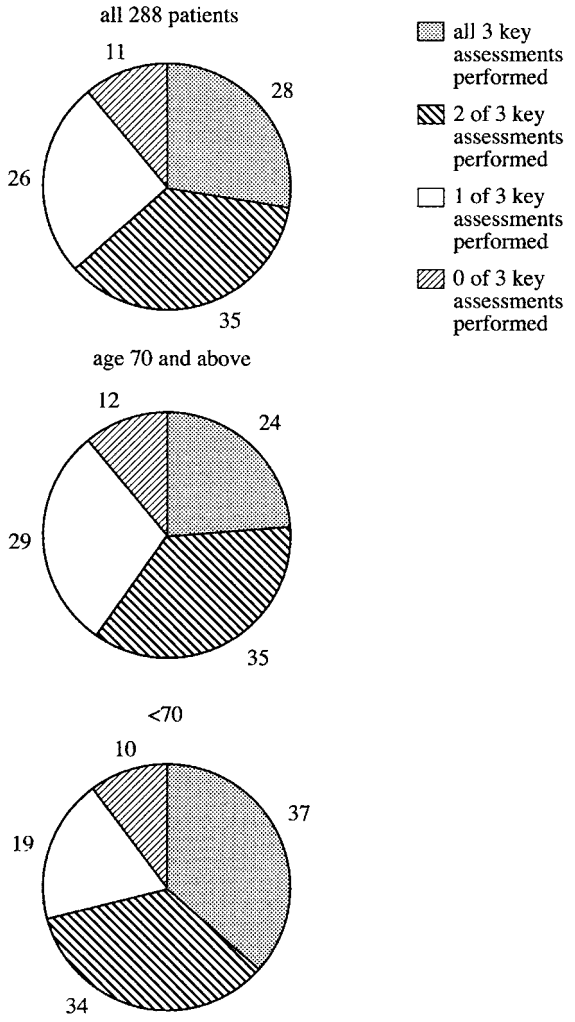

Figure 1. Key assessments in ARF (%).

In 73 patients the development of ARF was associated with sepsis, and here too there were key deficiencies in the initial assessments (Table 2): in particular, the recording of respiratory rate, assessment of oxygen status, measurement of C-reactive protein, CVP monitoring, and request for blood cultures.

The majority of cases (177/288) came from medical wards; 62 cases came from the surgical wards and 49 from critical care areas (ITU, HDU, CCU). There were no major differences in assessment and investigation between medical and surgical wards (Table 3), although chest radiography was requested more frequently on the medical wards ($p<0.001$) and bladder catheterization was more commonly performed on surgical wards ($p<0.01$). In patients developing ARF in a critical care setting (HDU/ITU/CCU), a significantly greater percentage of assessments and investigations were performed in comparison with medical and surgical wards, with the notable exception of renal tract imaging. The three key assessments were undertaken in 17/49 critical care patients (35%), 51/177 medical patients (29%), and 13/62 surgical patients (21%).

In 53 cases, ARF was judged to have been preventable, 36 of which were drug-related (Table 4). In eight cases, unrecognized volume depletion or overdiuresis was the cause, and in six, unrecognized obstructive uropathy. Other causes

Table 3 Investigation/assessments in medical, surgical and critical care wards

Assessment/investigation	Medical wards ($n=177$)	Surgical wards ($n=62$)	HDU/ITU/CCU ($n=49$)
Record of urine output	67	74	94
Record of respiratory rate	18	23	78
Bladder catheterization	58	79	94
Central venous pressure	19	21	94
Renal tract imaging	49	48	43
Chest radiography	72	44	100
Urinalysis	56	48	71
Blood cultures	41	29	63
C-reactive protein	18	11	27
Assessment of acid-base status	58	45	90
Assessment of oxygen status	18	19	88
Clotting studies	34	37	80
Calcium and phosphate studies	64	53	88

Table 4 Causes of preventable and iatrogenic ARF

	Preventable ARF	Iatrogenic ARF
ACEI/AII antagonist-related alone	7	11
+ fluid depletion	6	33
+ NSAIDs	1	4
+ fluid depletion & NSAIDs	2	5
+ contrast media	2	2
NSAIDs-related alone	11	19
(+ ACEI/AII)	(1)	(4)
+ fluid depletion	1	3
(+ fluid depletion & ACEI/AII)	(2)	(5)
+ aminoglycoside nephrotoxicity	2	2
Volume depletion/overdiuresis alone	8	5
(+ ACEI/AII)	(6)	(33)
(+ NSAIDs)	(1)	(3)
(+ NSAIDs & ACEI/AII)	(2)	(5)
+ Lithium toxicity	2	2
Aminoglycoside/vancomycin toxicity alone	2	2
(+ NSAIDs)	(2)	(2)
Obstructive uropathy	6	2
Other	3	9
Total	53	99

ACEI, angiotensin-converting enzyme inhibitor; AII, angiotensin II; NSAIDs, non-steroidal anti-inflammatory drugs.

included tumour lysis syndrome (1), drug-induced interstitial nephritis (1), and unrecognized vasculitis (1). Nineteen patients did not survive to leave hospital. Dialysis was required in eight of the 53 cases. There was no difference in long-term survival between preventable and non-preventable ARF (34% vs. 29% survival at 3 years).

ARF had an iatrogenic element in 99 cases (44 of which were also preventable), and virtually all of these were drug-related (Table 4). ACE inhibitors and AII antagonists were involved in 55 of these, particularly in association with fluid depletion. NSAIDs were also frequently implicated. Thirty-eight patients did not survive to leave hospital. Dialysis was required in 13 of the 99 cases. There was no difference in long-term survival between iatrogenic and non-iatrogenic ARF (29% vs. 30% survival at 3 years).

Discussion

Patients with ARF more often present to a non-specialist clinician than to a nephrologist. The purpose of this study was to examine the initial non-specialist management of this group of patients who are at high risk of mortality.

ARF is most frequently caused by an ischaemic or nephrotoxic insult to the kidney; a small percentage of cases may be caused by acute interstitial nephritis or acute glomerular nephritis. In patients with hospital-acquired ARF, the cause is frequently multifactorial. Common risk factors include hypotension and hypovolaemia, sepsis, congestive cardiac failure, renovascular disease, nephrotoxic drugs, pre-existing renal impairment, nephrotic syndrome and hepatic disease. Assessment of the patient with ARF therefore starts with a careful history and examination, including a thorough evaluation of the patient's notes and drug treatment records where available. This should then be complemented by institution of appropriate investigations and interventions. A diagnosis may often be made after clinical evaluation, assessment of volume status and simple urinalysis, supplemented by renal imaging.

Is urinalysis really useful? Positive protein values of 3+ and 4+ on reagent strip testing of the urine suggests intrinsic glomerular disease, a reagent strip positive for blood suggests the presence of red blood cells (>5/high power field). Although red-cell morphology may not be particularly useful[6] large numbers of red cells in the presence of proteinuria suggest a glomerular aetiology for ARF, strengthened by the finding of cellular casts. Increased numbers of white cells (>5/high power field) are non-specific, but are found more commonly with acute interstitial nephritis, infection and glomerulonephritis. Crystalluria when present may provide vital information.[7] Ethylene glycol poisoning produces a shower of oxalate crystals,

tumour lysis syndrome can produce urate crystal deposition, and a number of drugs may lead to ARF and crystalluria, including sulphonamides, acyclovir, triamterene, and indinavir. Testing the urine is part of the routine examination of a patient, and in the patient with ARF should be supplemented by microscopy of the spun deposit.

Does knowledge of simple urine biochemistry help to distinguish pre-renal ARF from established ARF? Various measures have been claimed to aid in the diagnosis of ARF including urine specific gravity, urine osmolality, urine/plasma creatinine and urea ratios, urinary sodium, fractional excretion of sodium (FE_{Na}), freewater clearance and creatinine clearance. All of these have limitations, and their specificity and sensitivity in clinical practice often means that a single measurement may be inconclusive except in extreme circumstances.[8] There will always be instances where a single estimation of urinary electrolytes should be interpreted with caution, such as in the elderly (who may already have an impaired concentrating ability), and patients on diuretics or with a salt-losing state. However, a trend in urinary sodium levels and FE_{Na} may provide valuable information,[9] and measurement of simple, easily repeatable urine biochemistry should still be considered in the initial investigation of patients with suspected ARF.

Is measurement of urine volume important? Although bladder catheterization is not essential in all cases of ARF, and strict attention to asepsis should be paid in those who are catheterized, it does enable measurement of hourly urine output and total urine volume. Urine volume may not be diagnostic in ARF, particularly when diuretics have already been administered, but it is nevertheless important to quantify. Low urine volumes in ARF are associated with a poorer prognosis and knowledge of urine volume is part of fluid balance management in any seriously ill patient.

Renal tract imaging is mandatory in ARF. The imaging modality of choice is renal ultrasound, which is easily performed in patients with impaired renal function, at the bedside if necessary, without associated morbidity. Contrast media examinations should be avoided.

In this study we found that the key assessments in the diagnosis and initial management of ARF were not performed frequently enough (Tables 2 and 3). More detailed assessments such as a thorough search for underlying sepsis, and measurement of other important parameters including oxygen status, acid-base status and clotting studies, were similarly lacking. Of the 288 cases of ARF identified, 53 could possibly have been prevented. As Table 4 demonstrates, drugs were most frequently implicated, in particular ACE inhibitors (ACEIs), angiotensin II (AII)-blocking agents, and non-steroidal anti-inflammatory drugs (NSAIDs). In 99 cases, ARF was iatrogenic (44 of which were also preventable) and drugs were again most frequently implicated (Table 4). Again ACEI/AII antagonists and NSAIDs, either alone or in combination, particularly in association with volume depletion, were the main culprits, despite the well-known potential dangers of ACEI/AII antagonists and NSAIDs.[10–13] The incidence of preventable and iatrogenic causes of ARF identified in this study are not unique. Elsewhere in the UK, Kalra *et al*. found that ACEIs could be causally implicated in 9/135 admissions for uraemia, and that renal function had not been checked in any patient after the start of treatment.[10] Baraldi *et al*. in Italy found that 39/109 patients with ARF of medical aetiology had drug-related ARF.[12] NSAIDs and ACEIs caused ARF in 24 and eight patients, respectively. The dangers of intercurrent vomiting and diarrhoea leading to acute renal insufficiency have recently been referred to as 'the Achilles heel of medical support for heart failure' in a publication from the Netherlands.[14] The combination of diuretics, ACEIs and NSAIDs were referred to as 'the triple whammy' in a report from Australia.[15] Finally, iatrogenic causes have been reported to account for 60–64% of ARF in referral hospitals in the USA.[16,17]

ARF has a cost in terms of morbidity, mortality, and burden on healthcare resources. Although morbidity and mortality in ARF have traditionally been attributed to the severity of the underlying condition rather than to ARF *per se*, this view was recently challenged by Levy and coworkers who looked at 16 248 hospital in-patients undergoing radiocontrast procedures.[18] They identified 183 subjects who developed ARF and paired them with 174 patients who did not develop ARF matched for age, baseline serum creatinine, and type of contrast study performed. Mortality in those without ARF was 7% compared with 34% in those developing ARF. After adjustment for comorbidity, renal failure was associated with an odds ratio risk of dying of 5.5. This study also suggested that important non-renal conditions such as sepsis, mental status changes, liver disease and gastrointestinal bleeding were more likely to develop in the subjects who developed ARF. We do not have comparative data for patients without ARF in East Kent, however, a report of mortality rates in patients aged $\geqslant 65$ years following acute inpatient admission at Connecticut acute-care hospitals found that survival at 1 year was 72%.[19] In our study, although 56% of patients survived to leave hospital, only 35% were alive at 1 year and only 28% were still alive after 3 years of follow-up. This suggests that

the development of ARF is not only related to increased mortality during the in-patient episode, but that this effect persists throughout subsequent follow-up, and is worthy of further study.

Assessing the burden of ARF on healthcare resources has not yet been properly addressed in this country. However, an analysis of the cost-effectiveness of treating renal failure in five geographically diverse teaching hospitals in the USA looked at survival, functional status, quality of life, and healthcare costs in 490 patients with ARF requiring dialysis. Median duration of survival was 32 days, and only 27% of patients were alive after 5 months. Overall, the estimated cost per quality-adjusted life-year (QALY) saved by initiating dialysis and continuing aggressive care rather than withholding dialysis and allowing death to occur was $128 200, over twice the threshold for cost-effective care (cited as $50 000 per QALY).[20] This compares with a cost of $8300 per QALY for bypass grafting of left main coronary artery disease. In our study 28/48 patients (58%) requiring dialysis treatment survived to leave hospital, and 27 (56%) were alive at 3 months, but only 17 (35%) were alive at 36 months post presentation. As yet no data exist for patients with ARF not requiring dialysis, but this will still represent a considerable cost burden. In our study, 133 of the 240 patients not requiring dialysis (55%) survived to leave hospital; at 3 months follow-up 108 (45%) were alive and at 36 months only 65 (27%) remained.

In this study, the initial assessment and management of patients with ARF was suboptimal, a significant proportion of ARF was preventable (18%), and roughly a third of ARF was iatrogenic in its genesis. The potential nephrotoxicity of several frequently-used drugs is clearly under-recognized. The development of local guidelines, easily available at the point of care, together with simple algorithms to aid investigation, diagnosis, and subsequent specialist referral, would help to address this problem. The approach to any patient presenting with renal failure should always involve history-taking, case note review including medication, physical examination including assessment of volume status, urinalysis/microscopy, and ultrasound assessment of kidney size and presence or absence of obstruction. This simple approach will begin to address the key questions in the diagnostic evaluation: (i) is renal failure prerenal, renal, or postrenal? (ii) is it acute or chronic? (iii) if acute or acute on chronic, is it easily reversible, rapidly progressive and/or established? (iv) what further investigation/treatment is immediately indicated? (v) should the patient be referred for specialist opinion (and when)?

Acknowledgements

We thank all the doctors who agreed to their patients being assessed, the pathology laboratories for their cooperation and E. Eryl Barrett of the University of Kent for statistical advice.

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