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Proc. R. Coll. Physicians Edinb. 1996; **26:** 393–401

ACUTE RENAL FAILURE*

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You came a long way from St Louis, but baby you still got a long way to go
St Louis Blues, 1914: W.C. Handy (1873–1958)

It is customary in a review to provide a historical perspective on the topic. Accordingly, this protocol for the treatment of acute renal failure (ARF) may be of interest—perhaps as an early precursor of a Royal Colleges' guideline.

Potassium citrate 15 grains	Senna or liquorice
Liq. Ammon. Acetatis 60 minims	Urea 30–60 g three times daily
Sp. Aetheris nitrosi 15 minims	Venesection
Aq. Chloroform ½ oz—in water, q.d.s.	5 minims tincture of digitalis

The initial recommendation is to give potassium citrate, despite the risk of inducing a hyperkalaemic cardiac arrest. This is followed by a combination of ammonia, ether and chloroform, just in case the patient is not already in uraemic coma, and some laxatives in case he does not have uraemic colitis. Urea supplementation seems at best unnecessary, and venesection would reduce oxygen delivery to the already ischaemic renal tubules. The final straw is a dose of digitalis, a drug which is very likely to accumulate in renal failure and to cause adverse effects.

If asked to date this protocol, most people would estimate the late 19th century. In fact, it is taken from Price's *Textbook of Medicine*, published in 1941.[1] This is well within living memory, and indeed this edition would have been in current use when the atomic bomb was dropped on Nagasaki in 1945. In other words, even in the nuclear age, patients with ARF might well have died as a result of their treatment rather than the disease. I do not think it is excessive to claim that we have come a long way since then. In this review, I hope to show how far we have come, and also to suggest ways in which we still have far to go.

AETIOLOGY

When studying trends in the aetiology of ARF, we are fortunate to have the meticulous records kept by Dr Anne Lambie and Professor James Robson. Table 1 compares the aetiologies of ARF for the first 20 years of the renal unit in Edinburgh (1959–1979), with the figures for 1994 from the renal unit database. As is well known, obstetric ARF has virtually disappeared, and 'surgical' or post-operative ARF, while it still occurs, is much less common.[2,3] One suspects that this reflects the identification and appropriate haemodynamic monitoring of 'high-risk' patients.

Breaking down the figures, in the medical category, the newcomers are renovascular disease—possibly being unmasked by the widespread use of ACE inhibitors; rhabdomyolysis with myoglobinuria (which is usually related to drug or alcohol abuse); and severe liver failure—many due to paracetamol poisoning[3,4]

*Based on a lecture delivered at the symposium on *Renal Medicine* held in the College on 20th September 1995.

(Table 2). The latter is now our single largest cause of ARF, although this reflects particular referral patterns to the Royal Infirmary. In the surgical group, the growth areas are cardiac and vascular surgery (Table 3).

TABLE 1

Comparison of aetiological classes of acute renal failure referred to the renal unit, Royal Infirmary, Edinburgh, for the years 1959 to 1979, and the year 1994.

	1959–1979		*1994*	
	Number	*Per cent*	*Number*	*Per cent*
Primary renal disease	75	9·8	20	8·7
Nephrotoxic agents	46	6·0	14	6·1
Obstruction	50	6·6	14	6·1
Ischaemic (medical)	193	25·3	132	57·6
Ischaemic (surgical)	351	46·0	48	21·0
Ischaemic (obstetric)	48	6·3	1	0·4
Total	763		229	

In 1994 there were 256 referrals to the ARF service in the Royal Infirmary, 123 of whom required renal replacement therapy; ARF remains a common and expensive problem. Treatment costs range from £5,500 for uncomplicated cases, to approximately £20,000 for protracted cases in intensive care.

TABLE 2

Comparison of aetiologies of acute renal failure referred to the renal unit, Royal Infirmary, Edinburgh, for the years 1959 to 1979, and the year 1994—*ischaemic ARF (medical)*.

	1959–1979		*1994*	
Diagnosis	*Number*	*Per cent*	*Number*	*Per cent*
Sodium and water depletion	27	14·0	20	15·2
Respiratory infection/failure	48	24·9	8	6·1
Septicaemia	32	16·6	24	18·2
Other infections	13	6·7	8	6·1
Acute cardiac failure/shock	21	10·9	17	12·9
Renovascular disease			11	8·3
Haemolytic-uraemic syndrome	21	10·9	2	1·5
Severe liver failure	23	11·9	27	20·5
Rhabdomyolysis			7	5·3
Other	8	4·1	8	6·1
Total	193		132	

Perhaps the most striking change in the last decade has been the shift of case-load from renal units into intensive therapy units (ITU).[5] In Edinburgh Royal Infirmary this trend accelerated acutely following the opening of a 12-bed ITU in 1991; a majority of ARF cases are now treated there. There are positive and perhaps negative aspects to this. On the one hand it offers the chance to define in a sophisticated way the haemodynamic setting in which ARF occurs. The downside, if there is one, relates to the logistics of shared care, and perhaps even the politics of it, which should not be underestimated. In the Royal Infirmary we are fortunate to enjoy an ongoing co-operative system for managing ARF

patients in ITU. This is not the case in many other centres, and there is a real risk of ARF management becoming split and diffused and so impede future progress.

One might perhaps expect that advances in resuscitation and circulatory support would have reduced the incidence of ARF. While it is likely that many cases of ARF are indeed prevented, it is also clear that catastrophically ill patients are now surviving in greater numbers. One recent patient survived 4 days of septic shock with a systolic blood pressure consistently below 80 mm Hg. She developed renal cortical necrosis—previously a condition almost entirely confined to obstetric cases—and remains on chronic haemodialysis.

TABLE 3

Comparison of aetiologies of acute renal failure referred to the renal unit, Royal Infirmary, Edinburgh, for the years 1959 to 1979, and the year 1994—*ischaemic ARF (surgical)*.

	1959–1979		*1994*	
Diagnosis	*Number*	*Per cent*	*Number*	*Per cent*
Trauma/burns	67	19·1	9	18·8
Pancreatic surgery	13	3·7	4	8·3
Cardiac surgery	20	5·7	8	16·7
Vascular surgery	42	12·0	15	31·3
Intrabdominal sepsis	100	28·5	1	2·1
Haemorrhagic shock	21	6·0	2	4·2
Post-operative complications	88	25·1	9	18·8
Total	351		48	

One cannot leave the topic of ARF aetiology without mention of two classic double-edged swords, ACE inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs)—so effective when used appropriately, yet so potentially disastrous in particular settings. It has been suggested that the increasing use of ACEIs is unmasking a reservoir of sub-clinical renovascular disease, and this trend may well continue. Certainly ARF in such cases is now virtually always associated with ACEIs. Similarly, NSAID use underlies many cases of ARF in nearly every aetiological category. Nephrologists recognise what can be referred to as the 'sepsis-non-steroidal syndrome', where relatively mild sepsis is associated with unexpectedly severe ARF. Most of our postoperative ARF is similarly linked, and the importance of renal prostaglandins in the auto-regulation of renal blood flow and preservation of renal function postoperatively should be emphasised. In a recent study we examined the effect of diclofenac used as postoperative analgesia after oesophagogastrectomy.[6] The results indicated the very striking increase in urinary prostaglandins on the first postoperative day, this being abolished by the NSAID (Fig 1). Even in uncomplicated cases there were significant reductions in sodium, water, and particularly potassium excretion. Two patients with postoperative sepsis both developed ARF. The Royal College of Anaesthetists have established a working party to look at this problem, but meanwhile, use of NSAIDs in this context continues to increase, in an attempt to improve post-operative pain control.

MANAGEMENT

What are the ways in which we have moved forward in our management of ARF? For some types of ARF, management can now be described as straightfor

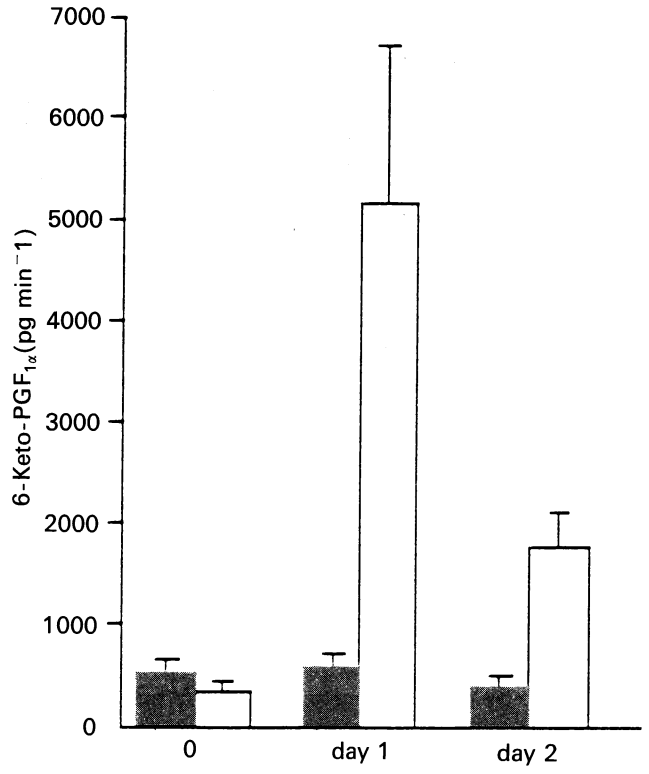

FIGURE 1

24-hour urinary excretion of 6-keto-prostaglandin F1α in patients undergoing oesophagogastrectomy, in patients given diclofenac (n=10) (■), and untreated controls (n=10) (□). (From—Power I, Cumming AD, Pugh GC. Effect of diclofenac on renal function and prostacyclin generation after surgery. *British Journal of Anaesthesia* 1992; **69:** 451–6).

ward. Obstructive uropathy is an example. From the initial ultrasound examination, to the insertion of antegrade nephrostomy catheters, to a post-obstructive diuresis can take less than an hour. Dialysis is rarely necessary. Although rhabdomyolysis is common, very aggressive and early volume expansion, alkalinisation of the urine with sodium bicarbonate, and the use of mannitol as an osmotic diuretic has led to a very low incidence of dialysis-requiring ARF.[4] Renovascular cases can be diagnosed readily by Doppler ultrasound, isotope scanning, and angiography, and even the most severe cases can often be revascularised by surgery or angioplasty.[7] Vasculitic diseases remain a problem, and are a significant cause of dialysis-requiring ARF. Nevertheless, the use of the anti-neutrophil cytoplasmic antibody test to facilitate early and accurate diagnosis, and potent immunosuppressive regimes, including plasmapheresis, have made the management of these cases almost routine. Essentially, if treatment is begun before permanent hyalinisation of glomeruli, most cases recover useful renal function.

We have also come a long way in the support of those patients who do require renal replacement. As a house officer in renal medicine in 1975, my first task when a patient required dialysis for ARF was to insert a Scribner shunt into an artery and vein at the wrist. This could take up to 2 hours of nervous exploration in the arms of what were frequently sick patients. The dialysis bath

was then prepared, and tailored to the patients needs by adding or discarding various sachets of powdered chemicals. Control of fluid removal during dialysis was done by adjusting a 'gate-clip' on the blood line—although as one of our nurses pointed out recently, this could be viewed as an early form of 'dialysis profiling'. In 1995, vascular access is achieved in minutes by cannulating a central vein and inserting a double-lumen catheter, and the control of dialysate composition and fluid removal during dialysis involves turning a dial.

In 1975, if a patient was intolerant of haemodialysis because of circulatory instability, the options were peritoneal dialysis (PD) if it was feasible, or nothing. In most centres, including our own, acute PD has virtually disappeared as a treatment for ARF, and has been supplanted by various techniques of continuous blood purification. The simplest one of these was CAVH—continuous arterio-venous haemofiltration. This technique used the arterio-venous pressure difference in a Scribner shunt to drive a haemofilter, which filtered 500–1000 mls/hr from the circulation. This 'impure' filtrate was replaced by intravenous infusion of clear crystalloid, and biochemical stability was achieved. By under-replacing the filtrate on an hourly basis, fluid overload was easily controlled. This method involved a return to arterial cannulation, and filtration was critically susceptible to falls in the patient's arterial pressure. Insertion of a pump in the system resolved both these problems, allowing use of venous access and ensuring consistent filtration pressure. This evolved technique, continuous veno-venous haemofiltration (CVVH), is now our most commonly used modality for ARF, and has proved a reliable and consistent form of renal replacement[8] (Fig 2).

Instinctively, we believe that this type of treatment is an advance, allowing successful treatment of patients who would have been untreatable in the past, and there is some evidence to support this view.[9,10] Theoretically, however, there are positive and negative aspects to such types of continuous treatment[11] (Table 4).
Fig 3 shows the outcome figures, kindly provided by Dr Ian Armstrong from the ITU database, for all patients with ARF treated in the ITU in the Royal Infirmary from 1991–94. There are 191 patients, 165 of whom received a continuous treatment (CVVH). 26 patients were treated only with an intermittent technique (haemodialysis or high-volume haemofiltration). The mortality in the CVVH group was 49 percent. In the intermittent group, only 2 of 26 patients died (8 per cent). The obvious and probably correct explanation, is that cardiovascularly stable patients are selected for intermittent therapy. However, it is perhaps rather surprising that the mean ages (continuous 56·3±16·5 yr, intermittent 53·7±16·4 yr) and Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) illness severity scores (continuous 25·8±7·9, intermittent 21·3±7·0, from a potential score of 70) were virtually identical in each group. If one was planning a comparative trial, these would be the kind of matched groups one would seek. We are looking at these cases further to check this observation.

So, we have come a long way, but perhaps some analytical retrospection is appropriate. Where should we be going next? What are the areas where we still have little success? A breakdown of outcome by diagnosis shows that problem areas, with very high mortality, include severe sepsis with shock, severe liver failure, and acute pancreatitis (Table 5).

These diagnoses lead into the area of multi-organ failure, and the important topic of inflammatory mediators as deleterious factors.[12] All of these conditions share a common feature, namely a pathological dilation of the systemic

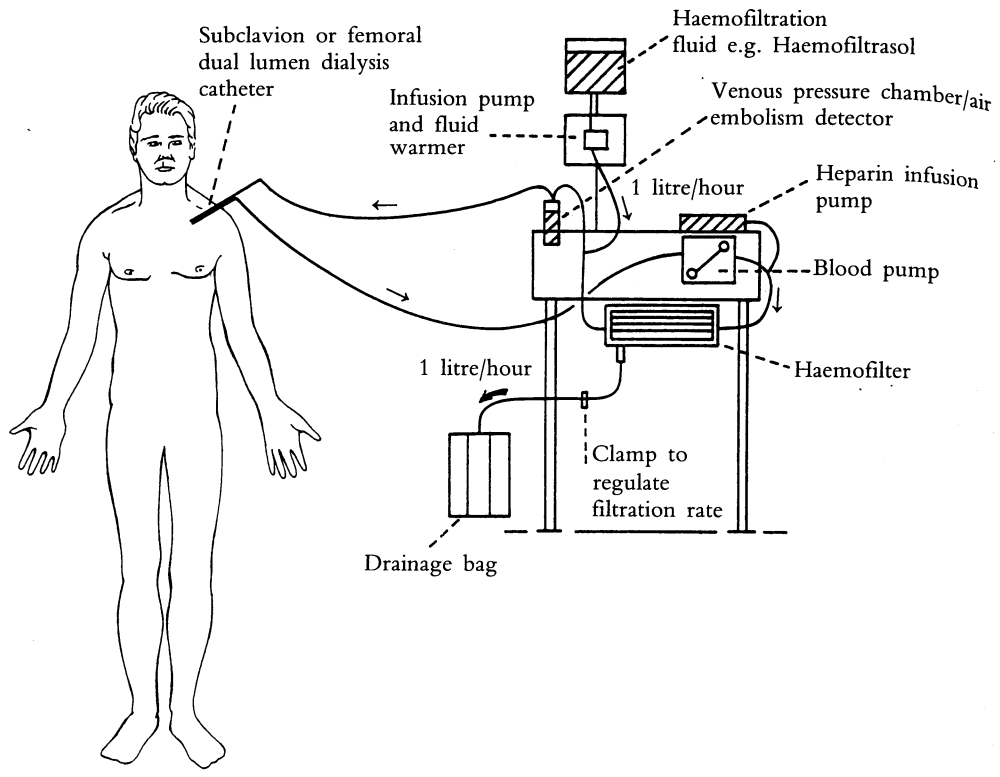

FIGURE 2

Diagram of Continuous Veno-Venous Haemofiltration (CVVH).

TABLE 4

Continuous blood purification in acute renal failure by continuous veno-venous haemofiltration—some arguments for and against.

For	*Against*
Slow continuous fluid removal	Continuous extracorporeal circulation
Steady-state biochemistry	Continuous anticoagulation
Technically simple	Cumulative errors in fluid balance
?Removal of inflammatory mediators	Continuous blood-membrane contact—? stimulation of mediator systems

vasculature, leading to relative underfilling of the circulation and renal dysfunction which is resistant to volume expansion.[13] This is largely due to activation of mediator systems in blood, primarily by endotoxin. It has been suggested that the plasma kallikrein-bradykinin system is high in the hierarchy of such mediator systems. We have shown that inhibition of this system is beneficial in both septic shock[14] and in severe liver disease.[15] Administration of the kallikrein inhibitor, aprotinin, reversed the pathological dilatation of the systemic circulation and improved kidney function. Recent results with the combination of a kallikrein inhibitor and a kinin receptor antagonist are very encouraging,[16] and pharmacological manipulation of mediator systems may soon enter the clinical arena.[17]

ITU acute renal failure: outcomes.

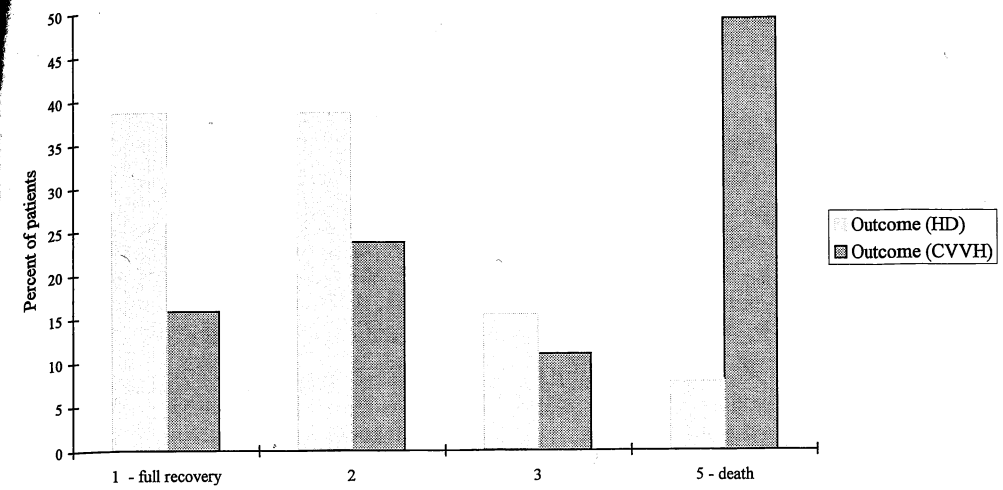

FIGURE 3

Outcome figures for ARF patients treated in ITU in the Royal Infirmary from 1991–94. 191 patients were treated. 165 received a continuous treatment (CVVH). 26 received an intermittent technique only (haemodialysis or high-volume haemofiltration).

1 = full recovery; 5 = death; 2,3 = intermediate levels of morbidity (on discharge from ITU).

TABLE 5

Outcome in the main aetiological categories for patients with acute renal failure treated in the intensive care unit of the Royal Infirmary of Edinburgh, 1991–1994. Survival refers to leaving intensive care. Excludes categories with <3 patients.

Aetiology	*Survivors*	*Non-survivors*
Respiratory infection/failure	21	18
Septicaemia	12	14
Acute cardiac failure/cardiogenic shock	14	4
Severe liver failure	11	21
Medical (miscellaneous)	5	3
Acute pancreatitis	0	4
Trauma	4	0
Hepatobiliary surgery	3	2
Vascular surgery	16	3
Surgical intra-abdominal sepsis	9	9
Surgical (miscellaneous)	2	1

In ARF, the renal tubules have classically been considered as the passive victims of various insults—ischaemic, toxic, metabolic. However, studies in our laboratory have shown that renal tubular epithelial cells can express the gene for Interleukin 1β, a cytokine mediator with potent pro-inflammatory and haemodynamic effects.[18] This was shown for both cells in culture and in renal biopsy specimens. The tubules may be as much 'sinners' as 'sinned against', particularly in ARF with multi-organ failure.

FUTURE RESEARCH

We have come a long way—but one of the biggest barriers in the way of further

progress is the difficulty of performing clinical trials in ARF. Heterogeneity of case-mix, geographic dispersal of patients, difficulty in standardising treatment, multiple factors affecting outcome, and problems in defining measures of benefit, are all factors in this.[19] Many pharmaceutical companies have developed, or are developing, compounds which might theoretically benefit ARF, and manyof these have been successfully used in animal models. Examples are endothelin receptor antagonists, and thromboxane synthetase inhibitors such as U63, 577A.[20–22] Something of a 'holy grail' in this area would be a method of measuring renal blood flow in real time at the bed-side. With Dr Peter Hayes' liver research group, we have recently used a thermodilution catheter placed in the renal vein to directly measure renal venous flow in ARF. As an example, in a patient studied by Dr Ewan Forrest 4 weeks after a complicated cardiac surgical procedure, a value of 220 ml/min for the left kidney was obtained, suggesting a total renal blood flow of around 500 ml/min, i.e. approximately 80 per cent of normal. This is rather in excess of what is usually quoted for patients in established ARF. The technique can also be used to examine the effect of interventions. For example, an 80 per cent increase in renal blood flow over 1 hour was achieved by a single dose of the adenosine antagonist, theophylline, in patients with severe liver disease.[23] This technique provides new opportunities for clinical studies of the efficacy of pharmacological intervention in ARF.

Finally, another area in which we have a long way to go is that of regeneration and repair. Essentially, once the initial insult to the kidney has occurred, treatment is supportive and relies on the intrinsic healing of the kidney. Approximately 30 per cent of ARF patients do not recover normal renal function, and 10 per cent remain dialysis-dependent. Reducing this toll requires an understanding of the mechanisms which lead to irreversible scarring and fibrosis rather than regeneration. A whole array of cellular and humoral factors comes into play here—growth factors, cytokines, collagenases, metalloproteinases, growth response genes, to name but a few.[24,25] To illustrate the complex interactions, Dr Alison Reith and I have shown using zymographic detection that human tubular epithelial cells in primary culture produce both urokinase-type plasminogen activator (uPA), and its major inhibitor, PAI1. uPA has important effects on extracellular matrix formation and remodelling, through activation of metalloproteinases. We also showed that production of uPA and PAI1 are upregulated by Interleukin 1β.[26] This cytokine is expressed by leucocytes, and indeed by tubular cells themselves, in response to inflammation and, more relevant here, ischaemia. Such mechanisms are amenable to pharmacological manipulation, and there is the potential to render the repair process in the kidney both more rapid and more complete.[27]

In conclusion, we have moved steadily forward at every stage of ARF from initiation and causation, through support, to healing and recovery. There remains an unacceptably high toll of mortality and long-term morbidity—but the way ahead is open and full of interest.

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