Editorial

Medical treatment of acute tubular necrosis

Renal function is acutely impaired in about 5% of hospital admissions. In all instances, the immediate priorities are the same. First, recognition and treatment of life-threatening complications: most notably hyperkalaemia and pulmonary oedema, the latter usually iatrogenic. Second, diagnosis and correction of intravascular volume depletion. Two physical signs are reliable, excepting in absolute extremis: reduction in the height of the jugular venous pulse, and postural drop in blood pressure, lying and sitting if standing is not prudent. If either of these signs are present, then fluid of a nature similar to that lost should be infused rapidly through a large-bore cannula placed in a vein in the antecubital fossa, or a catheter inserted using the Seldinger technique into the femoral vein. The infusion should be monitored closely, and stopped promptly when the jugular venous pressure has risen and the postural drop disappeared, lest fluid overload and pulmonary oedema ensue. Needless to say, vigorous efforts should then be made to diagnose and treat the underlying condition: and in those patients without obvious evidence of severe circulatory disturbance, particular care must be taken to ensure that cases of obstruction or nephritis are not missed—by urgent ultrasound examination of the kidneys to detect pelvicalyceal dilatation, stick-testing of the urine for protein and blood, and microscopy of the urinary sediment to look for red cells and cellular casts.

However, the vast majority of cases do not have urinary obstruction or nephritis, but have renal failure secondary to impairment of renal perfusion, which produces a spectrum of disease. At the mild end are those with ‘pre-renal’ renal failure, where restoration of circulatory volume leads to rapid improvement in renal function. At the severe end is the condition widely known as acute tubular necrosis, where similar restitution of the circulation does not have this effect. How should these cases be managed? It is more than likely, when the ward round comes to such a patient, that someone will suggest a dose of frusemide, and perhaps ‘renal dose’ dopamine in addition. It is an indictment of nephrologists that no-one knows whether these agents should be given, despite the fact that acute tubular necrosis is common, and that the proposed treatments have been available for many years. If ‘evidence’ were required, then none would be treated: but then the same goes for calcium in hyperkalaemia, volume repletion in those with no blood pressure, and pulling children out of the way of buses.

Shilliday, Quinn and Allison from the renal unit at the Glasgow Royal Infirmary deserve considerable credit for performing a study that should, perhaps, have been done many years ago: a prospective, randomized, placebo-controlled, double-blind study examining the effects of loop diuretics on renal recovery, dialysis and death in patients with acute renal failure. Two hundred and seventy-eight oliguric adults with acute renal impairment leading to a serum creatinine of \( > 180 \) mmol/l were assessed. Those who recovered following adequate hydration were excluded (25%); as were any with ultrasonographic evidence of obstruction; any given loop or osmotic diuretics within the previous 12 h (or large doses of loop diuretics within the previous 48 h); and any who refused consent (a further 40%). Ninety-six patients remained, four of whom were subsequently excluded from analysis. All were given dopamine (continuous infusion at a dose of 2 \( \mu \)g/kg/min) and mannitol (100 ml of a 20% solution every 6 h for a maximum of three days), and were randomized to receive either frusemide (\( n = 32 \); torasemide (\( n = 30 \)), a loop diuretic very similar to frusemide and produced by Boehringer Mannheim (UK) Pharmaceuticals, who supported the study; or placebo (\( n = 30 \)). These study drugs, administered in a double-blind fashion, were given by intravenous infusion over one hour every six hours for up to 21 days, initially 3 mg/kg each dose, with subsequent dosage reduction according to a sliding scale if renal function recovered. Patients given frusemide or torasemide had a significant increase in urine output in the first 24 h compared to placebo, but there was no significant difference in any major outcome (renal recovery, requirement for dialysis, or death) after 21 days.

Does this study mean the end of discussion on ward rounds about whether or not to reach for the frusemide and dopamine? I doubt it. Some might
argue about the specific details of the treatment given, in particular the concomitant use of both dopamine and mannitol. Others might point out that those randomized were clearly very ill, since 60% or so died, and argue that benefit might be found in less severe cases. Most will concede, however, from the findings of this and other studies, that evidence of benefit is unlikely to be found in populations recruited into randomized trials, no matter how many times the precise details of dosage of loop diuretics, dopamine, mannitol or various other similar agents are juggled. But many will draw on their personal experience of cases in which there has seemed to be benefit, and published reports of the same, that evidence use of erythropoietin. Colony-stimulating factors are given routinely to hasten the regeneration of blood cells in a variety of conditions. The use of other growth factors has been reported in other conditions. Dressings coated with epidermal growth factor can increase the rate of skin growth, and parenterally administered epidermal growth factor has been reported to speed the healing of peptic ulcers. Insulin-like growth factor–1 has been tried in diabetes, growth hormone receptor deficiency and AIDS wasting. As regards the kidney, in several animal models of acute renal failure there is compelling evidence that administration of exogenous growth factors can accelerate the process of recovery. For instance, in the rat with renal ischaemia induced by temporary clamping of the renal artery, both epidermal growth factor and recombinant human insulin-like growth factor–1 increase the rate of cellular regeneration and speed the return of normal function. Epidermal growth factor has also been shown to be effective in promoting renal recovery in the rat with mercuric chloride nephrotoxicity, and hepatocyte growth factor is efficacious in a mouse model of acute renal failure. Whilst these particular substances may not prove to be effective treatments for acute tubular necrosis in man, it is more than likely that some suitable growth factor does exist and will be found. The answer might come from a wide variety of sources, ranging from detailed study of animal models of acute tubular necrosis to the screening of DNA/cDNA libraries for molecules homologous to those representing known growth factors, or the screening of expression libraries for proteins with the ability to stimulate the growth of renal cells in culture. Such an answer might also go some way to dealing with another of the more substantial clinical mysteries: why, when one of a man’s kidneys is removed, does his other kidney get bigger, but not his nose?

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References
2. Shilliday IR, Quinn KJ, Allison ME. Loop diuretics in the management of acute renal failure: a prospective, double-


