ON THE ONSET OF ACUTE TUBULAR NECROSIS WITH A VIEW TOWARDS PREVENTION

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Although the pathogenic mechanism or mechanisms of what has been termed "acute tubular necrosis" (ATN) remain hypothetical, experimental and clinical studies have cleared the way to better prevention.

'Pre-renal' acute renal failure

When due to uncompensated loss of extra-cellular fluid and/or blood volume, it may precede the onset of ATN. Blood urea and plasma creatinine levels rise. Urine volume is usually decreased to less than 400ml/24h. A high urinary urea and low sodium concentration or a high urine/plasma osmolarity ratio, and a normal urinary sediment are usually sufficient confirmation of the 'pre-renal' nature of renal dysfunction, if cirrhosis, the nephrotic syndrome or heart failure can be ruled out. In cases verging on ATN, the other indices proposed do not always help to delineate the two conditions. The renal response to volume expansion, after ruling out a deficiency in myocardial function clinically or, in difficult cases, by pressure monitoring with a Swan Ganz catheter, constitutes the best criterion.

Fluid lost may be: water and electrolytes (gastrointestinal losses, sweating, insensible losses or urinary losses due to glycosuria or high osmotic loads during naso-gastric feeding, excessive use of diuretics, or diabetes insipidus), blood (traumatic haematomas, haemothorax, haemoperitoneum, external bleeding, or gastrointestinal bleeding, or haematomas due to excessive anticoagulant therapy), or plasma (burns).

Despite awareness of the importance of maintaining adequate hydration and electrolyte balance during illness, a patient's state of hydration is not always easy to evaluate. In the absence of peripheral oedema and of any sign of heart failure, particularly in patients with a recent history of fluid and weight loss, salt and fluid administration should be tried.

In traumatic shock, volume expansion should be started as soon as possible and continued until shock is corrected, urinary output rises and central venous pressure is restored to normal levels. Failure to attain these objectives, or recurrence of symptoms, usually indicate continuing blood loss and the necessity of
surgical haemostasis. This type of early aggressive management of casualties of the Viet Nam war reduced the number of immediate post-traumatic acute renal failure to 0.16 percent [1].

In patients with extensive burns, adequate compensation for plasma exudation during the first 48 hours prevents initial renal failure. Although administration of fluid and electrolytes alone has been advocated, replacement of at least part of the losses by albumin, according to accepted formulas is, in our experience, to be preferred.

Appropriate management of 'pre-renal' acute renal failure leads to rapid restoration of urinary output and recovery of renal function. It is probable that delayed or insufficient treatment alone do not account for those cases where the subsequent course is that of ATN, which is then due to other pathogenic factors. But we believe that ATN is more liable to occur in the volume deficient patient when these pathogenic factors become prevalent.

**Acute tubular necrosis**

*ATN following diagnostic procedures [2]*

Acute renal failure may follow the administration of radio-opaque dyes for X-ray examination. Reports concern intravenous administration of dye for nephro-urography in diabetics or patients with myeloma, oral cholecystography (particularly with bariamidyl) and angiography. Adequate hydration of the patient before the diagnostic procedure, avoiding massive injections of dye during angiography can prevent the onset of renal failure in the rare cases where it is liable to occur. Except in diabetics, where injection of radio-opaque dyes should be avoided when not indispensable for diagnosis, there is no reason to restrict the use of these remarkable diagnostic techniques when appropriately applied, even in patients already in renal failure. In high-risk patients, non-traumatic techniques (ultrasonography and scanner) can sometimes procure the necessary information.

*ATN following certain forms of therapy*

Among the newer drugs which have become available in recent years, a rising number have proved to be nephrotoxic when used alone or in association with other medications. Nephrotoxicity is related to abnormal retention of the drug which can be recognised when trough plasma concentration rises above therapeutic levels. Retention may be due to decreased metabolism due to liver failure, or, more commonly, to decreased renal excretion in the case of renal failure. Guidelines for utilisation of these drugs are based on their plasma half-life values, daily doses being adapted to renal function. Monitoring of plasma concentration is recommended in patients with renal failure. But the margin between therapeutic and toxic plasma levels is narrow, control of plasma levels requires adequate laboratory facilities and in acutely ill patients with changing renal function, dosage is not easily adapted. It is thus to be feared that, in the coming years, an increasing number of patients will be at risk of incurring renal failure due to drug toxicity.
unless the following rules are observed: use potentially nephrotoxic drugs, particularly antibiotics [3], only when absolutely necessary, avoid nephrotoxic combinations, monitor plasma creatinine during the time of administration, discontinue administration if it rises, adapt dosage and monitor plasma concentrations in patients with renal impairment.

Excessive administration of Dextran is still being reported as a cause of renal failure, which can be avoided by giving no more than 1 litre at a time, and for short periods.

Acute renal failure due to incompatible blood transfusion still occurs (2 percent of cases in a recent study). Limiting indications for blood transfusion to cases where it appears indispensable should help to reduce the number of these unfortunate accidents most often due to negligence. In our hospital, some 100,000 units of blood have been transfused over the past 5 years. Four cases of mis-matching, with one case of ATN, were due to the presence of irregular antibodies in the recipient.

Acute tubular necrosis due to shock [4]

Shock is the greatest producer of renal failure, which ranges in severity from ‘pre-renal’ acute renal failure to bilateral cortical necrosis. Early treatment of shock is usually followed by improvement in the patient’s circulatory status and renal function. Disorders which may be associated with shock, e.g. intravascular coagulation, haemolysis, liberation of vaso-active substances, etc., will contribute to multiple organ failure, severe residual renal failure, or even irreversible shock, when circulatory failure is prolonged.

Physicians should be trained to recognise the symptoms of even minor forms of circulatory insufficiency, to analyse its cause and mechanism and to institute appropriate therapy without delay. The more complex cases are best managed in a well-staffed, well-equipped intensive care ward where adequate monitoring and supportive care can be procured.

Patient follow-up is of no less importance. As long as the initial disease persists, shock may recur in a more or less overt fashion and renal function again decrease after initial recovery. This is particularly common in patients with post-operative peritonitis after abdominal surgery where decreasing renal function is, in itself, an indication for re-operating.

Onset of oliguria in the acutely ill patient in the absence of shock

Once obstruction of the urinary tract has been ruled out, other aetiologies must be considered. Obstructive jaundice can cause oliguria which should be avoided by maintaining normal hydration. Accidental or suicidal contact with nephrotoxic chemicals can sometimes be found by close questioning of the patient or his entourage. Administration of a nephrotoxic drug or anaesthetic may be held responsible when no other cause is found.

In the absence of any apparent cause, and in a patient with two kidneys of normal size, a renal biopsy is recommended to determine whether renal failure is not due to some other type of nephropathy.
Non-oliguric acute renal failure [6]

This is defined as an acute elevation of blood urea and plasma creatinine associated with continuing urinary output of iso-osmotic urine. It has been reported in 20 to 60 percent of cases of acute renal failure.

The aetiologic determinants are the same as those of ATN. It has been held to be more frequent in patients with acute renal failure due to antibiotic nephrotoxicity, where its onset is insidious. But rapidly progressive restoration of urinary output with residual renal failure may follow appropriate treatment of oliguria. Additional use of diuretics, such as furosemide, may be followed by immediate restoration of urinary output. As there is no conclusive evidence that diuretics radically modify the course of renal function in these patients, and as they may be harmful when used inappropriately, many authors do not recommend their use. We have continued using them to help restore and maintain urinary output with no ill effects, and with a decreased demand for dialysis in many patients. But they cannot be used indiscriminately to treat oliguria, and require close monitoring of the patient.

The course of non-oliguric renal failure is usually less severe than in the oliguric form. But oliguria may set in secondarily when aetiologic factors remain present. This is particularly frequent in post-operative complications of abdominal surgery.

Renal cortical necrosis

The presenting symptoms and aetiologies are the same as in ATN, and its occurrence is thus unpredictable at the onset of oliguria. More frequent in renal failure complicating pregnancy, it has been attributed to severe renal ischaemia associated with intravascular coagulation [5]. Early administration of heparin has been advocated, but there is no proof that this constitutes better prevention than early aggressive aetiologic and symptomatic treatment of shock alone which, in the great majority of cases, will prevent cortical necrosis and severe residual renal failure.

Conclusion

Despite improved management of patients, acute renal failure requiring dialysis has been estimated in France and England at 30 patients per million inhabitants [7,8] per year and mortality still averages 50 percent. The majority of these patients are presumed to be suffering from ATN.

The critical cases now tend to constitute the majority of those now being treated. Many are septic cases and the often necessary use of nephrotoxic antibiotics may contribute to the onset or prolongation of renal failure. But, although not reflected in improved survival rate, the chances of survival in individual cases have been increased by judicious surgical tactics and intensive care, sometimes at the price of prolonged anuria and of various degrees of residual renal functional impairment.

Yet there is no doubt that acute renal failure still occurs in patients where it
could have been avoided. For this reason, physicians should be trained to main-
tain normal hydration, blood volume and urinary output, to use diuretics judi-
ciously, to recognise and manage "pre-renal" acute renal failure and shock, to use
blood transfusions with all the necessary precautions, to manage potentially
nephrotoxic procedures and drugs, to monitor and manage high-risk pregnancies.

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