Acute renal failure in CF

Acute renal failure in people with cystic fibrosis

Kevin W Southern

Time to reflect on antibiotic strategies for CF lung infection

The putative gene in cystic fibrosis (CF) encodes a protein, cystic fibrosis transmembrane conductance regulator (CFTR), which has an important role in transepithelial salt transport. The major organ affected in CF is the lung, with remorseless and intense chronic airway infection resulting from disabled clearance of dehydrated airway surface liquid. Airway inflammation leading to end stage lung damage is associated with respiratory morbidity and early death. The outlook for people with CF has improved considerably with a proactive approach to treatment of airway infection as one of the cornerstones of its management. Recent data from the US CF registry suggest a continuing improvement in median predicted survival to over 35 years (http://www.cff.org/research/2006NACFC/Plenary III). With an improving outlook, perspectives have changed and expectations of people with CF and their carers have broadened. A survey of acute renal failure (ARF) in patients with CF published in this issue of Thorax (see p 541) is particularly timely when reflecting on how best to achieve the goal of increased survival while balancing risks to patients."

ACUTE RENAL FAILURE AND CF

There are several reasons why people with CF are at risk of ARF. The salt transport defect makes people with CF prone to salt loss and consequently fluid imbalance and dehydration. The impact of CFTR dysfunction on pancreatic function and architecture results in significant hypoinsulinaemia (CF-related diabetes) in a significant proportion of older patients with CF, again posing a challenge to fluid balance and the long-term possibility of diabetic kidney disease. Finally, as a cohort, these patients are exposed to industrial quantities of potentially nephrotoxic chemotherapeutic agents (in our CF centre some children have received a cumulative intravenous dose of over 300 g of the aminoglycoside tobramycin). Given cumulative exposure to potentially nephrotoxic drugs and the increased prevalence of CF-related diabetes in older people with CF, an increased incidence risk of ARF might be expected in the older age group; however, this was not the case in this survey where the majority of cases were children (only three over 18 years). This may represent better response rates from paediatric centres to this survey, and further studies are needed to examine this finding.

ROLE OF CFTR IN THE KIDNEY

Paradoxically for a condition in which salt transport is a primary abnormality, people with CF have apparently normal renal function. The CFTR gene is expressed abundantly in the kidney, particularly in the nephron, but CFTR appears to be functionally redundant at this site. Studies on a transgenic cfr knockout mouse model suggest that the absence of CFTR does not affect the ability of the kidney to manage fluid and salt imbalance, but that different salt and fluid transport processes are involved. Interestingly, CFTR does appear to have a role in the pathophysiology of autosomal recessive polycystic kidney disease, where fluid secretion into the cysts appears to be mediated through CFTR. The increased incidence of nephrocalcinosis in CF does not appear to relate to an intrinsic renal problem and is more likely related to hyperoxaluria.

Given the apparent pivotal role of CFTR in other organs, the lack of impact of CFTR dysfunction on the kidney is remarkable. It is even possible that absent CFTR function in the kidney may protect people with CF from renal insults, and certainly it has been recognised for many years that people with CF have increased renal clearance of many drugs including aminoglycoside antibiotics. More research is needed into the CF renal condition to understand the impact of CFTR dysfunction on renal physiology.

RELEVANCE OF ACUTE RENAL FAILURE IN CF

The incidence risk of ARF reported by Bertenshaw et al is significantly higher than the non-CF population and is consistent with other recent reports. The authors suggest this may be an increasing phenomenon, quoting local figures, although there are no previous national data to assess this. Because of problems with recruitment and case verification, it is likely that the incidence risk quoted is an underestimate. It is important that CF teams reflect on these figures and, as a first line, adopt “common sense” procedures to prevent inadvertent renal damage. Patients should be monitored more closely during periods of hot weather and during fasts, particularly if using aminoglycoside antibiotics (for example, to improve a chest condition before a general anaesthesia). In addition, patients should avoid the concomitant use of potentially nephrotoxic agents such as ibuprofen, frusemide and aminoglycosides. If concomitant use is unavoidable, then careful monitoring is imperative.

Given the increased incidence of ARF in CF, there is a strong argument for more formal assessment of renal function on a regular basis in order to highlight at risk individuals. The glomerular filtration rate can be estimated by formulae that employ serum creatinine and other parameters such as height, weight and age. The Schwarz formula (40*height (cm)/serum creatinine (μmol/l)) is commonly used; however, many formulae exist but none has been formally validated in CF. A concern is that these formulae

References:


may overestimate the glomerular filtration rate in people with CF and more formal direct measurement may be required for individuals who are particularly at risk (for example, using $^{51}$Cr-EDTA or timed urine collections).

**SHOULD WE ALTER/REDUCE OUR USE OF AMINOGLYCOSIDES?**

Aminoglycosides provide excellent dose-dependent killing of *Pseudomonas aertaogena*, which remains the primary pathogen in CF. They act synergistically with a number of classes of antibiotics including cephalosporins, and have been used in combination in an attempt to prevent the emergence of resistance. A systematic review comparing single and combination intravenous antibiotic strategies could only identify weak evidence to support this strategy. This highlights the challenge of evaluating treatments for life-threatening infections in the CF population using tools to monitor renal function in this population. Thorax 2007;62:472-473. doi:10.1136/thx.2006.072355

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