Kidney Disease and Cystic Fibrosis

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Kidney Function
The function of the kidneys is to remove waste products from the body and also regulate body fluid levels. Each kidney consists of millions of functional units (called nephrons), collections of specialist cells (the glomeruli) which filter fluid from the blood into a looped tubule, where the lining cells further filter and excrete chemicals before the fluid passes out into a collecting duct as urine. Traditionally, the kidney has been thought to be one of the organs not affected by the CF condition, despite the fact that the CFTR protein abnormality is expressed in renal tubule cells.

Kidney Stones
There is some evidence that kidney stones may be more common in CF patients because of increased levels of oxalate chemicals absorbed through the bowel wall into the blood and subsequently excreted through the kidney. These oxalates can be concentrated in the urine and precipitate out to form small stones, particularly during periods of dehydration.

Kidney Disease and CF Treatment
More recently, kidney disease has come to light in CF, not as a primary manifestation of the condition, but as a result of treatment. Most people with CF require medications to treat disease in other parts of the body, and a number of these agents end up being excreted from the body via the kidneys. Unfortunately, some of these have the potential to damage the sensitive renal tubule cells (i.e. are nephrotoxic), including non steroidal anti-inflammatory agents and immune suppression agents such as cyclosporin used after organ transplant.
Some groups of antibiotics are also known to have an acute toxic effect on the kidney, particularly aminoglycosides (such as tobramycin), and also colomycin. Whilst this acute damage is usually reversible, long term use may, over time, cause clinical disease by diminishing the number of functioning nephrons. We have recently shown that some adult patients with CF have suffered episodes of acute kidney failure, usually as a result of treatment with antibiotics for chest infections, and similar problems have also been described in children.

Measurement of Kidney Function
Because the kidney has an enormous reserve capacity, such damage may only become apparent after prolonged exposure to such agents when sufficient nephrons have been damaged and this reserve has been used up. Normal measures of kidney function (simple blood tests) will not detect this lack of reserve: it is necessary to use some form of direct measure of the ability of the kidney to excrete chemicals to work out its overall capacity. The best way of doing this is to use a radioactive isotope which is only excreted from the body through the kidney, but such tests are expensive, time consuming and involve radiation.

A more common method in clinical practice is to use the ability of the kidney to expel a protein (creatinine) produced by natural muscle turnover within the body. Creatinine is only removed from the body via the kidney, and nearly all is lost through simple glomerular filtration. A creatinine clearance test, which compares the amount of creatinine present in the urine over 24 hours with that in the blood, is a reasonably accurate measure of kidney function. We looked at creatinine clearance in 80 adult CF patients, and found that 47% of them had a low creatinine clearance – i.e. they had evidence of renal impairment. Indeed, this correlated well with their lifetime use of nephrotoxic antibiotic therapy, particularly IV aminoglycosides. These are commonly given for chest exacerbations in CF due to Pseudomonas aeruginosa. Although IV colomycin also had a nephrotoxic effect, this was only apparent when it was given in combination with tobramycin.
Unfortunately, aminoglycosides are one of the most powerful antibiotic groups available to treat *Pseudomonas aeruginosa*, which infects most patients with CF at some stage in their lives (most adults are chronically infected), and in many their use cannot be avoided. For this reason, we advise that aminoglycoside antibiotics should only be used when necessary in CF patients, with alternatives being considered where possible during acute chest exacerbations. Some paediatric centres administer 3 monthly IV antibiotics routinely to prevent pulmonary exacerbations: where possible these should not include an aminoglycoside. Furthermore, the combination of an IV aminoglycoside with IV colomycin is best avoided. As far as we are aware, there is no evidence that inhaled antibiotics (such as TOBI®) have a long term deleterious effect on the kidney.

Aminoglycoside antibiotics act best to kill bacteria when their concentration is above a certain level in the blood, but toxic effects on the kidney are related to the overall exposure of the nephrons. Thus, bacterial killing can be maximised and kidney damage minimised by giving pulses of aminoglycosides - traditionally, these were administered as a bolus three times a day. Recently, it has been shown that once daily administration is as effective in treating exacerbations, but may be less nephrotoxic in children. Whichever regime is used, it is important to measure blood levels of aminoglycosides to ensure that only sufficient is used to achieve adequate bacterial killing, whilst minimising any toxic effects.

We also concluded that the measurement of kidney function was important in those CF patients who were undergoing frequent courses of IV antibiotics. However, the creatinine clearance test requires the collection of all urine produced over 24 hours, which is time consuming and may not be possible in younger children. A number of formulae have therefore been developed to allow an estimation of renal function – all these rely upon comparing the blood creatinine level with various parameters, such as weight, age, and sex. These include the widely used Cockcroft Gault, and more recently the MDRD and aMDRD formulae. They are commonly used in the assessment of kidney function in non-CF patients with chronic renal failure, and for the estimation of drug dosing in other adult patients. However, they all assume that the individual has a normal muscle mass and nutritional state, which is often not the case in CF people, especially those who are sufficiently affected by the CF condition to require repeated doses of antibiotics.

We looked at a group of adult CF patients who had undergone a traditional creatinine clearance measurement of renal function, and compared the results with those obtained using a number of formulae to estimate renal function. We found that all the formulae used for estimation gave erroneous results, and these results were most misleading in those patients who had the worst kidney function. From this we concluded that formulae methods of estimation of renal function in CF patients are not appropriate and other methods must be used.

