Abstract

Kidney disease is becoming increasingly common in CF. This review looks at the effect of CFTR on the kidney, the problems with measuring renal function effectively in CF, the causes and incidence of renal dysfunction, and its pathophysiology. Strategies to reduce aminoglycoside toxicity are discussed.

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Keywords: Renal disease; Measurement of renal function; Creatinine clearance; Aminoglycosides; Fosfomycin

1. Introduction

Cystic fibrosis is one of the success stories of modern medicine — whereas in the 1950s most individuals with the
disease died before the age of 5, medical advances mean that those born in the 21st century will live into their fifth or sixth decade. Indeed, the latest UK CF Registry (capturing nearly all the UK’s >9000 patients) indicates that the median survival is already over 41 years, and very few patients die in childhood.

Furthermore, many adolescents transitioning to the adult sector can now expect to have normal or near-normal lung function, attributed to better therapy, organisation of care, and improving socio-economic factors.

However, the ageing of the CF population has brought with it unforeseen problems and complications and there has been a paradigm shift in outlook in the adult healthcare sector, from a focus on the care of lung disease to the management of a complex multi-system chronic illness. One of these complications has been the emergence of the involvement of the kidney in the CF condition. Although CFTR is found in the kidney, mainly in the proximal and distal tubules, and its inactivation can cause low molecular weight proteinuria [1], its exact role and effect in CF related kidney disease is unknown and primary renal disease is an unusual feature, in contrast to secondary renal dysfunction that is becoming increasingly common. Nephrogenesis is completed by thirty-six weeks of gestation [2]; nephron numbers are genetically determined (the human average is 1 million per kidney) and they do not regenerate. Following birth, there is a gradual decline in their number, but the attrition rate is accelerated by chronic infection, diabetes, and vascular disease, all of which can be present in CF.

Furthermore, CF individuals are in danger of acute kidney injury and the development of chronic renal disease through exposure to multiple potentially nephrotoxic agents including aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs) and immune-suppressants. Nephropathy can also result from abnormalities in salt transport [3], colonisation with *Pseudomonas aeruginosa* (Psu) [4], and the development of Cystic Fibrosis Related Diabetes (CFRD) requiring insulin [5].

This paper reviews the problems with measuring renal dysfunction in CF, its path-physiology, and discusses renoprotective strategies in order to decrease the incidence of this important complication.

### 2. Diagnosis and screening of renal dysfunction

Renal blood flow, glomerular filtration, and tubular resorptive capacity all play their part in defining renal function. In humans, the assessment of renal function is limited to measuring the Glomerular Filtration Rate (GFR), renal blood flow, and estimation and measurement of proteinuria and creatinine clearance derived from various formulae.

Although GFR has always been considered the best clinical estimate of renal function and correlates well with both clinical severity and disturbances in renal function [6], it has its limitations. It cannot be assessed directly and is determined indirectly by measuring the clearance of suitable filtration markers that are not reabsorbed, secreted or metabolised by the kidney, such as Cr-EDTA, inulin, $^{99}$Tc-DTPA and iohexol [7]. However, tests involving these markers are costly, time consuming, need intravenous infusions and accurate sample collection, all of which are problematic. Also, many CF patients do not have normal or stable serum creatinine levels, which further complicates its measurement.

GFR is also insensitive in the detection of early renal dysfunction: up to 30% of nephrons can cease to function before GFR alters, since the remainder compensate by increasing their filtration rate [8,9]. It is only with a further loss of renal tissue that GFR will reduce.

Due to the difficulty of directly measuring GFR, indirect methods based on the clearance of physiological products through the kidney have been devised. One such test is the clearance of creatinine (CCI). Creatinine, a muscle breakdown product, is produced in a predictable way in stable individuals and is only minimally reabsorbed by the renal tubules. However, because the measurement of CCI depends upon the accurate urine collection, it is subject to error in adults and impractical in young children, a number of formulae based on serum creatinine, muscle mass, and physical constants have been devised to estimate it (eCCL).

Formulae including the abbreviated Modification of Diet in Renal Disease (aMDRD) equation [10] and the Cockcroft-Gault formula (CGF) [11] are widely used clinically and have been advocated in those with CF [12]. However although these formulae are simple to use in daily practice, they are not reliable when the serum creatinine is unstable, overestimating CCI and therefore GFR when the creatinine is rising, and vice versa [13,14]. They have not been validated in CF and furthermore, this lack of validation is particularly important because many CF patients are in a hypermetabolic state [15], have diminished muscle mass, and have limited exercise capacity [16], all of which can influence creatinine production.

Data published from our own unit [17] comparing 74 adult CF patients with no previous history of renal problems and a normal range of serum creatinine, with 29 healthy age and BMI matched control subjects, showed these formulae to be unreliable. Measured creatinine clearance was compared with eCCL using various formulae: all (including the popular CGF and aMDRD-derived estimates) compared less favourably in CF patients than controls and grossly over-estimated renal function in CF patients with reduced CCI (<80 ml/min)[Table 1]. These formulae should be used and interpreted with caution in CF patients; generally they overestimate creatinine clearance and therefore underestimate the degree of renal dysfunction in the CF population.

Drugs such as aminoglycosides can cause proximal tubular damage, leading to acute tubular necrosis resulting in electrolyte leak from a defect in the urinary concentrating capacity and the elevated urinary excretion of certain tubular enzymes.

Hence over the past 40 years attention has been directed towards the evaluation of urinary enzymes as non-invasive biomarkers of renal tubular damage. They can be sensitive tools useful in the early diagnosis of acute renal injury before conventional laboratory assays become deranged [18–20], and they reflect sub-clinical toxicity and might have an important role in screening for early renal damage. They may also indicate the site of primary tubular damage because of their localisation in tubular lysosomes (N-acetyl-β-D-glucose-aminidase [NAG]) and...
Table 1
Comparison of mCCL and eCCL (CGF and abbreviated MDRD [4 variable]) in renally impaired CF patients (mCCL < 80 ml/min).

<table>
<thead>
<tr>
<th>n</th>
<th>Mean mCCL (S.D.)</th>
<th>eCCL formula</th>
<th>Mean eCCL (S.D.)</th>
<th>% eCCL within 33% of mCCL</th>
<th>Bias</th>
<th>95% CI for bias</th>
<th>LOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCCL &lt; 80</td>
<td>35</td>
<td>63.5 (12.3)</td>
<td>CGF</td>
<td>81.7 (18.1)</td>
<td>60%</td>
<td>18.3</td>
<td>13.6 to 23</td>
</tr>
<tr>
<td>mCCL ≥ 80</td>
<td>39</td>
<td>100.7 (13.8)</td>
<td>aMDRD</td>
<td>79.3 (20.2)</td>
<td>65%</td>
<td>15.8</td>
<td>10.5 to 22.0</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>83.1 (22.9)</td>
<td>CGF</td>
<td>102.3 (16.6)</td>
<td>95%</td>
<td>1.6</td>
<td>−3.5 to 6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>aMDRD</td>
<td>95.1 (16.1)</td>
<td>84%</td>
<td>−5.6</td>
<td>−11.1 to −0.1</td>
</tr>
</tbody>
</table>

The role of aminoglycosides in renal dysfunction in CF

Aminoglycosides are commonly used in the treatment of gram-negative diseases including pseudomonal infections. These agents are lipid and water-soluble molecules that following IV administration have a rapid compartmental distribution and achieve peak serum levels within 30 min. Many are highly effective against *Psa*, are relatively cheap compared to other classes of antibiotics and widely used in CF. Activity is related to their peak levels and also the post-antibiotic effect (a continuing bactericidal action when the drug is no longer detectable). However, since CF patients have an accelerated renal clearance and altered pharmacokinetics [31] high doses of intravenous antibiotics need to be administered (3–5 mg aminoglycoside/kg body weight/dose) to achieve therapeutic concentrations. Aminoglycosides do not bind well to plasma proteins and are eliminated via glomerular filtration; up to 15% of the filtered dose is reabsorbed by the proximal tubule through a saturable mechanism, which once exceeded results in the disruption of lysosomal function by binding to brush border membranes and subsequent cellular apoptosis [32,33]. Aminoglycoside induced nephrotoxicity is a dose-limiting feature, and unfortunately toxic levels are close to the therapeutic range [34].

In a study of 80 stable CF adults chronically infected with *Psa* and no previous history of renal disease [35] we showed an association between lifetime intravenous aminoglycoside exposure and reduced renal function. Recently, this was confirmed by Jain et al. [36] who suggested that renal hyper-filtration may also play a part in CF. In our study, up to 42% had CCI below the normal range (determined by the CGF and 24 h urine collection) and there was a strong correlation ($r = −0.32, p = 0.0055$) between aminoglycoside use and diminishing renal function [Fig. 1]. Interestingly, this relationship was potentiated by the co-administration of intravenous colistin ($r = −0.42, p < 0.0002$), but there was no correlation with colistin when used in combination with other antibiotics alone. Unfortunately, the emergence of multi-resistant epidemic strains of *Psa*, such as the Liverpool epidemic strain, often sensitive only to aminoglycosides and colistin, means those chronically infected with such strains frequently require repeated courses of these toxic antibiotics for good clinical reasons.

Some paediatric centres administer routine 3-monthly intravenous anti-pseudomonal antibiotic therapy, including an aminoglycoside, in an attempt to maintain lung function and prevent pulmonary exacerbations. This increases the lifetime exposure to these toxic drugs, exacerbates the development of resistance patterns [37], has not been shown to confer any benefit in pulmonary function [38], and may be associated with higher mortality [39]. The potential short-term benefit does not outweigh the propensity for long term renal damage.
3.2. How can aminoglycoside toxicity be prevented?

Although the obvious way to diminish toxicity would be to reduce or eliminate aminoglycoside use, this is not practicable as these drugs are not only effective against Pseudomonas aeruginosa, but also cheap and familiar to many CF clinicians. There are several ways in which their toxic effects can be limited:

3.3. Dosing intervals

One strategy is to give more aminoglycoside less frequently. Increasing the dosing interval will reduce the basal serum aminoglycoside level and the accumulation of the drug within the kidney, whilst theoretically still allowing the high peak serum levels and post-antibiotic effect to potentiate bacterial killing (Fig. 2) [40]. Adeboyeku et al. [41] showed that twice daily dosing of tobramycin and ceftazidime was comparable to thrice daily dosing in 146 CF patients. Although a number of studies comparing treatment outcomes and side-effects of a once daily dosing regimen did not show benefit [42–44], the TOPIC trial [43] demonstrated equal efficacy between once and thrice daily tobramycin when administered with thrice daily ceftazidime and based on urinary marker analysis there was also less acute renal damage in children, but no difference was shown in adult patients.

Many centres now give aminoglycosides once daily, on the basis of convenience in adults, since it reduces the complexity of drug level monitoring [45]. This is reflected in the US guidelines [46] where a once daily dosing is preferred but the UK guidance [47] includes either a once or thrice daily dosing schedule when aminoglycosides are used in the treatment of pulmonary exacerbations.

Since the toxicity of aminoglycosides varies with renal clearance and is dose dependent, serum peak and trough levels

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**Fig. 1.** Correlation between renal function (mCCl) and lifetime use of IV nephrotoxic antibiotics. Reproduced from Pediatr Pulmonol 2005 Jan;39(1):15–20 with permission of John Wiley & Sons, Inc.

**Fig. 2.** Effects of saturable uptake on kidney cortical accumulation in single daily versus three times daily dosing. Reproduced from [Thorax, Prayle A, Watson A, Fortnum H, Smyth A., Jul;65(7):654–8, 2010] with permission from BMJ Publishing Group Ltd.
should be closely monitored to confirm that levels are within therapeutic and non-toxic ranges. Optimum peak serum levels for tobramycin (measured half an hour after completion of an IV dose) are 8–12 mg/l, and <1 mg/l for the trough dose [47]. Where once daily dosing is used, only the trough level is measured [47,48].

3.4. Dosing route

A further strategy to diminish nephrotoxicity is to optimise the route of administration by the use of nebulised therapy. High dose nebulised versions of tobramycin, currently available for the prophylactic suppression of chronic pseudomonas infection in CF patients, have excellent lung deposition, low systemic penetration (12%) and higher sputum levels than IV preparations. However, the role of nebulised tobramycin as a renal sparing alternative to the IV form in the treatment of acute respiratory exacerbations in CF patients has not been well explored.

In a pilot randomised crossover trial in 14 adult CF patients [49], during a respiratory exacerbation we gave Tobramycin Nebulised Solution (TNS) at a standard CF dose of 300 mg bid in conjunction with another IV antibiotic and compared it with the IV preparation. Although the mean improvement in spirometry was similar in both arms, there was much less expression of markers of acute renal injury in the urine [Table 2] in the TNS arm. This suggests that TNS is effective in treating acute pulmonary exacerbations in CF, but causes less acute renal damage than the IV preparation. This mode of administration needs further exploration and larger suitably powered studies are now required to confirm this effect and how it relates to long-term nephrotoxicity.

Nevertheless, even inhaled antibiotics reach significant serum levels and acute renal failure can occur with both nebulised tobramycin [50] and colistin [51].

3.5. Competitive inhibition

Agents which compete for the renal binding sites may reduce the toxic effects of aminoglycosides. One such drug is fosfomycin (1,2-epoxy-propyl-phosphonic acid). Animal studies have shown that it may protect against aminoglycoside nephrotoxicity by competing for the binding site within the proximal tubular cell, therefore preventing cellular apoptosis. Isolated in 1969 from Streptomyces fradiae [52] and now produced synthetically, it is unique and was first used in patients with CF in 1984 [53]. After IV administration 90% is excreted unchanged through the kidney within 24 h. Not bound to serum proteins, it has a half life of 1.5–2 h, with a large volume of distribution and diffuses well into lung tissue [54]. It is well tolerated by CF patients [55] and has the added benefit of possessing effective anti-pseudomonal properties.

In a pilot prospective randomised crossover trial we examined this effect in CF [56] and showed that the addition of IV fosfomycin in 8 adult CF patients during acute exacerbations reduced the urinary levels of renal tubular enzymes elevated by IV tobramycin, suggesting that it may protect the lysosomal membrane and hence renal function. Larger studies are required to confirm this effect.

4. Aminoglycosides and acute renal failure in CF

Although episodes of acute renal failure (ARF) can occur with inhaled preparations, they are more commonly associated with intravenous therapy [50,57,58].

We reported 8 cases of ARF in adult CF patients from our centre [59], implicating intravenous tobramycin and a later survey of 55 UK CF centres [57] found up to 10.5 cases ARF/10,000 CF patients/year. However, few reports were obtained from adult centres, suggesting that the true incidence may be much higher. In 88% of cases aminoglycosides (76% — gentamicin) were prescribed at the onset of ARF or within the preceding week, and where renal biopsy was performed, 85% demonstrated acute tubular necrosis (all having received gentamicin). Half required renal dialysis and a complete recovery was seen in 92%.

Gentamicin, commonly used in paediatric CF practice is more nephrotoxic than other aminoglycosides. Its structure (two amino sugars joined to a hexose nucleus) reduces its absorbability and its subsequent accumulation potentiates tubular necrosis and ultimately renal dysfunction [60] — it should not be used in CF patients.

5. Immuno-suppression post-transplant

Survival following lung transplantation has improved considerably over the last two decades, and in CF up to 50% can expect to survive for more than 7 years [61]. However, they can also expect to develop a life-time of transplant related complications, either related to rejection or the toxic effects of immune suppressive therapy and renal dysfunction is well-recognised as part of this spectrum, occurring in up to 35% of all lung transplant recipients [61].

Calcineurin inhibitors including cyclosporine impair endothelial cell function, with a subsequent decrease in the production of

<table>
<thead>
<tr>
<th>Urinary marker (log10)</th>
<th>High dose nebulised tobramycin Mean change SD</th>
<th>IV tobramycin Mean change SD</th>
<th>Mean diff between treatments</th>
<th>95% CI p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAG (iu/mmol)</td>
<td>0.02 ± 0.51</td>
<td>0.74 ± 0.44</td>
<td>−0.72</td>
<td>−1.11 to −0.33</td>
</tr>
<tr>
<td>AAP (iu/mmol)</td>
<td>−0.37 ± 0.69</td>
<td>0.82 ± 0.62</td>
<td>−1.19</td>
<td>−1.72 to −0.66</td>
</tr>
<tr>
<td>α-GST (mcg/mmol)</td>
<td>0.01 ± 0.06</td>
<td>0.99 ± 0.90</td>
<td>−0.99</td>
<td>−1.47 to −0.51</td>
</tr>
<tr>
<td>Collagen IV (mcg/mmol)</td>
<td>−0.08 ± 0.01</td>
<td>0.38 ± 0.36</td>
<td>−0.46</td>
<td>−0.83 to −0.08</td>
</tr>
</tbody>
</table>
vasodilators such as prostaglandins and nitric oxide. There is a resultant increased release of endothelin and thromboxane, both potent vasoconstrictors [62,63] and can cause vasoconstriction of the afferent and efferent glomerular arterioles [64]. This leads to reduction in renal blood flow and GFR contributing to the development of renal failure [65,66]. In addition, there have been reports of calcineurin inhibitor toxicity and associated haemolytic uraemic syndrome (HUS) following lung transplantation in this patient group [67].

In recently published data using eGFR, an analysis of 993 adult lung transplant recipients from the US CF Foundation Patient Registry (2000–2008) [68] showed that significant renal dysfunction increased over time, and this worsened with age and in females. Overall, renal dysfunction (equivalent to at least stage 3 chronic kidney disease) was common with a 2 year and 5 year risk of 35 and 58% respectively, with 10% eventually requiring haemodialysis. Although no association was found with antibiotics, the results were extracted from registry data where aminoglycoside use was not well recorded.

Furthermore, those with Cystic Fibrosis Related Diabetes (CFRD) requiring insulin had a significantly higher risk of developing post-transplant renal dysfunction similar to the post-transplant renal complications in non-CF diabetes mellitus [69], emphasising the importance of early and aggressive management of CFRD to minimise the long-term risks.

6. Other renal problems in CF

Despite the problems inherent in measuring renal function in CF and problems with nephrotoxic drugs there is increasing evidence of other renal pathologies in the CF patient population. These are illustrated briefly below.

6.1. Nephrolithiasis

Low urine volume associated with salt depletion and dehydration, hyper-oxyuria, hyper-uricosuria and hyper-calciuria [70] all occur in CF and contribute to increased nephrolithiasis and nephrocalcinosis, which has been found in 90% of autopsies [70]. Furosemide and prednisolone are associated with hyper-calciuria and the prolonged episodes of immobilisation that can occur in CF result in hyper-calcemia and hyper-calciuria.

Importantly, repeated antibiotic use leads to the destruction of intestinal oxalate degrading bacteria such as Oxalobacter formigenes, with the subsequent absorption of gut oxalates which are then re-excreted through the kidney with resulting crystallisation and oxalate stone formation. The incidence of renal stones is up to 6% [71–74] compared to <2% in healthy matched controls [75].

6.2. Amyloidosis

Secondary amyloidosis occurs as a result of chronic infection and inflammation where it can cause the nephrotic syndrome [76,77]. Although colchicine may confer benefit [78], the prognosis is poor with most cases dying within one year. It is increasingly being recognised in CF.

6.3. IgA nephropathy

High levels of IgA are present in the circulation in CF patients, presumably because of recurrent infections and chronic inflammation. Deposition of this increased IgA in the kidney can cause further immune activation leading to glomerulonephritis. In addition the presence of liver disease in CF, impairs immune complex clearance and increases the risk of renal deposition [79]. IgA nephropathy is associated with many autoimmune conditions: when CF is also present the prognosis is poor, with 25% mortality. It remains the most commonly reported cause of glomerulonephritis in CF patients [80], present in up to 80% of cases where renal biopsy was performed [81].

7. Cystic Fibrosis Related Diabetes Mellitus (CFRD)

CFRD, discussed as a separate review in this series, is unique and distinct: although uncommon in childhood, its prevalence increases with age and it affects up to 50% of adults [82]. Despite the fact that it is a risk factor for the development of chronic kidney disease compounded by increasing age, worse pulmonary function, malnutrition, liver dysfunction and steroid use [83] in these patients, few studies have investigated it.

Although assessment of US CFF Registry data over a 10 year period found a 2.3% annual prevalence of at least stage 3 kidney disease which doubled with every 10 years of life and with the diagnosis of CFRD [5], this should be viewed with caution since the definition of renal function was based on eGFR, which underestimates the degree of renal damage in CF. Further studies are needed to assess the impact of this increasingly common renal complication in CF.

The lack of a satisfactory screening tool for diabetes in this susceptible population means that the renal consequences of this common CF complication may be underplayed. Current guidance [84,85] recommends an oral glucose tolerance test (OGTT) for the diagnosis of diabetes mellitus where the thresholds for significant glucose intolerance are drawn from a non-CF diabetic population at risk of developing micro-vascular complications with non-CF specific outcomes. In CF different complications occur early and better methods to make an early diagnosis of CFRD are needed.

One such method is ambulatory Continuous Glucose Monitoring (CGM), a stronger predictor of the development of CFRD than the OGTT [86] and we have demonstrated it to be a valuable screening test for CFRD [87].

In the non-CF population, micro-albuminuria (defined as a persistent urine albumin level of >15 mg/l or an albumin-creatinine ratio (ACR) ≥2.5 mg/mmol in males and 3.5 mg/mmol in females) can be used as an indicator of renal damage. Although microalbuminuria occurs in CFRD [88], its use in CF has been questioned due to the possible contributory role of other factors — chronic infection with repeated use of potentially nephrotoxic drugs, sepsis and acute dehydration, and it may well be a less sensitive indicator of progression to diabetic nephropathy.

Micro-vascular complications similar to those seen in Type 1 diabetes do occur in CFRD, but with a lower prevalence of
retinopathy and a higher prevalence of microalbuminuria [89]; this is likely to increase over the coming decades, as the CF population ages.

8. Future perspectives

As CF patients age and have an increased lifetime exposure to potentially nephrotoxic therapy and worsening glucose intolerance, renal disease is now more commonly recognised as a feature of CF.

However, assessment of renal dysfunction in CF is hampered by the lack of suitable monitoring tests of renal function. The focus of new antibiotic development remains on chronic infection with *Psa*, still the main pathogen leading to advanced CF lung disease. With the problems of multi-resistant *Psa* species and those associated with aminoglycosides, there is a need for other antibiotics that possess anti-pseudomonal activity and an increased need for new approaches in the treatment of pulmonary infection. Strategies to limit the effect of nephrotoxic drugs, particularly aminoglycosides, and the early recognition of CRF and its timely treatment to prevent renal complications will need to be further developed.

Authorship statement

Both authors have contributed equally to drafting the manuscript. MW edited and approved the final draft.

Conflicts of interest statement

Both authors have no conflicts of interest to declare.

References


