Biomarkers for Kidney Injury in Cystic Fibrosis

31

Kevin J. Downes and Stuart L. Goldstein

Contents

K.J. Downes (✉)
Department of Pediatrics, Perelman School of Medicine, The University of Pennsylvania, Philadelphia, PA, USA

Division of Infectious Diseases, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: downeskj@email.chop.edu; kjdownes@yahoo.com

S.L. Goldstein
Division of Nephrology and Hypertension, Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: Stuart.Goldstein@cchmc.org

V.B. Patel, V.R. Preedy (eds.), *Biomarkers in Kidney Disease*, Biomarkers in Disease: Methods, Discoveries and Applications, DOI 10.1007/978-94-007-7699-9_12

Abstract

Cystic fibrosis (CF) is an autosomal recessive disease affecting sodium and chloride transport predominantly in the lungs and digestive system. Patients with this disease develop recurrent and chronic respiratory tract infections often necessitating repeated and aggressive antimicrobial therapy. Patients also commonly develop pancreatic insufficiency, diabetes, malabsorption, and liver problems. The role of the CF gene mutation in the kidney is not well described. However, patients with CF are at risk for development of acute kidney injury (AKI) due to receipt of nephrotoxic medications, particularly antibiotics, as well as long-term renal damage from long-standing diabetes and repeated nephrotoxin exposures. The traditional marker of kidney injury and function, serum creatinine, is an unreliable marker of kidney function and injury in patients with CF and low muscle mass: it often overestimates true kidney function and does not detect kidney injury until a significant number of nephrons have been affected. Novel biomarkers, such as cystatin C (CysC), retinol-binding protein (RBP), kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL) have been studied preliminarily in this population but hold significant promise for early detection of AKI, risk stratification, and prognosis. With advances in medical therapies leading to substantial improvement in lifetime survival among CF patients, the long-term ramifications of the disease and its treatments on the kidney are becoming apparent. Methods to improve detection of kidney injury and risk of development of chronic kidney disease in patients with CF are paramount. This chapter reviews the available literature on the causes and impact of AKI in patients with CF, as well as the strengths, limitations, and potential uses of traditional and novel biomarkers of kidney injury in this population.

Keywords

Acute kidney injury • Aminoglycosides • Chronic kidney disease • Cystic fibrosis • Urinary biomarkers

Abbreviations

AG	Aminoglycoside
AKI	Acute kidney injury
B_2M	Beta-2-microglobulin
BUN	Blood urea nitrogen
CCl	Creatinine clearance
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes

CKD	Chronic kidney disease
CysC	Cystatin C
eCCl	Estimated creatinine clearance
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
IL-18	Interleukin-18
IV	Intravenous
KIM-1	Kidney injury molecule-1
L-FABP	Liver-type fatty acid-binding protein
NAG	*N*-Acetyl-β-D-glucosaminidase
NGAL	Neutrophil gelatinase-associated lipocalin
NSAIDs	Nonsteroidal anti-inflammatory drugs
RBP	Retinol-binding protein
SCr	Serum creatinine
TDM	Therapeutic drug monitoring
UCr	Urine creatinine

Key Facts of Cystic Fibrosis and Kidney Injury

- Cystic fibrosis (CF) is an autosomal recessive genetic disease.
- A defect in the cystic fibrosis transmembrane conductance receptor (CFTR) leads to impaired sodium and chloride transport across epithelial cells.
- As a result of abnormal electrolyte transport, patients develop thick mucus which predisposes them to chronic and recurrent pulmonary infections, intestinal malabsorption, and pancreatic insufficiency.
- The impact of CFTR on kidney disease in CF has not been fully elucidated.
- The majority of kidney injury in this population stems from secondary insults from nephrotoxin administration (antibiotics, immunosuppressive medications), formation of renal stones, and CF-related diabetes (CFRD).
- As survival for patients with CF increases, so do opportunities for kidney injury and the likelihood of development of chronic kidney disease (CKD).
- The traditional marker of kidney injury and function, serum creatinine, is often inaccurate in patients with CF and decreased muscle mass.
- Novel serum and urine biomarkers hold great promise for the early detection and prognostication of acute kidney injury in patients with CF and other high-risk populations.

Definitions

Acute kidney injury (AKI) An acute, reversible decline in kidney function manifested by an increase in serum creatinine (SCr) combined with an inability of the kidney to regulate fluid and electrolytes appropriately.

Albuminuria The presence of albumin, a plasma protein, in the urine; this often reflects damage to the glomerulus (the filter) of the kidney.

Aminoglycoside A class of antibiotic used to treat certain bacterial infections.

Biomarker A molecule (protein, enzyme, etc.) found in the body (blood, urine, tissue, etc.) that signifies the presence of a disease.

Chronic kidney disease (CKD) A progressive and often irreversible loss of kidney function.

Creatinine A by-product of muscle breakdown; its concentration in the serum is often reflective of kidney function because it is nearly exclusively cleared by the kidney. Elevated serum creatinine concentrations reflect impaired kidney function.

Creatinine clearance (CCl) Describes how much creatinine is removed from the body by the kidney; used as a proxy for kidney function and glomerular filtration rate.

Drug clearance A measure of the amount of drug eliminated from the serum in a given amount of time.

Glomerular filtration rate (GFR) A measure of kidney function describing the rate of fluid filtered by the kidney.

Nephrotoxin A drug or medically administered substance (i.e., intravenous contrast) which can have injurious effects on the kidney.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease that predisposes individuals to chronic and recurrent pulmonary infections, intestinal malabsorption, and pancreatic insufficiency. A defect in the cystic fibrosis transmembrane conductance receptor (CFTR) leads to impaired sodium and chloride transport across epithelial cells and is the underlying cause of the clinical manifestations of CF. In the human kidney, CFTR is present predominantly in the proximal and distal tubules (Crawford et al. 1991), but the impact of CFTR on kidney disease in CF has not been fully elucidated. Despite the presence of CFTR in the kidney, primary kidney diseases are relatively rare in CF patients. Thus, the majority of kidney injury in this population stems from secondary insults from nephrotoxin administration, formation of renal stones, and CF-related diabetes (CFRD). As survival for patients with CF increases, so do opportunities for kidney injury and the likelihood of development of chronic kidney disease (CKD). Improved methods for early detection of kidney injury are needed.

This chapter reviews the causes and methods of detection of acute kidney injury (AKI) in CF patients, with a focus on nephrotoxin-associated kidney injury, which is the most prevalent and potentially modifiable cause of kidney injury in this population. The impact of AKI in CF patients and the potential roles of novel urinary and serum kidney injury biomarkers in AKI detection are also discussed. Laboratory methods of biomarker measurement are not reviewed and can be found elsewhere in this book.

Kidney Injury Definitions

Acute kidney injury, formerly denoted acute renal failure, is defined as an acute, reversible increase in serum creatinine (SCr) and nitrogenous waste products combined with an inability of the kidney to regulate fluid and electrolytes appropriately (Andreoli 2009). Traditionally, the method for monitoring kidney injury (acute or chronic) has been through surveillance of SCr and blood urea nitrogen (BUN) measurements and monitoring urine output. Serum creatinine can be monitored directly or used to estimate the glomerular filtration rate (GFR) or creatinine clearance (CCl) through a variety of derived formulae. A number of AKI definitions have been developed based on the magnitude of SCr or estimated creatinine clearance (eCCl) changes and/or a reduction in urine output. Figure 1 displays the AKI

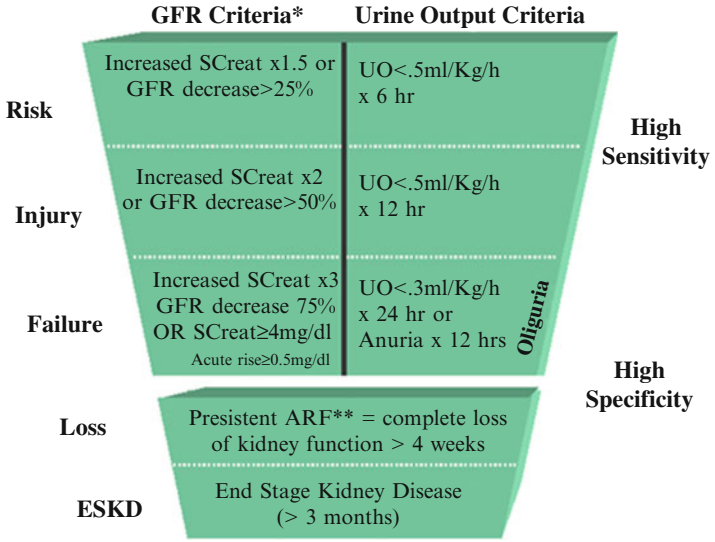

Fig. 1 RIFLE classification scheme for acute renal failure (*ARF*). The classification system includes separate criteria for creatinine and urine output (*UO*). A patient can fulfill the criteria through changes in serum creatinine (*SCreat*) or changes in UO or both. *Abbreviations*: *ARF* acute renal failure, *GFR* glomerular filtration rate (©2004; licensee BioMed Central Ltd. This is an Open Access article. http://ccforum.com/content/8/4/R204. Reproduced with permission from Bellomo et al. 2004)

classification scheme of the RIFLE criteria (Bellomo et al. 2004), which is one of the most frequently employed AKI definitions for adults. This classification system demonstrates how SCr-, GFR-, and urine output-based criteria relate and can be applied to identify patients with AKI. Most AKI definitions have been studied and validated in specific patient populations. However, there is no universally accepted and validated definition for AKI specific to patients with CF. As will be discussed below, SCr-based definitions of AKI may be inadequate in patients with CF due to the limitations and inaccuracies of SCr in this population.

Similar to AKI, chronic kidney disease (CKD) encompasses a number of stages which reflect the degree of kidney dysfunction. Chronic kidney disease typically reflects sustained ($\geq$3 months) and significant (GFR $<$60 mL/min/1.73 m^2) impairment (K/DOQI 2002). A reduction in kidney function to this degree, referred to as stage 3 CKD, generally equates to a loss of half of normal adult kidney function. Persistent kidney damage, manifest as structural or function abnormalities, can also meet the CKD definition.

The Impact of Kidney Injury in Cystic Fibrosis

The incidence of kidney injury in CF may be significantly higher than in the non-CF population. Bertenshaw and colleagues estimated the incidence of acute renal failure in individuals with CF to be between 4.6 and 10.1 cases per 10,000 per year, more than 100 times the average rate of kidney injury in children and three to eight times that of adults (Bertenshaw et al. 2007). This survey study identified patients by physician report and defined acute renal failure as, "raised plasma creatinine for age." Despite the use of this broad definition, the majority of subjects included in the study (54 %) had severe renal impairment requiring dialysis, making it likely that many patients with modest changes in SCr, which would constitute AKI by recently validated definitions, were not reported. Therefore, this study may actually underestimate the true incidence of AKI in the CF population.

Acute kidney injury has both short- and long-term ramifications, and even small changes in SCr of 0.3–0.5 mg/dL are independently associated with worse outcomes, including mortality, in children and adults (Moffett and Goldstein 2011; Chertow et al. 2005). Meanwhile, children and adults who sustain AKI are also at increased risk for long-term mortality and the development of chronic kidney disease (Askenazi et al. 2006; Wehbe et al. 2011), including AKI resulting from exposure to nephrotoxic medications (Menon et al. 2014). Data on the impact of AKI episodes in CF patients are more limited. Among adults with CF, episodes of AKI correlate with some markers of chronic kidney impairment (Florescu et al. 2012). This cohort study followed 113 adult patients in the United States with CF for up to 8.5 years. While there were no significant changes in BUN ($p = 0.92$) or SCr ($p = 0.2$) among the entire study population, individuals who experienced an episode of AKI had a significant increase in BUN ($P = 0.002$) and a nearly significant increase in SCr ($P = 0.056$) at the end of follow-up. Only the use of inhaled colistin correlated with AKI episodes ($p = 0.03$).

Unfortunately, there are limited additional data about the long-term outcomes of CF patients in relation to episodes of AKI specifically. Yet, there is mounting evidence that patients with CF sustain repeated renal insults over time from a variety of etiologies. As survival for patients with CF increases, the risk of developing CKD rises. Quon et al. estimated that the age-adjusted prevalence of CKD is about twice that of the United States general population (Quon et al. 2011). A strong association has been described between patients CFRD requiring insulin and the development of CKD (Quon et al. 2011). Meanwhile, others have noted an association between repeated intravenous (IV) aminoglycoside (AG) use and long-term renal impairment (Al-Aloul et al. 2005a). Ultimately, the development of CKD is more likely to result from repeated or chronic insults than progression of primary kidney disease.

Children with CF may also develop chronic renal dysfunction. In a retrospective analysis of children with CF who had GFR measured by ^{99m}Tc-DTPA at a single center, Prestidge et al. found that 6 % (4/63) had evidence of stage 2 CKD (GFR $<$90 mL/min/1.73 m^2, persistent abnormalities in urinary sediment, abnormal renal imaging): one child with reduced GFR and three others with persistent microscopic hematuria (Prestidge et al. 2011). Although the rate of renal impairment in this study was low, the authors observed that 40–56 % of children had evidence of glomerular hyperfiltration depending on the definition used (GFR $>$2 standard deviations for age or $>$90th percentile for age). In diabetic adults without CF, glomerular hyperfiltration precedes the development of albuminuria and subsequent GFR decline (Moriya et al. 2012) and it is possible, as the authors suggest, that glomerular hyperfiltration in CF patients similarly portends subsequent kidney function decline, although this has not been established.

The impact of repeated nephrotoxic insults in the CF population becomes most apparent in patients undergoing lung transplantation. In a large cohort study of pediatric lung transplant recipients, patients with CF had more rapid decline in kidney function following lung transplant than other transplant recipients (Hmiel et al. 2005). In this study, Kaplan-Meier analyses determined that older age at transplant and diagnosis of CF were both associated with loss of renal function over time. Broekroelofs similarly found that rate of renal function loss was greatest among lung transplant recipients who also had CF ($-$10 mL/min/year, range: $-$14 to $-$6 mL/min/year) compared to others (Broekroelofs et al. 2000). Meanwhile, using data from the CF Foundation Patient Registry, Quon determined that the 2-year risk of post-lung transplant kidney dysfunction among CF patients was 35 % (95 % CI: 32–39 %) and the risk increased substantially with increasing age (Quon et al. 2012). There are a number of potential reasons why patients with CF are at high risk for development of renal impairment following lung transplantation: receipt of repeated and chronic nephrotoxic medications prior to and following transplantation (calcineurin inhibitors, antibiotics), diabetic nephropathy, and the presence of kidney stones. Renal reserve may be impaired heading into transplant, because of the numerous insults sustained prior to the procedure, and compounded by infection, receipt of additional antibiotic courses, and advanced diabetic disease afterward (Hmiel et al. 2005). With the high risk of development of CKD for patients with CF undergoing lung transplantation, it is paramount to identify means to reduce insults to the kidney prior to transplant.

Causes of Acute Kidney Injury in Cystic Fibrosis

There are a number of potential causes of AKI in patients with CF including toxins, intrinsic renal disease, obstruction, and other insults. In this population, the most likely inciting factor is the use of nephrotoxic medications. Individuals with CF have frequent lung infections which contribute to a decline in lung function over time, and aggressive antimicrobial therapy is used in both the acute and long-term management of CF lung disease. Unfortunately, a number of antibiotics commonly administered in the CF population, most notably aminoglycosides and colistin, have nephrotoxic effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also frequently used in CF to mitigate lung inflammation but can have detrimental effects on the kidney. Other nephrotoxic medications such as antihypertensive medications and immunosuppressants, although less commonly given, diabetic nephropathy, renal stones, and other causes may also contribute to kidney injury in this population; each of these potential causes will be discussed in further detail below.

Antibiotics

Aminoglycosides are a commonly used class of antibiotics in CF because of their activity against Gram-negative bacteria, particularly *Pseudomonas aeruginosa*, the most common pathogen infecting the lungs of patients with CF. These are concentration-dependent antibiotics, meaning that bacterial killing is optimized at high concentrations. To take advantage of this property, AGs are typically administered in high doses once daily to maximize killing and allow sufficient time for clearance of the medication prior to re-dosing. However, nephrotoxicity is a known side effect of AGs and the cellular mechanisms leading to toxicity are complex. Aminoglycoside nephrotoxicity results from accumulation of drug within proximal tubule cells leading to cytotoxicity, apoptosis, and cell death (Rougier et al. 2004). After glomerular filtration, a portion of the drug binds to an endocytic receptor, megalin, located on the apical surface of the proximal tubule epithelial cell and is endocytosed (Moestrup et al. 1995). Expression of megalin is directly related to the degree of drug accumulation as it is the principle receptor for AG uptake in the kidney (Schmitz et al. 2002), as well as a number of other important ligands. Following endocytosis, the drug accumulates within lysosomes, causes damage to membrane phospholipids and is released into the cytosol where cellular toxicity occurs (Servais et al. 2005). Tubule cell damage and apoptosis then lead to a reduction in the glomerular filtration rate (GFR) and impaired kidney function (Lopez-Novoa et al. 2011).

Most reports of AKI in patients with CF have implicated AG as the cause (Bertenshaw et al. 2007; Al-Aloul et al. 2005b; Drew et al. 2003; Kennedy et al. 2005; Smyth et al. 2008). In a survey of CF centers in the United Kingdom, an AG was administered prior to onset of AKI in 88 % of cases reported (Bertenshaw et al. 2007). An additional risk factor such as dehydration, underlying renal disease, or long-term receipt of a nephrotoxic drug also often accompanies cases of aminoglycoside-associated AKI (Smyth et al. 2008). Yet, the true incidence of

AG-associated AKI in the CF population had not been known. This is because detection of AKI is reliant upon systematic SCr measurement, which is rarely performed. Among children with CF, AKI rates during AG courses of up to 20 % have been described when SCr is monitored daily (Downes et al. 2014). But, detection of AKI is significantly impacted by the frequency of SCr measurement. Nonsystematic SCr measurement, which is common practice, and dependence upon a suboptimal marker (SCr) lead to an underestimation of the actual incidence of AKI.

Similar to AG, the antibiotic colistin has broad Gram-negative activity and is used often in patients with CF to treat more resistant pathogens. It is a polymyxin antibiotic whose nephrotoxic potential is recognized but not well understood. The mechanism of nephrotoxicity is thought to be similar to the mechanism by which the drug exhibits its antibacterial activity: increasing cell membrane permeability (Lewis and Lewis 2004). Damage to renal tubule cells leads to acute tubular necrosis, mitochondrial dysfunction, and impaired kidney function (Dai et al. 2014). Historically, colistin was associated with nephrotoxicity in up to 50 % of recipients (Falagas and Kasiakou 2006). However, newer formulations of the drug, careful monitoring of patients, and avoidance of coadministration with other known nephrotoxins have led to a reduction in reported toxicity.

The nephrotoxic potential of colistin in patients with CF is conflicting. In a retrospective review of 52 patients receiving 135 courses of colistin at a single center, Ledson and colleagues found that there was no change in renal function following receipt of the drug among the 122 evaluable courses (Ledson et al. 1998); colistin was used in combination with other drugs in 85 % of courses in this study. Meanwhile, in a randomized trial of IV colistin monotherapy versus combination antipseudomonal therapy (Conway et al. 1997), recipients of monotherapy did not demonstrate a change in creatinine clearance after 12 days, while those who received IV colistin in combination with another non-AG antibiotic had a significant decline by day 12 (day 1 = 109 mL/min vs. day 12 = 91 mL/min, $p < 0.01$). Nevertheless, reports of kidney injury with colistin are less prevalent than with IV aminoglycosides in CF, perhaps owing to the different frequency of use of these agents.

There have been no studies directly comparing the development of kidney injury from AG vs. colistin in CF patients. But, receipt of repeated courses of nephrotoxic antibiotics may be associated with long-term renal damage even in the absence of detected SCr-based AKI. In a prospective study of 80 CF outpatients with *Pseudomonas aeruginosa*, Al-Aloul and colleagues found a strong correlation between IV AG use and diminishing kidney function ($r = -0.32$, $P = 0.0055$) as determined by measured creatinine clearance (Al-Aloul et al. 2005a). Figure 2 displays the inverse correlation between kidney function and number of courses of IV nephrotoxic antibiotics found in this study. The association between decreased renal function and repeated antimicrobial exposure was not significant for regimens including IV colistin with a beta-lactam antibiotic ($r = 0.02$, $p = 0.83$). However, there was a significant association between renal function decline and receipt of IV aminoglycosides with a beta-lactam antibiotic ($r = -0.35$, $p = 0.0018$); the effect was more pronounced when an IV aminoglycoside was coadministered with colistin ($r = -0.51$, $p < 0.001$).

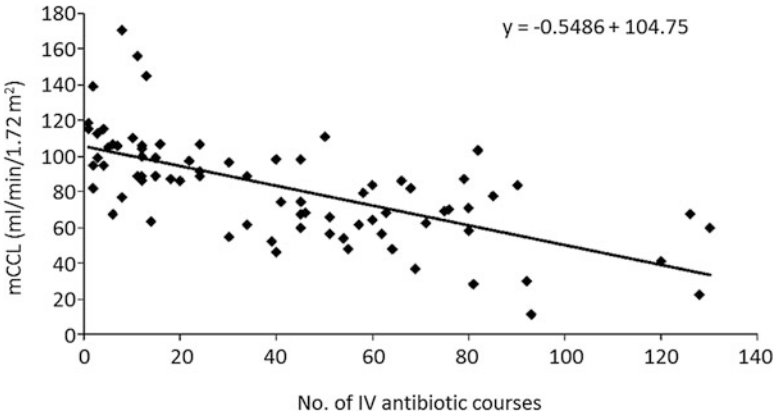

Fig. 2 Correlation between renal function (mCCL) and lifetime use of IV nephrotoxic antibiotics (courses containing aminoglycosides and/or colistin). $R = 0.65$, $P < 0.00001$. *Abbreviations*: *mCCL* measured creatinine clearance (Reproduced with permission from Al-Aloul et al. 2005. ©2004 John Wiley & Sons, Inc)

NSAIDs

Beyond the treatment of pain, nonsteroidal anti-inflammatory drugs (NSAIDs) may have a role in the treatment of chronic lung inflammation in CF patients. However, NSAIDs alter kidney function through their effects on prostaglandins (Weir 2002) and in the setting of altered renal blood flow (dehydration, shock, etc.) may compromise renal perfusion and lead to kidney injury. Despite their potential adverse effects, NSAIDs have rarely been reported to have significant nephrotoxic effects in patients with CF. In a single-center retrospective study of patients on chronic ibuprofen, 50 % patients had to discontinue the therapy due to adverse events (Fennell et al. 2007) but only one (2 %) discontinued the drug due to renal toxicity. Similarly, Lahiri et al. reported that high-dose ibuprofen was not associated with increased non-creatinine biomarkers of kidney injury (Lahiri et al. 2014); these biomarkers will be discussed in further detail below.

Other Nephrotoxins

A number of other medications administered in patients with CF may be toxic to the kidneys, as with other groups of patients. Lung transplantation is an important option for CF patients with severe and end-stage lung disease. Immunosuppressant medications such as the calcineurin inhibitors cyclosporine and tacrolimus have important therapeutic roles in transplant recipients but can lead to rapid decline in kidney function following transplant (Quon et al. 2012; Hmiel et al. 2005; Broekroelofs et al. 2000). These medications contribute to kidney injury and a reduction in GFR by causing vasoconstriction of afferent and efferent glomerular arterioles (Lanese and Conger 1993). Their nephrotoxic effects may be compounded by years of prior

nephrotoxin receipt in CF patients and may unmask decreased renal reserve (Hmiel et al. 2005). Antihypertensives such as loop diuretics and angiotensin-converting enzyme inhibitors may alter renal hemodynamics causing kidney injury (Ferguson et al. 2008). And antimicrobials such as acyclovir and amphotericin have their roles in CF care for the treatment of herpes virus and fungal infection, respectively, but may also be nephrotoxic.

Diabetes

In 2012, nearly 20 % of individuals with CF had cystic fibrosis-related diabetes (CFRD) with more than a third of adults being affected (Cystic fibrosis foundation patient registry 2012 annual data report 2013). Similar to type I and type II diabetes in patients without CF, CFRD causes long-term kidney damage. In a study using registry data from Germany and Austria (Konrad et al. 2013), the rate of diabetic nephropathy (defined as the presence of microalbuminuria) was similar among adults with CFRD (25.2 %) compared to non-CF patients with type I (17.2 %) or type II diabetes (24.7 %, p-values not reported) after adjustment for demographics. Using the US CF Registry data from 2001 to 2008, Quon determined that CFRD requiring insulin therapy was a significant risk factor for the development of stage 3 CKD as defined by an estimated GFR <60 mL/min/1.73 m^2 (Quon et al. 2011). Considering that this study was a retrospective analysis of registry data with reliance on eGFR for detection of CKD, this may actually underestimate the impact of CFRD on CKD development. CFRD requiring insulin therapy is also a significant risk factor for renal dysfunction following lung transplant (HR 1.30; 95 % CI, 1.02–1.67) (Quon et al. 2012). While the microvascular complications of CFRD can lead to chronic renal insufficiency, it is unknown whether CFRD also contributes to episodes of acute kidney injury or compounds the nephrotoxic effects of antibiotics in the CF population.

Stones

Patients with CF are at higher risk for nephrocalcinosis compared to the general population which can contribute to an impairment of kidney function. In a single-center cohort study of pediatric CF patients, the prevalence of risk factors for stone formation was high – hyperoxaluria (N = 58/83, 78 %), hypocitraturia (57/76, 75 %), hypercalciuria (16/87, 18 %), and hyperuricuria (15/83, 18 %) (Andrieux et al. 2010). However, no patients had symptomatic kidney stone formation and only 2 % had stones diagnosed by ultrasonography. Some studies have reported a prevalence of nephrolithiasis as high as 21 % (Terribile et al. 2006). Microscopic nephrocalcinosis may also be a frequent occurrence in CF patients, and the increased sodium secretion that occurs in CF may lead to dehydration and low urine volumes, further compounding the risk for stone formation. Repeated exposure to antimicrobials may alter gut flora and decrease the *Oxalobacter formigenes*, which leads to

reduced degradation of oxalate and an increased risk of hyperoxaluria and stone formation (Sidhu et al. 1998).

Markers of Kidney Injury in Cystic Fibrosis

With the myriad of potential causes of kidney injury in patients with CF, the long-term ramifications of repeated and chronic renal insults on kidney function is becoming more apparent as patients with this disease live longer. Traditional markers of kidney function and injury such as serum creatinine are inadequate. And, there is a need for accurate and sensitive markers of kidney injury and incorporation of these markers into routine CF care. Yet, the ideal biomarkers for AKI detection among patients with CF have not been established, and further research is urgently needed.

Novel biomarkers for kidney injury may be clinically useful for early detection of AKI. These biomarkers, of which several have been identified and will be discussed below, are more sensitive than traditional SCr measurements in detecting kidney injury directly and are under investigation for their utility in risk stratification and prognostication in AKI (Parikh et al. 2005). Increased levels have been associated with poor clinical outcomes irrespective of SCr measurements (Haase et al. 2011; Parikh et al. 2005). Serum biomarkers often reflect abnormal kidney function (impaired GFR), while urinary biomarkers may reflect kidney injury and/or function (compromised reabsorption). Depending on the process, urinary biomarkers also have the potential to signify specific sections of the nephron that are affected. This type of specificity could be useful to elucidate the mechanism of underlying injury. However, the determination of the optimal biomarkers for use in specific clinical settings has not been established.

The following sections will discuss the utility of traditional and novel biomarkers for detection of kidney injury in CF. Many of the biomarkers reviewed in this section are described in more detail in other chapters in this book. Therefore, this section will focus primarily on these biomarkers in CF patients specifically. Of note, few studies explicitly examine the role of biomarkers in AKI detection in CF patients. The majority of studies attempt to establish the relationship between biomarkers of interest and GFR. This section summarizes available data and, when applicable, provides guidance as to how kidney injury biomarkers can be used or studied in the future to improve AKI detection in patients with CF.

Serum Creatinine and Estimated GFR

The glomerular filtration rate is widely considered the best measure of kidney function. Direct measurement of GFR, however, is difficult, often costly, and frequently impractical in the hospitalized setting. Serum creatinine is the traditional biomarker most often used for simple assessment of kidney function as well as detection of kidney injury. Creatinine, a product of muscle breakdown, undergoes

glomerular filtration and is excreted in the urine. Because there is minimal extrarenal clearance of creatinine in healthy individuals, renal creatinine clearance is used as a surrogate for kidney function (Perrone et al. 1992). Twenty-four hour urine collection allows for calculation of CCl but is methodologically tedious and prone to error. Therefore, serum creatinine values are used to estimate CCl and GFR through implementation of a number of derived formulae. These formulae tend to be most reliable in the setting of stable kidney function and thus stable SCr. And the validity of these formulas is based on the assumptions that SCr is completely filtered and that the rate of production equals the rate of renal excretion (Perrone et al. 1992). In the setting of unstable renal function or ongoing kidney injury, unfortunately, these criteria are not always met.

Changes in SCr values are nonspecific, often delayed, and do not directly reflect cellular kidney injury. A demonstrable change in SCr is not detected until significant renal mass, roughly 70–80 %, has been affected (Pfaller and Gstraunthaler 1998). Creatinine is formed as a result of muscle breakdown which makes it an additionally problematic marker of kidney function and injury in patients with CF, who frequently have reduced muscle mass compared to healthy patients. Because of this, SCr-based formulae for estimating GFR are often inaccurate and typically underestimate renal impairment in patients with CF (Al-Aloul et al. 2007). Al-Aloul compared measured CCl from timed urine collections with ten SCr-based formulae used to estimate CCl in 74 adult CF patients and 29 healthy, age- and BMI-matched control subjects (Al-Aloul et al. 2007) and concluded that all formulae for estimating CCl were unreliable in CF patients. The correlation between estimated and measured creatinine clearance ranged from 0.55 to 0.7 with a bias of −9.1 to 22.9 depending on the equation used. The formulae were also less accurate in CF patients than in healthy controls. Additionally, the two equations most commonly used clinically for estimating CCl, the Cockcroft-Gault formula (Cockcroft and Gault 1976) and the abbreviated MDRD equation (Rule et al. 2004), grossly overestimated renal function in adult CF patients with reduced CCl (<80 mL/min, Table 1) in their study population.

Although traditional monitoring for kidney injury involves SCr measurement, the sensitivity of this parameter is poor. While more accurate methods of estimation of kidney function are available, such as 24-h urine creatinine collection or nuclear GFR studies, they are typically used to assess GFR at a single time point. These approaches are generally not practical in the hospitalized setting and cannot generally be used for monitoring or early detection of AKI due to the methodological rigor involved in their use.

Aminoglycoside Clearance

Therapeutic drug monitoring (TDM) is used to try to improve efficacy and minimize toxicity from aminoglycosides. The goal of TDM is to maximize effectiveness and safety by determining patient-specific doses and dosing intervals through drug level monitoring. Trough levels are typically monitored to assure adequate clearance of

Table 1 Comparison of mCCl and eCCl (CGF and abbreviated MDRD [four variable]) in renally impaired CF patients (mCCl <80 mL/min)

	N	Mean mCCl (SD)	eCCl formula	Mean eCCl (SD)	% eCCl within 33 % of mCCl	Bias	95 % CI for bias	Limits of agreement
mCCl <80	35	63.5 (12.3)	CGF	81.7 (18.1)	60 %	18.3	13.6–23.0	−9.7–46.3
			aMDRD	79.3 (20.2)	65 %	15.8	10.5–22.0	−17.5–50.1
mCCl ≥80	39	100.7 (13.8)	CGF	102.3 (16.6)	95 %	1.6	−3.5–6.7	−30.4–33.6
			aMDRD	95.1 (16.1)	84 %	−5.6	−11.1–−0.1	−39.6–28.4
Total	74	83.1 (22.9)	CGF	92.6 (20.1)	78 %	9.7	5.5–13.5	−24.9–43.9
			aMDRD	88 (19.7)	77 %	4.9	0.3–9.5	−35.3–45.1

Reproduced with permission from Al-Aloul et al. (2007). Elsevier ©2006

aMDRD abbreviated Modification of Diet in Renal Disease formula, *CI* confidence interval, *CGF* Cockcroft-Gault formula, *eCCl* estimated creatinine clearance, *mCCl* measured creatinine clearance, *N* number, *SD* standard deviation

the drug and elevated serum trough concentrations most closely relate to nephrotoxicity (Bertino et al. 1993). Both sophisticated and simple methods have been developed to determine an individual patient's pharmacokinetic parameters (volume of distribution, elimination rate constant, total body clearance) based on serum drug concentrations (Tod et al. 2001). Although there is variability in monitoring practices between CF centers, TDM is almost universally used.

In theory, AG clearance should be directly related to kidney function since these drugs are almost exclusively eliminated via glomerular filtration. Unfortunately, the correlation between GFR and actual drug clearance in CF patients is variable. Some studies (Town et al. 1996) describe a significant correlation between the measured creatinine clearance and tobramycin total body clearance ($r = 0.52$, $p = 0.02$). Other more recent studies (Soulsby et al. 2010), however, observed that tobramycin clearance correlates poorly with measured GFR in both adults ($r = 0.1$, $p = 0.71$) and children ($r = 0.25$, $p = 0.19$) with CF. Figure 3 displays Bland-Altman plots comparing GFR estimated via tobramycin clearance and measured GFR.

Aminoglycoside clearance is more reflective of kidney function than of kidney injury. Changes in drug clearance over time may suggest that an individual has sustained injury, but the extent of kidney injury needed to result in clinically significant alterations in drug clearance has not been described. Theoretically, longitudinal monitoring of tobramycin clearance could be used to identify chronic renal insufficiency. However, to our knowledge, no studies have demonstrated decreased AG clearance as a marker of CKD in patients with CF.

In a recent population pharmacokinetic study, Alghanem observed that AG clearance appears to be stable over time in patients with CF despite receipt of multiple courses of therapy over several years (Alghanem et al. 2013). The authors evaluated 1,075 aminoglycoside courses in 166 patients aged 14–66 years; subjects received as many as 28 courses over a 15 year period. There were no significant changes in kidney function (based on eCCl) over time, and only a single patient had moderate renal impairment (eCCL 45–58 mL/min). Additionally, there was little change in aminoglycoside clearance from one course to the next (between-occasion variability = 11 %), and no significant trends were detected in AG clearance over time based on the number of prior aminoglycoside courses. The authors concluded that in the population of CF patients they studied, there was no decline in AG clearance over time.

These findings contrast with data from other studies suggesting an increased prevalence of kidney dysfunction over time in patients with CF (Quon et al. 2011; Al-Aloul et al. 2005a). The discrepancy may lie in the variable relationship between AG clearance and eGFR in CF patients. Creatinine clearance had only a weak relationship to AG clearance in the Alghanem study which likely reflects the unreliable nature of SCr-based equations for estimating kidney function in CF patients. Additionally, Alghanem and colleagues relied on drug levels drawn within 72 h of the start of therapy in the majority (83 %) of cases. It is possible that patients with mild/moderate underlying renal dysfunction do not demonstrate impaired drug clearance early in antibiotic courses. The mechanism of AG toxicity is dependent upon accumulation of drug in proximal tubule cells, and decreased AG clearance

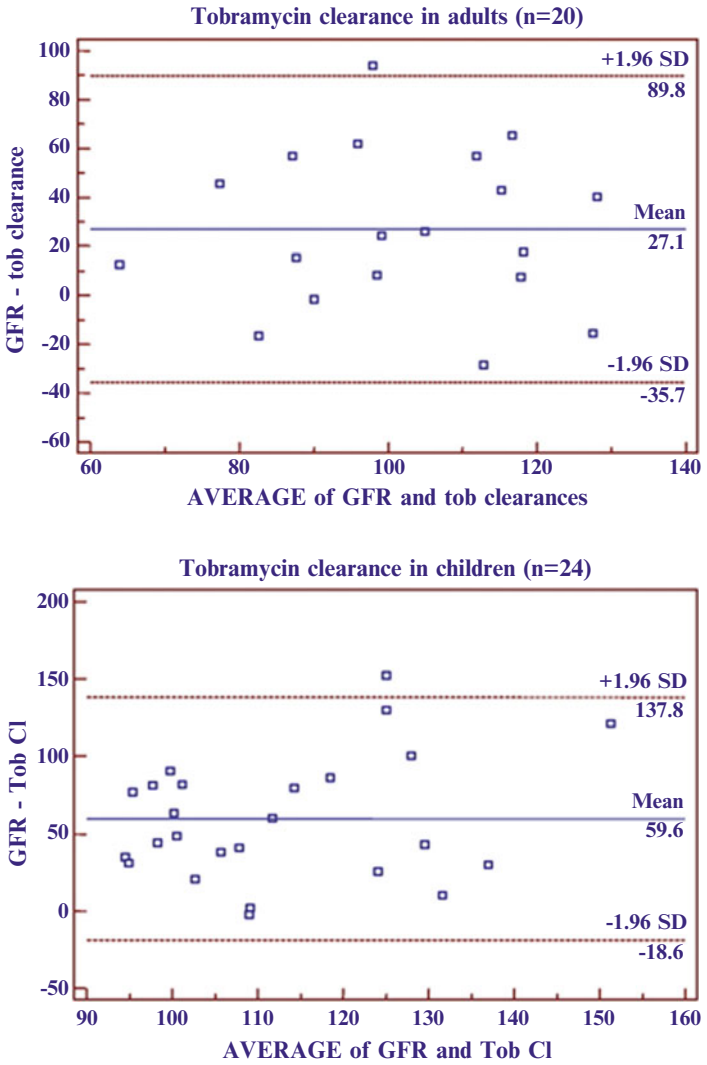

Fig. 3 Bland and Altman analysis for differences between tobramycin clearance and measured GFR in mL/min/1.73 m^2 in adults (**a**) and children (**b**). The *x-axis* represents the average GFR and the *y-axis* represents the difference between the measured GFR and tobramycin clearance (Reproduced with permission from Soulsby et al. 2010. ©2010 Elsevier)

may not manifest until a sufficient amount/duration of drug has been administered. Serial AG level measurements would be needed to determine when individuals pass the cutoff that leads to impaired kidney function, but the frequency of measurement needed to accurately capture this may be impractical. Ultimately, the inconsistent relationships between AG clearance and measured and estimated CCl make it difficult to rely on drug clearance as a marker of kidney injury.

N-Acetyl-β-D-glucosaminidase (NAG)

In the setting of kidney injury, enzymes located within tubular epithelial cells may be released into the urine. *N*-Acetyl-β-D-glucosaminidase (NAG) is one such enzyme. NAG is a proximal tubule lysosomal enzyme and detection in the urine increases in the setting of a number of causes such as nephrotoxic injury and diabetic nephropathy (Skalova 2005). Although not specific to a particular mechanism of injury, it is a sensitive marker of renal tubular injury and has been studied in a variety of patient populations. Typically, NAG is expressed as a ratio with urinary creatinine to account for biologic variability.

In patients with CF, NAG has been primarily studied in the context of nephrotoxin receipt, in particular aminoglycosides, and is a highly sensitive and specific marker of tubular injury in this population (Godson et al. 1988). Urinary levels of NAG increase significantly during courses of IV gentamicin (Godson et al. 1988), amikacin (Halacova et al. 2008), and tobramycin (Steinkamp et al. 1986; Glass et al. 2005; Etherington et al. 2007; Master et al. 2001; Riethmueller et al. 2009; Smyth et al. 2005). Elevated levels of NAG can even be observed during courses of inhaled tobramycin (Guy et al. 2010).

Most studies of NAG have confirmed that urinary concentrations increase despite stable serum creatinine. Glass studied 22 children with normal GFR and stable SCr receiving IV tobramycin three times daily for 14 days (Glass et al. 2005). NAG significantly increased following completion of therapy compared to measurements obtained prior to the start of the drug ($p < 0.0001$). Steinkamp studied 14 subjects before, during, and after receipt of 10 mg/kg/day of IV tobramycin with azlocillin and observed a six- to tenfold increase in urinary NAG during therapy (Steinkamp et al. 1986). Meanwhile, Etherington measured urinary NAG in 88 patients receiving IV tobramycin or colistin on days 1, 14, and at first clinic follow-up (Etherington et al. 2007). Although there were no changes in SCr, a 3.5-fold increase in urinary NAG occurred between day 1 and 14, and NAG excretion was higher in subjects receiving tobramycin compared to colistin (day 14 median NAG ratio, 2.24 vs. 0.98, $p < 0.001$), suggesting an increased risk of tubular toxicity from tobramycin. Additionally, NAG was higher at each time point of the study for subjects with CFRD.

Studies of urinary NAG in CF patients also provide some evidence that tubular injury from nephrotoxic antibiotics may be sustained. In the study by Glass, urinary NAG levels remained higher than pretreatment levels at 4 weeks after the course ($p < 0.001$) (Glass et al. 2005). Meanwhile, Etherington observed that the majority (80 %) of patients who received multiple courses of treatment during the study period had day 1 NAG levels that were significantly higher in subsequent courses ($p < 0.001$) (Etherington et al. 2007). And, almost half (46 %) of patients had an elevated NAG level at their clinic follow-up visit. Although NAG values returned to normal during follow-up assessments in the study by Steinkamp, the study was small ($N = 14$), and follow-up measurements were obtained at 4–120 days after treatment cessation (Steinkamp et al. 1986).

Urinary NAG has also been used to monitor for nephrotoxicity in several studies comparing different dosing regimens of aminoglycosides (Master et al. 2001;

Riethmueller et al. 2009; Smyth et al. 2005). Two of these studies showed lower NAG values with once-daily administration (Master et al. 2001; Smyth et al. 2005), providing evidence for the improved safety of once-daily dosing. Although NAG levels were similar between the once- and thrice-daily tobramycin groups in a randomized trial, significant rises in urinary NAG develop during AG therapy despite stable serum creatinine (Riethmueller et al. 2009).

Urinary NAG is a sensitive marker of proximal tubule kidney injury receiving nephrotoxic medications, and several studies in CF patients have observed increasing and often elevated values over the course of AG therapy without a demonstrable change in serum creatinine. This corroborates that NAG is a more sensitive marker of tubular injury than SCr during aminoglycoside courses and that it may have a role in detection of subclinical kidney injury in patients receiving these medications. However, longitudinal studies are needed which seek to elucidate the relationship between episodes of kidney injury detected by changes in NAG and long-term renal outcomes.

Urinary Albumin

The presence of albuminuria may result from glomerular damage due to increased permeability or may signal proximal tubule dysfunction and decreased reabsorption of the protein (Vaidya et al. 2008). Albumin is freely filtered by the glomerulus, and urinary detection can be increased in the setting of non-pathologic conditions which cause proteinuria, such as dehydration and vigorous exercise. Microalbuminuria, defined as 30–300 mg/L (Vaidya et al. 2008), is often present in patients with diabetes including CF patients with CFRD. In a large cohort study of CF children and adults, CFRD contributed to a sevenfold increased odds (95 % CI: 2.5–20.0, $p = 0.0002$) of persistent microscopic albuminuria: 10.7 % of patients with CFRD versus 1.6 % of CF patients without CFRD (Lind-Ayres et al. 2011). Transient microalbuminuria was present in a similar percentage of patients with and without CFRD in this study, which was comparable to the rate found in the general population (~6–7 %).

Other factors aside from diabetes may also contribute to the development of albuminuria in CF patients. Lind-Ayres found that a significantly higher percentage (40 %) of patients who had undergone lung transplant, all of whom either had CFRD or glucose intolerance, had persistent microscopic albuminuria. Meanwhile, in a small cohort study assessing proteinuria via 24-h urine collection, CF genotype was the only factor associated with the presence of high (>150 mg/day, $N = 6/22$) vs. low (<150 mg/day, $N = 16/22$) proteinuria (Cemlyn-Jones and Gamboa 2009). The multifactorial nature of albuminuria and its high prevalence in the CF population limits the utility of albuminuria as a marker of acute kidney injury. Persistent detection of microalbuminuria heralds the onset of nephropathy in patients with CFRD. But, the predictive capability of a single measurement is limited. Whether albuminuria can be used as a reliable marker of acute kidney injury is yet to be determined. Additional studies which provide data on serial urine albumin measurements would be needed to determine its potential role for it in AKI detection.

Table 2 Results for correlations between measured GFR and estimated renal function (95 % confidence interval reported in brackets)

Test	*R* value (adults)	*R* value (children)
Cystatin C	0.64 [0.43–0.78] $P = 0.0059$	0.61 [0.39–0.76] $P = 0.0011$
Cockcroft and Gault equation (adults) or Schwartz (children)	0.51 [0.36–0.75] $P = 0.0252$	0.60 [0.34–0.74] $P = 0.0015$
Tobramycin clearance	0.10 [−0.83–0.52] $P = 0.7117$	0.25 [−0.04–0.50] $P = 0.1920$
aMDRD equation (adults) or updated Schwartz (children)	0.29 [−0.17–0.65] $P = 0.2145$	0.60 [0.28–0.80] $P = 0.001$

Reproduced with permission from Soulsby et al. (2010), ©2010 Elsevier

Cystatin C (CysC)

Cystatin C is a low molecular weight protein that is freely filtered by the glomerulus and reabsorbed by proximal tubule cells via megalin-assisted endocytosis (Kaseda et al. 2007). It does not undergo tubular secretion, and its function is to serve as an extracellular inhibitor of cysteine proteases. Injury to proximal tubule cells leads to increased excretion in the urine, while elevated plasma levels are reflective of impaired glomerular filtration. Therefore, it may be a useful marker of proximal tubule injury as well as a functional marker of impaired GFR. Numerous studies have examined its role as a serum marker of GFR in a variety of populations, including CF.

Soulsby compared the correlation between measured GFR, using a radioisotope technique, and eGFR using SCr-based equations, serum CysC levels, and tobramycin clearance in adults and children with CF (Soulsby et al. 2010). The results for the correlations are shown in Table 2. CysC had the strongest correlation with measured GFR for both adults and children. However, CysC had no advantage over SCr-based equations for detecting the 4/47 patients with impaired kidney function (measured GFR <90 mL/min/1.73 m^2). The sensitivity and specificity of CysC for detection of decreased GFR was 100 % and 85.7 %, respectively. There was very poor correlation between tobramycin clearance and measured GFR ($R =$ 0.1 and 0.25 for adults and children, respectively), and the correlation between tobramycin clearance and CysC was not reported. Given the low prevalence of renal dysfunction in this population, the authors concluded that CysC offers no benefit over SCr-based estimates of GFR.

This study contrasts with an earlier study by Beringer which demonstrated superiority of CysC to SCr-based methods for GFR estimation in both CF patients and healthy, age-matched controls (Beringer et al. 2009). GFR estimates based on a CysC-based equation (GFR = 100/CysC – 14 Tidman et al. 2008) provided greater precision in both the CF and control populations. And, for those with CF, the CysC-based equation demonstrated a significantly higher AUC for the prediction of impaired kidney function (measured GFR <90 mL/min/1.73 m^2) compared with the Cockcroft-Gault equation (AUC 0.928 vs. 0.556, $p = 0.005$) and aMDRD equation (AUC 0.928 vs. 0.539, $p = 0.003$).

Serum CysC has also shown utility during AG courses in CF patients. Halacova measured serum CysC, CysC clearance, creatinine clearance, urinary NAG, and amikacin clearance in 71 patients receiving intermittent infusion amikacin therapy for 12 days (Halacova et al. 2008). Serum CysC levels increased throughout amikacin treatment ($P < 0.001$, Dunnett's multiple comparisons test) and 80 % of patients demonstrated CysC levels above the normal range. Consequently, the estimated GFR using a CysC-based equation demonstrated a significant decline over the course of amikacin treatment. Conversely, there were no significant changes in creatinine clearance or serum creatinine from day 0 compared with day 12, although serum creatinine was above the normal range in 45 % ($N = 32$) of patients on day 12 of therapy. Figure 4 shows a comparison of the creatinine clearance and CysC clearance values over the course of amikacin in this study. The GFR estimated by SCr was significantly higher than that predicted by CysC: 1.76 ± 0.02 versus 1.18 ± 0.04 mL/s/1.73 m^2 ($\sim 105.6 \pm 1.2$ vs. 70.8 ± 2.4 mL/min/1.73 m^2), $p < 0.0001$. ROC analyses demonstrated that serum CysC and CysC clearance were better predictors of amikacin clearance than creatinine clearance: AUC values of the ratios of amikacin clearance to creatinine clearance, CysC, and CysC clearance on day 12 compared to day 0 were 0.51, 0.92, and 0.84, respectively.

Urinary CysC may also be beneficial for AKI monitoring during aminoglycosides, which are reabsorbed in the proximal tubule via the same endocytic receptor, megalin, as CysC. In a rat model, significant changes in urinary CysC could be detected as early as day 1 of gentamicin therapy (Hoffmann et al. 2010). However, to our knowledge, this urinary biomarker has not been studied in patients with CF. It holds promise for the noninvasive detection of AKI during aminoglycoside courses and warrants investigation.

Beta-2-Microglobulin (β_2M)

Beta-2-microglobulin is another low molecular weight protein which, similar to CysC, is filtered by the glomerulus and reabsorbed in the proximal tubule. It is the light chain of the major histocompatibility class I molecule and, unlike CysC, is not a useful serum biomarker due to its expression on the cell surface of all nucleated cells (Ferguson et al. 2008). Its role as a kidney injury biomarker is limited to detection in the urine which increases in the setting of impaired proximal tubule function. In a rat model of nephrotoxicity (Sasaki et al. 2011), β_2M increased on day 1 of gentamicin, and the rate of increase was higher than other urinary biomarkers (CysC, NGAL, NAG).

Data on the role of β_2M in patients with CF are limited. In a prospective case-control study evaluating the role of serum β_2M as a marker of lung inflammation, Kearns et al. measured β_2M in CF outpatients ($N = 12$), CF patients receiving antibiotics for a pulmonary exacerbation ($N = 6$), and healthy controls ($N = 10$) (Kearns et al. 1989). Serum β_2M values were significantly lower in healthy controls than both CF groups ($p < 0.05$), but there were no differences in urinary values of β_2M between healthy controls and patients with CF. Meanwhile, in a randomized

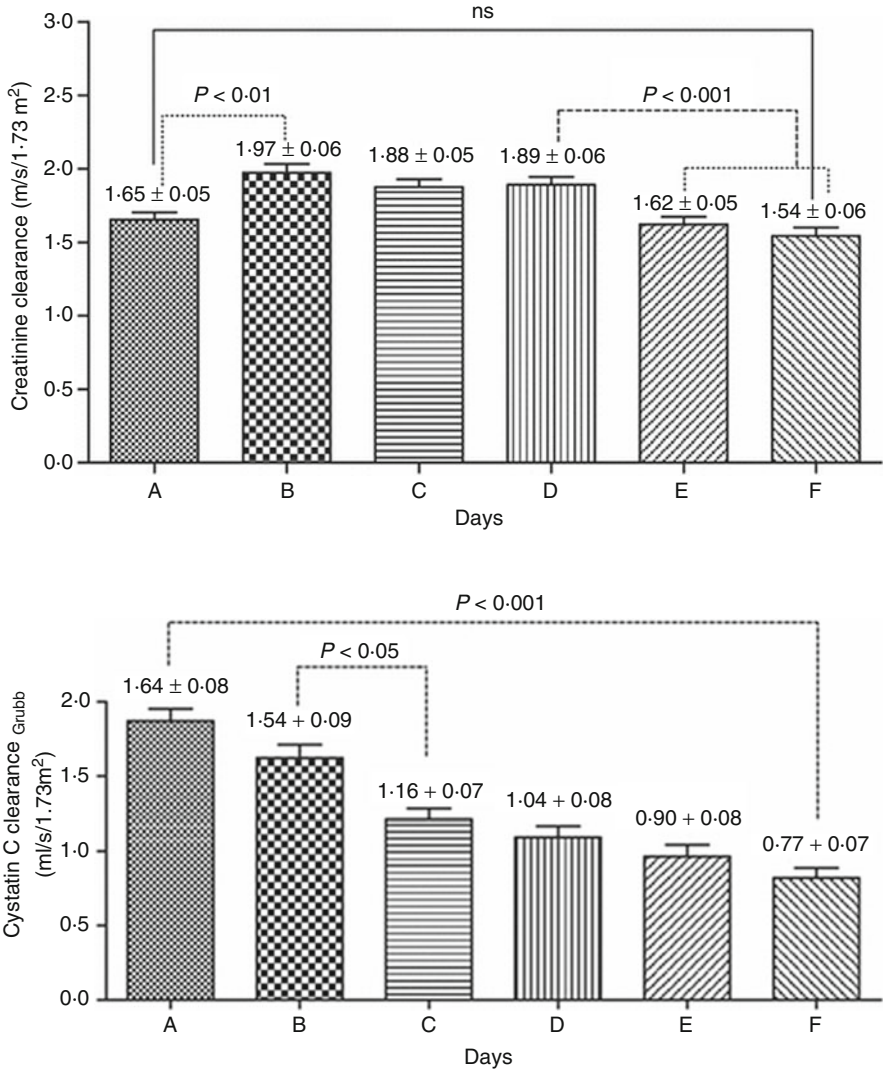

Fig. 4 Comparison of creatinine clearance (**a**) and cystatin C clearance (**b**) during amikacin therapy in CF patients. Data are expressed as column bars (mean ± SEM). *A*: Day before start of amikacin treatment (day 0). *B–F* 3rd, 5th, 7th, 10th, and 12th day of amikacin treatment (Reproduced with permission from Halacova et al. 2008. ©2008 Blackwell Publishing Ltd)

controlled trial of once- versus thrice-daily IV tobramycin, combined with ceftazidime, urinary β_2M was higher in the thrice-daily group (0.87 ± 0.5 mg/L vs. 0.18 ± 0.2 mg/L, $P < 0.01$), although values were in the normal range for both groups (Vic et al. 1998). The study population was small ($N = 22$) but SCr was unchanged over the course of therapy in both groups. Unfortunately, this data

combined with the fact that β_2M is unstable in acidic urine make it an impractical kidney injury biomarker in the clinical setting.

Retinol-Binding Protein (RBP)

Retinol-binding protein (RBP) is a hepatically synthesized chaperone for vitamin A transport to tissues. It is freely filtered by the glomerulus and reabsorbed in the proximal tubule via megalin (Christensen et al. 1999). RBP is a sensitive marker of tubule dysfunction and can be detected in the urine soon after nephrotoxin exposure (Ferguson et al. 2008). This biomarker has been studied preliminarily in CF patients. Glass measured urinary RBP and NAG in 22 children with CF receiving a 14-day course of IV tobramycin (Glass et al. 2005). Measurements were performed immediately prior to and following therapy, as well as 4 weeks following completion of therapy. Urinary NAG ($P < 0.001$) and RBP ($P = 0.03$) both increased over the course of therapy. Unlike NAG, however, urinary RBP returned to pretreatment levels at 4-week follow-up. Interestingly, pretreatment levels of RBP were elevated in 18 of 21 subjects with prior AG receipt vs. zero for NAG. However, there were no differences in RBP following therapy based on the number of prior aminoglycoside courses.

Given that RBP is a chaperone for vitamin A transport, serum levels may be affected by nutritional status or the presence of liver disease in CF patients. In fact, patients with CF have lower plasma RBP levels than age- and sex-matched controls (Mrugacz et al. 2005) which could be a result of underlying pancreatic insufficiency associated with this disease. In this context, the findings by Glass that urinary RBP both: (a) increased during therapy and (b) was higher at baseline among subjects with prior AG receipt are particularly interesting. These data suggest that RBP may be a highly sensitive marker for both acute and chronic tubular dysfunction in the CF population. Additional studies assessing the relationship between aminoglycoside receipt and RBP levels should be performed, and the time course of elevation of RBP during aminoglycosides needs to be elucidated.

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein involved in iron homeostasis whose expression is upregulated in the setting of ischemia or infection. In humans, increased urinary levels can be detected following a variety of kidney insults and becomes elevated prior to SCr-based AKI develops (Gaspari et al. 2010; Hirsch et al. 2007). Increased levels have been associated with poor clinical outcomes irrespective of SCr changes (Haase et al. 2011; Singer et al. 2011). Urinary NGAL concentrations may reflect dysfunction in glomerular filtration, impaired proximal tubule reabsorption, and increased production by distal nephrons, depending on the mechanism of injury (Kuwabara et al. 2009). Similar to RBP

and cystatin C, urinary excretion is increased in the setting of nephrotoxic proximal tubule injury (Kuwabara et al. 2009).

The role of NGAL as a marker of kidney injury in CF has not been defined. In a study evaluating serum NGAL (Zughaier et al. 2013), values were higher in patients with CF compared to healthy controls ($P < 0.001$) yet similar when compared among CF patients with stable disease vs. those experiencing a pulmonary exacerbation. Meanwhile, when peripheral monocytes of both CF and healthy patients were infected with *Pseudomonas aeruginosa*, NGAL secretion increased. This raises the possibility that serum NGAL varies in response to lung infection and whether this influences its utility as a kidney injury urinary biomarker has been debated (Nazareth and Walshaw 2013). Nevertheless, the relationship between serum and urinary concentrations in the setting of proximal tubule injury, as would result from aminoglycoside exposure, has not been explored in CF patients. Animal studies show a time-dependent increase in urinary NGAL following administration of gentamicin (Zhou et al. 2014) suggesting that it may be a useful marker to determine the optimal duration of aminoglycoside therapy in CF patients. Additionally, the trajectory of NGAL values over the course of therapy may be a good indicator of drug accumulation given the saturability of megalin-facilitated endocytosis.

Kidney Injury Molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1) is a transmembrane protein located predominantly (~90 %) in the proximal tubule (Zhou et al. 2008; Chiusolo et al. 2010). Its gene expression, and subsequent protein detection in the urine, is increased in the setting of both ischemia and toxin administration, specifically gentamicin (Zhou et al. 2008; Chen et al. 2010). Changes in KIM-1 precede rises in SCr following ischemic and toxic insults (Tu et al. 2014; Torregrosa et al. 2015), making it a useful biomarker of AKI development and severity.

As with many biomarkers of kidney injury, KIM-1 has not been extensively studied in the CF population. Urinary KIM-1, NAG, and protein were studied in 52 children and young adults to determine the impact of high-dose ibuprofen use on kidney biomarkers (Lahiri et al. 2014). Half of subjects were on high-dose ibuprofen therapy, and there were no differences in mean biomarker concentrations between the groups: KIM-1 $= 0.306 \pm 0.28$ ng/mg creatinine in subjects on ibuprofen vs. 0.381 ± 0.28 ng/mg creatinine in subjects not receiving the medication ($P = 0.34$). The authors did observe a correlation between KIM-1 values and lifetime AG exposure ($r = 0.35$, $P = 0.012$), although other factors which could influence this association (age, recent AG exposure, receipt of oral antibiotics, etc.) were not explored. Of note, this was a small study conducted in relatively healthy CF patients for whom urinary biomarkers were measured at only a single point in time. Therefore, results may not be reflective of the long-term effects of ibuprofen on the kidney. Longitudinal studies are needed in patients with CF to define its role in detection of AKI.

Other Urinary Biomarkers

There are a number of other novel AKI biomarkers that have been studied in non-CF populations. Interleukin-18 (IL-18), liver-type fatty acid-binding protein (L-FABP), and clusterin, for example, may have a role in AKI detection or prognostication. But studies are needed in patients with CF to determine their utility in this population.

Biomarkers and the Future of Kidney Injury in Cystic Fibrosis

Kidney injury is becoming an increasingly recognized issue in patients with CF. The untoward effects of repeated antibiotic courses, CF-related diabetes, and other insults on the kidney lead to an increased risk of development of chronic kidney disease in this population (Al-Aloul et al. 2005a; Wehbe et al. 2012; Quon et al. 2011). As lifetime survival in patients with CF increases, the long-term ramifications of this disease and the associated treatments on renal health are becoming more evident. It becomes paramount, therefore, to identify and employ strategies which seek to characterize those at highest risk for AKI, improve detection of kidney injury, and mitigate its long-term risks.

While diabetes may provide the highest threat to long-term kidney function, the major risk factor for development of AKI in CF patients is the receipt of nephrotoxic antibiotics such as aminoglycosides. There are no well-recognized methods for decreasing the toxic effects of these antibiotics, aside from early discontinuation of therapy. Unfortunately, avoidance of these medications is not a feasible or advisable approach considering the impact of recurrent and chronic lung infections in this population. While there is general agreement that monitoring of aminoglycoside drug levels and renal function is necessary, there is a lack of consistency regarding the optimal monitoring strategy to both identify and prevent AKI. Traditional monitoring for kidney injury via measurement of serum creatinine is suboptimal.

Urinary biomarkers are highly sensitive for kidney injury. In general, however, they have not been extensively studied in patients with CF, and their role in monitoring for kidney injury in these patients has not been defined. There are a number of avenues for future research in this field. In theory, biomarkers could be used to risk stratify CF patients prior to start of nephrotoxic therapy and indicate specific patients in whom alternative antibiotics should be considered. An improved correlation between biomarkers and aminoglycoside pharmacokinetic parameters (AUC, clearance) may allow for noninvasive and rapid monitoring of renal drug handling. Biomarkers may detect AKI earlier than with SCr and promote implementation of nephro-protective strategies in patients receiving nephrotoxins. Alternatively, they could be used to monitor the impact of interventions which seek to reduce kidney injury.

The majority of studies conducted in CF patients have focused on determining which biomarker is most reflective of kidney function in this population. While important, the overall utility of these novel biomarkers lies in their ability to improve the safety of nephrotoxic medications, promote earlier detection of AKI, and identify

patients at higher risk for poor short- and long-term outcomes. Ultimately, biomarker-driven trials will be needed prior to their implementation in the clinical setting.

Potential Applications to Prognosis, Other Diseases, or Conditions

A number of urinary and serum biomarkers have been identified which are highly sensitive for the detection of kidney injury. These biomarkers increase in the serum or urine following a variety of insults such as nephrotoxin receipt, ischemia, and sepsis. Although these biomarkers have not been extensively studied in the CF population, they show promise for improving the earlier detection of AKI compared to traditional biomarkers in a variety of clinical scenarios. Urinary biomarkers also have prognostic implications and have been linked to poor outcomes irrespective of serum creatinine. These biomarkers could be used clinically to identify patients at highest risk for morbidity and mortality. Urinary and serum biomarkers are applicable in a variety of settings where patients are at risk for kidney injury: critical illness, patients receiving nephrotoxins, cardiac bypass, and other. Since the mechanism and severity of kidney injury relates to release/expression/excretion of these biomarkers, they should have utility in multiple patient populations at risk for or sustaining kidney injury.

Summary Points

- Cystic fibrosis (CF) is a genetic disease that predisposes patients to recurrent and chronic respiratory tract infections.
- Patients with CF are at risk for development of acute kidney injury (AKI) due to receipt of nephrotoxic medications, particularly antibiotics, as well as long-term renal damage from long-standing diabetes and repeated nephrotoxin exposures.
- With advances in medical therapies leading to substantial improvement in lifetime survival among CF patients, the long-term ramifications of the disease and its treatments on the kidney may become apparent.
- Chronic kidney disease is prevalent in patients with CF, and means to detect and mitigate kidney insults are important to stem long-term deleterious effects.
- The traditional marker of kidney injury and function, serum creatinine, is unreliable in patients with CF as it often overestimates true kidney function and does not detect kidney injury until a significant number of nephrons have been affected.
- Biomarkers, such as cystatin C (CysC), retinol-binding protein (RBP), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and others, hold significant promise for early detection of AKI, risk stratification, and prognosis.

- Additional research is urgently needed to explore and define the potential roles of these novel biomarkers in detection of both acute kidney injury and chronic kidney disease in the CF population.

References

Al-Aloul M, Miller H, Alapati S, Stockton PA, Ledson MJ, Walshaw MJ. Renal impairment in cystic fibrosis patients due to repeated intravenous aminoglycoside use. Pediatr Pulmonol. 2005a;39(1):15–20.

Al-Aloul M, Miller H, Stockton P, Ledson MJ, Walshaw MJ. Acute renal failure in CF patients chronically infected by the Liverpool epidemic Pseudomonas aeruginosa strain (LES). J Cyst Fibros. 2005b;4(3):197–201.

Al-Aloul M, Jackson M, Bell G, Ledson M, Walshaw M. Comparison of methods of assessment of renal function in cystic fibrosis (CF) patients. J Cyst Fibros. 2007;6(1):41–7.

Alghanem S, Paterson I, Touw DJ, Thomson AH. Influence of multiple courses of therapy on aminoglycoside clearance in adult patients with cystic fibrosis. J Antimicrob Chemother. 2013;68(6):1338–47.

Andreoli SP. Acute kidney injury in children. Pediatr Nephrol. 2009;24(2):253–63.

Andrieux A, Harambat J, Bui S, Nacka F, Iron A, Llanas B, Fayon M. Renal impairment in children with cystic fibrosis. J Cyst Fibros. 2010;9(4):263–8.

Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S, Goldstein SL. 3–5 year longitudinal follow-up of pediatric patients after acute renal failure. Kidney Int. 2006;69(1):184–9.

Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12.

Beringer PM, Hidayat L, Heed A, Zheng L, Owens H, Benitez D, Rao AP. GFR estimates using cystatin C are superior to serum creatinine in adult patients with cystic fibrosis. J Cyst Fibros. 2009;8(1):19–25.

Bertenshaw C, Watson AR, Lewis S, Smyth A. Survey of acute renal failure in patients with cystic fibrosis in the UK. Thorax. 2007;62(6):541–5.

Bertino Jr JS, Booker LA, Franck PA, Jenkins PL, Franck KR, Nafziger AN. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. J Infect Dis. 1993;167(1):173–9.

Broekroelofs J, Navis GJ, Stegeman CA, van der Bij W, de Boer WJ, de Zeeuw D, de Jong PE. Long-term renal outcome after lung transplantation is predicted by the 1-month postoperative renal function loss. Transplantation. 2000;69(8):1624–8.

Cemlyn-Jones J, Gamboa F. Proteinuria in cystic fibrosis: a possible correlation between genotype and renal phenotype. J Bras Pneumol. 2009;35(7):669–75.

Chen F, Smith R, Gu YZ, Collins ND, Nioi P. Toxicoepigenetic alteration of the kidney injury molecule 1 gene in gentamicin-exposed rat kidney. Toxicol Sci. 2010;117(2):375–80.

Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005;16(11):3365–70.

Chiusolo A, Defazio R, Zanetti E, Mongillo M, Mori N, Cristofori P, Trevisan A. Kidney injury molecule-1 expression in rat proximal tubule after treatment with segment-specific nephrotoxicants: a tool for early screening of potential kidney toxicity. Toxicol Pathol. 2010;38(3):338–45.

Christensen EI, Moskaug JO, Vorum H, Jacobsen C, Gundersen TE, Nykjaer A, Blomhoff R, Willnow TE, Moestrup SK. Evidence for an essential role of megalin in transepithelial transport of retinol. J Am Soc Nephrol. 1999;10(4):685–95.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

Conway SP, Pond MN, Watson A, Etherington C, Robey HL, Goldman MH. Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis. Thorax. 1997;52(11):987–93.

Crawford I, Maloney PC, Zeitlin PL, Guggino WB, Hyde SC, Turley H, Gatter KC, Harris A, Higgins CF. Immunocytochemical localization of the cystic fibrosis gene product CFTR. Proc Natl Acad Sci U S A. 1991;88(20):9262–6.

Cystic fibrosis foundation patient registry 2012 annual data report. Bethesda; 2013. Maryland

Dai C, Li J, Tang S, Xiao X. Colistin-induced nephrotoxicity in mice involves the mitochondrial, death receptor, and endoplasmic reticulum pathways. Antimicrob Agents Chemother. 2014;58 (7):4075–85.

Downes KJ, Rao MB, Kahill L, Nguyen H, Clancy JP, Goldstein SL. Daily serum creatinine monitoring promotes earlier detection of acute kidney injury in children and adolescents with cystic fibrosis. J Cyst Fibros. 2014;13(4):435–41.

Drew J, Watson AR, Smyth A. Acute renal failure and cystic fibrosis. Arch Dis Child. 2003;88 (7):646.

Etherington C, Bosomworth M, Clifton I, Peckham DG, Conway SP. Measurement of urinary *N*-acetyl-b-D-glucosaminidase in adult patients with cystic fibrosis: before, during and after treatment with intravenous antibiotics. J Cyst Fibros. 2007;6(1):67–73.

Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care. 2006;10(1):R27.

Fennell PB, Quante J, Wilson K, Boyle M, Strunk R, Ferkol T. Use of high-dose ibuprofen in a pediatric cystic fibrosis center. J Cyst Fibros. 2007;6(2):153–8.

Ferguson MA, Vaidya VS, Bonventre JV. Biomarkers of nephrotoxic acute kidney injury. Toxicology. 2008;245(3):182–93.

Florescu MC, Lyden E, Murphy PJ, Florescu DF, Fillaus J. Long-term effect of chronic intravenous and inhaled nephrotoxic antibiotic treatment on the renal function of patients with cystic fibrosis. Hemodial Int. 2012;16(3):414–9.

Gaspari F, Cravedi P, Mandala M, Perico N, de Leon FR, Stucchi N, Ferrari S, Labianca R, Remuzzi G, Ruggenenti P. Predicting cisplatin-induced acute kidney injury by urinary neutrophil gelatinase-associated lipocalin excretion: a pilot prospective case-control study. Nephron Clin Pract. 2010;115(2):c154–60.

Glass S, Plant ND, Spencer DA. The effects of intravenous tobramycin on renal tubular function in children with cystic fibrosis. J Cyst Fibros. 2005;4(4):221–5.

Godson C, Ryan MP, O'Halloran D, Bourke S, Brady HR, FitzGerald MX. Investigation of aminoglycoside nephrotoxicity in cystic fibrosis patients. Scand J Gastroenterol Suppl. 1988;143:70–3.

Guy EL, Bosomworth M, Denton M, Conway SP, Brownlee KG, Lee TW. Serum tobramycin levels following delivery of tobramycin (Tobi) via eFlow advanced nebuliser in children with cystic fibrosis. J Cyst Fibros. 2010;9(4):292–5.

Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M, Goldstein SL, Makris K, Ronco C, Martensson J, Martling CR, Venge P, Siew E, Ware LB, Ikizler TA, Mertens PR. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol. 2011;57(17):1752–61.

Halacova M, Kotaska K, Kukacka J, Vavrova V, Kuzelova M, Ticha J, Prusa R. Serum cystatin C level for better assessment of glomerular filtration rate in cystic fibrosis patients treated by amikacin. J Clin Pharm Ther. 2008;33(4):409–17.

Hirsch R, Dent C, Pfriem H, Allen J, Beekman 3rd RH, Ma Q, Dastrala S, Bennett M, Mitsnefes M, Devarajan P. NGAL is an early predictive biomarker of contrast-induced nephropathy in children. Pediatr Nephrol. 2007;22(12):2089–95.

Hmiel SP, Beck AM, de la Morena MT, Sweet S. Progressive chronic kidney disease after pediatric lung transplantation. Am J Transplant. 2005;5(7):1739–47.

Hoffmann D, Fuchs TC, Henzler T, Matheis KA, Herget T, Dekant W, Hewitt P, Mally A. Evaluation of a urinary kidney biomarker panel in rat models of acute and subchronic nephrotoxicity. Toxicology. 2010;277(1–3):49–58.

Kaseda R, Iino N, Hosojima M, Takeda T, Hosaka K, Kobayashi A, Yamamoto K, Suzuki A, Kasai A, Suzuki Y, Gejyo F, Saito A. Megalin-mediated endocytosis of cystatin C in proximal tubule cells. Biochem Biophys Res Commun. 2007;357(4):1130–4.

Kearns GL, Berry PL, Bocchini Jr JA, Hilman BC, Wilson JT. Renal handling of beta 2-microglobulin in patients with cystic fibrosis. DICP. 1989;23(12):1013–7.

Kennedy SE, Henry RL, Rosenberg AR. Antibiotic-related renal failure and cystic fibrosis. J Paediatr Child Health. 2005;41(7):382–3.

Konrad K, Scheuing N, Badenhoop K, Borkenstein MH, Gohlke B, Schofl C, Seufert J, Thon A, Holl RW. Cystic fibrosis-related diabetes compared with type 1 and type 2 diabetes in adults. Diabetes Metab Res Rev. 2013;29(7):568–75.

Kuwabara T, Mori K, Mukoyama M, Kasahara M, Yokoi H, Saito Y, Yoshioka T, Ogawa Y, Imamaki H, Kusakabe T, Ebihara K, Omata M, Satoh N, Sugawara A, Barasch J, Nakao K. Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. Kidney Int. 2009;75(3):285–94.

Lahiri T, Guillet A, Diehl S, Ferguson M. High-dose ibuprofen is not associated with increased biomarkers of kidney injury in patients with cystic fibrosis. Pediatr Pulmonol. 2014;49 (2):148–53.

Lanese DM, Conger JD. Effects of endothelin receptor antagonist on cyclosporine-induced vasoconstriction in isolated rat renal arterioles. J Clin Invest. 1993;91(5):2144–9.

Ledson MJ, Gallagher MJ, Cowperthwaite C, Convery RP, Walshaw MJ. Four years' experience of intravenous colomycin in an adult cystic fibrosis unit. Eur Respir J. 1998;12(3):592–4.

Lewis JR, Lewis SA. Colistin interactions with the mammalian urothelium. Am J Physiol Cell Physiol. 2004;286(4):C913–22.

Lind-Ayres M, Thomas W, Holme B, Mauer M, Caramori ML, Moran A. Microalbuminuria in patients with cystic fibrosis. Diabetes Care. 2011;34(7):1526–8.

Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int. 2011;79 (1):33–45.

Master V, Roberts GW, Coulthard KP, Baghurst PA, Martin A, Roberts ME, Onishko CR, Martin AJ, Linke RJ, Holmes M, Jarvinen A, Kennedy D, Colebatch KA, Hansman D, Parsons DW. Efficacy of once-daily tobramycin monotherapy for acute pulmonary exacerbations of cystic fibrosis: a preliminary study. Pediatr Pulmonol. 2001;31(5):367–76.

Menon S, Kirkendall ES, Nguyen H, Goldstein SL. Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. J Pediatr. 2014;165(3):522–7.e2.

Moestrup SK, Cui S, Vorum H, Bregengard C, Bjorn SE, Norris K, Gliemann J, Christensen EI. Evidence that epithelial glycoprotein 330/megalin mediates uptake of polybasic drugs. J Clin Invest. 1995;96(3):1404–13.

Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clin J Am Soc Nephrol. 2011;6(4):856–63.

Moriya T, Tsuchiya A, Okizaki S, Hayashi A, Tanaka K, Shichiri M. Glomerular hyperfiltration and increased glomerular filtration surface are associated with renal function decline in normo- and microalbuminuric type 2 diabetes. Kidney Int. 2012;81(5):486–93.

Mrugacz M, Tobolczyk J, Minarowska A. Retinol binding protein status in relation to ocular surface changes in patients with cystic fibrosis treated with daily vitamin A supplements. Eur J Pediatr. 2005;164(4):202–6.

National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39:S1–S266.

Nazareth D, Walshaw M. A review of renal disease in cystic fibrosis. J Cyst Fibros. 2013;12 (4):309–17.

Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol. 2005;16(10):3046–52.

Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem. 1992;38(10):1933–53.

Pfaller W, Gstraunthaler G. Nephrotoxicity testing in vitro – what we know and what we need to know. Environ Health Perspect. 1998;106 Suppl 2:559–69.

Prestidge C, Chilvers MA, Davidson AG, Cho E, McMahon V, White CT. Renal function in pediatric cystic fibrosis patients in the first decade of life. Pediatr Nephrol. 2011;26(4):605–12.

Quon BS, Mayer-Hamblett N, Aitken ML, Smyth AR, Goss CH. Risk factors for chronic kidney disease in adults with cystic fibrosis. Am J Respir Crit Care Med. 2011;184(10):1147–52.

Quon BS, Mayer-Hamblett N, Aitken ML, Goss CH. Risk of post-lung transplant renal dysfunction in adults with cystic fibrosis. Chest. 2012;142(1):185–91.

Riethmueller J, Ballmann M, Schroeter TW, Franke P, von Butler R, Claass A, Junge S, Doering G, Stern M. Tobramycin once- vs thrice-daily for elective intravenous antipseudomonal therapy in pediatric cystic fibrosis patients. Infection. 2009;37(5):424–31.

Rougier F, Claude D, Maurin M, Maire P. Aminoglycoside nephrotoxicity. Curr Drug Targets Infect Disord. 2004;4(2):153–62.

Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med. 2004;141(12):929–37.

Sasaki D, Yamada A, Umeno H, Kurihara H, Nakatsuji S, Fujihira S, Tsubota K, Ono M, Moriguchi A, Watanabe K, Seki J. Comparison of the course of biomarker changes and kidney injury in a rat model of drug-induced acute kidney injury. Biomarkers. 2011;16(7):553–66.

Schmitz C, Hilpert J, Jacobsen C, Boensch C, Christensen EI, Luft FC, Willnow TE. Megalin deficiency offers protection from renal aminoglycoside accumulation. J Biol Chem. 2002;277 (1):618–22.

Servais H, Van Der Smissen P, Thirion G, Van der Essen G, Van Bambeke F, Tulkens PM, Mingeot-Leclercq MP. Gentamicin-induced apoptosis in LLC-PK1 cells: involvement of lysosomes and mitochondria. Toxicol Appl Pharmacol. 2005;206(3):321–33.

Sidhu H, Hoppe B, Hesse A, Tenbrock K, Bromme S, Rietschel E, Peck AB. Absence of *Oxalobacter formigenes* in cystic fibrosis patients: a risk factor for hyperoxaluria. Lancet. 1998;352(9133):1026–9.

Singer E, Elger A, Elitok S, Kettritz R, Nickolas TL, Barasch J, Luft FC, Schmidt-Ott KM. Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. Kidney Int. 2011;80(4):405–14.

Skalova S. The diagnostic role of urinary *N*-acetyl-beta-D-glucosaminidase (NAG) activity in the detection of renal tubular impairment. Acta Medica (Hradec Kralove). 2005;48(2):75–80.

Smyth A, Tan KH, Hyman-Taylor P, Mulheran M, Lewis S, Stableforth D, Prof Knox A. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis – the TOPIC study: a randomised controlled trial. Lancet. 2005;365(9459):573–8.

Smyth A, Lewis S, Bertenshaw C, Choonara I, McGaw J, Watson A. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. Thorax. 2008;63(6):532–5.

Soulsby N, Greville H, Coulthard K, Doecke C. What is the best method for measuring renal function in adults and children with cystic fibrosis? J Cyst Fibros. 2010;9(2):124–9.

Steinkamp G, Lutge M, Wurster U, Schulz-Baldes JG, Grone HJ, Ehrich JH. Renal function in cystic fibrosis: proteinuria and enzymuria before and after tobramycin therapy. Eur J Pediatr. 1986;145(6):526–31.

Terribile M, Capuano M, Cangiano G, Carnovale V, Ferrara P, Petrarulo M, Marangella M. Factors increasing the risk for stone formation in adult patients with cystic fibrosis. Nephrol Dial Transplant. 2006;21(7):1870–5.

Tidman M, Sjostrom P, Jones I. A Comparison of GFR estimating formulae based upon s-cystatin C and s-creatinine and a combination of the two. Nephrol Dial Transplant. 2008;23(1):154–60.

Tod MM, Padoin C, Petitjean O. Individualising aminoglycoside dosage regimens after therapeutic drug monitoring: simple or complex pharmacokinetic methods? Clin Pharmacokinet. 2001;40 (11):803–14.

Torregrosa I, Montoliu C, Urios A, Andres-Costa MJ, Gimenez-Garzo C, Juan I, Puchades MJ, Blasco ML, Carratala A, Sanjuan R, Miguel A. Urinary KIM-1, NGAL and L-FABP for the diagnosis of AKI in patients with acute coronary syndrome or heart failure undergoing coronary angiography. Heart Vessels. 2015 Nov;30(6):703–11.

Town DJ, Vinks AA, Jacobs F, Heijerman HG, Bakker W. Creatinine clearance as predictor of tobramycin elimination in adult patients with cystic fibrosis. Ther Drug Monit. 1996;18 (5):562–9.

Tu Y, Wang H, Sun R, Ni Y, Ma L, Xv F, Hu X, Jiang L, Wu A, Chen X, Chen M, Liu J, Han F. Urinary netrin-1 and KIM-1 as early biomarkers for septic acute kidney injury. Ren Fail. 2014 Nov;36(10):1559–63.

Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. Annu Rev Pharmacol Toxicol. 2008;48:463–93.

Vic P, Ategbo S, Turck D, Husson MO, Launay V, Loeuille GA, Sardet A, Deschildre A, Druon D, Arrouet-Lagande C. Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. Arch Dis Child. 1998;78(6):536–9.

Wehbe E, Brock R, Budev M, Xu M, Demirjian S, Schreiber MJ Jr, Stephany B. Short-term and long-term outcomes of acute kidney injury after lung transplantation, J Heart Lung Transplant. 2011. Epub ahead of print.

Wehbe E, Brock R, Budev M, Xu M, Demirjian S, Schreiber MJ, Stephany B. Short-term and long-term outcomes of acute kidney injury after lung transplantation. J Heart Lung Transplant. 2012;31(3):244–51.

Weir MR. Renal effects of nonselective NSAIDs and coxibs. Cleve Clin J Med. 2002;69 Suppl 1: Si53–8.

Zhou Y, Vaidya VS, Brown RP, Zhang J, Rosenzweig BA, Thompson KL, Miller TJ, Bonventre JV, Goering PL. Comparison of kidney injury molecule-1 and other nephrotoxicity biomarkers in urine and kidney following acute exposure to gentamicin, mercury, and chromium. Toxicol Sci. 2008;101(1):159–70.

Zhou X, Ma B, Lin Z, Qu Z, Huo Y, Wang J, Li B. Evaluation of the usefulness of novel biomarkers for drug-induced acute kidney injury in beagle dogs. Toxicol Appl Pharmacol. 2014;280 (1):30–5.

Zughaier SM, Tangpricha V, Leong T, Stecenko AA, McCarty NA. Peripheral monocytes derived from patients with cystic fibrosis and healthy donors secrete NGAL in response to Pseudomonas aeruginosa infection. J Investig Med. 2013;61(6):1018–25.