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ORIGINAL ARTICLE

Renal function in pediatric cystic fibrosis patients in the first decade of life

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Abstract With increasing life expectancy and the need for lung transplantation in the cystic fibrosis (CF) population, there are increasing reports of chronic kidney disease (CKD). However, values for baseline or longitudinal glomerular filtration rate (GFR) as measured by exogenous clearance markers are lacking in this population. Retrospective cross-sectional study in 2 to 18-year-olds cared for at a single CF center who had a GFR measured by plasma disappearance of Technetium-99 m diethylenetriaminepentaacetic acid (mGFR). The primary outcome was evidence of renal dysfunction as defined by CKD stage II or below (mGFR<90 ml/min/1.73 m^2, persistent abnormalities in urinary sediment, abnormal renal imaging). Of 63 patients evaluated, four had apparent renal dysfunction, one demonstrated decreased mGFR, and three others had persistent microscopic hematuria. The mean mGFR was substantially higher (140±24 ml/min/1.73 m^2) than expected or previously reported for healthy children. We did not demonstrate the presence of significant renal impairment after limited aminoglycoside exposure in the first decade following diagnosis with CF. However, we did document the presence of glomerular hyperfiltration in a significant proportion of our CF patients.

Keywords Pediatrics · Glomerular filtration rate · Chronic kidney disease · Hyperfiltration

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Introduction

Cystic fibrosis (CF) is the commonest potentially lethal inherited disease in our population. It is a multi-system metabolic disease due to mutations affecting the cystic fibrosis transmembrane regulator (CFTR) protein, and respiratory involvement is responsible for most morbidity and mortality. As mean life expectancy of CF patients in Canada has increased from 16 years to over 47 years between 1970 and 2007 [1], more concern has arisen about non-pulmonary organs, including the kidneys.

Although kidney disease is not usually a primary problem in CF, CFTR expression and function has been demonstrated in the kidney [2] and abnormalities in renal tubular function [3] along with an increased risk of renal injury due to a propensity for dehydration are both well described in CF [4, 5]. In addition, the need to use potentially nephrotoxic antibiotics or anti-rejection drugs (post lung transplantation) may lead to acute or chronic renal injury. Recent reports of renal tubular dysfunction [6],

acute kidney injury [7, 8], and renal failure post lung transplantation [9–12] (coincident with the increasing incidence of lung transplantation [1, 13]), also raise concerns regarding renal dysfunction in the CF population and highlight the need for further research into this area.

The majority of renal function studies in patients with CF come from the adult population. Most utilized timed urine collection for creatinine clearance and were performed in order to compare published estimating equations for glomerular filtration rate (GFR) in the CF population, not to identify patients with, or at risk of, renal dysfunction [14, 15]. Creatinine clearance is frequently an unreliable method of estimating renal function, in both children (due to difficulties with accurate urine collection) and CF patients (due to increased tubular secretion of creatinine); in general, it tends towards overestimation of GFR [16–19]. More-accurate studies of GFR in the CF population using exogenous clearance markers exist but are quite heterogeneous in methodology and often limited by small numbers [20–30].

Current recommendations for evaluating GFR in adult and pediatric chronic kidney disease populations call for the use of an age-appropriate estimating equation derived from the relevant population of interest (Schwartz or Counahan-Barrett formula for children) or use of an exogenous plasma marker disappearance method [16]. Unfortunately, creatinine-based GFR estimating equations suffer from inaccuracy in patients with malnutrition, liver disease, abnormal protein intakes, or in the setting of medications or tubular conditions that affect urinary excretion of creatinine [31], any or all of which may be present in the CF population.

As no internationally accepted recommendations for evaluating, monitoring, or classifying renal (dys)function in the CF population exist, and values for baseline or longitudinal glomerular filtration rate (GFR) as measured by exogenous clearance markers are lacking, the primary objective of this study was to establish the prevalence of renal dysfunction as defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) [32], in a pediatric CF population. The gold standard measurement of function chosen was a two-point single injection of ^{99m}Tc-DTPA (the measured GFR, mGFR). Repeated urinalysis and a renal ultrasound completed the evaluation process.

Patients and methods

Study design

This was a retrospective cross-sectional study performed in CF patients cared for at BC Children's Hospital (BCCH) who had at least one ^{99m}Tc-DTPA mGFR between January 2006 and May 2009. All studies were performed as part of the patient's regular medical care. This study received approval from the University of British Columbia ethics review board and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Setting

The study was performed at a tertiary care pediatric referral center servicing a population of 4.4 million. The CF clinic currently cares for 120 children and adolescents. All patients have an annual urinalysis, serum creatinine, and urea measurements. In addition, since 2006, all patients receiving intravenous aminoglycoside therapy have renal function formally evaluated via a ^{99m}Tc-DTPA nuclear GFR. This test is performed early in the first course of aminoglycoside therapy, and then annually if they receive subsequent aminoglycoside doses.

The CF clinic follows a "first growth *Pseudomonas aeruginosa*" eradication policy, using two intravenous anti-pseudomonal antibiotics; tobramycin at a standard starting dose of 12 mg/kg/day divided three times daily, and piperacillin-tazobactam for 14 days. These drugs are followed by 3 weeks of oral ciprofloxacin and 6 months of nebulized colistimethate. Patients with chronic *Pseudomonas aeruginosa* and pulmonary exacerbation are treated with intravenous tobramycin and piperacillin if the organisms are sensitive. Patients with very severe disease receive 2- or 3-monthly courses of the same antibiotics, also depending on microbial sensitivity testing. During aminoglycoside therapy, in the absence of a dose change, monitoring consists of trough and peak levels on the third dose and once weekly thereafter. Serum creatinine is measured weekly during therapy. No patients are routinely prescribed non-steroidal anti-inflammatory drugs.

Participants

A total of 67 children and adolescents (0.5-20 years of age), identified from radiology and CF clinical databases as having a mGFR assessment during the eligibility period of January 2006 to May 2009 were screened for study inclusion. Inclusion criteria included a confirmed diagnosis of CF (positive sweat chloride test and/or known CF genotype) and an eligible mGFR. Exclusion criteria were age less than 2 years at the time of mGFR.

Definitions

The primary outcome of renal dysfunction (CKD stages II-V) was defined as per NKF-K/DOQI and included at least one or

more of the following: urine dipstick positive for blood or protein on three or more occasions, ultrasound evidence of structural renal anomalies, or a mGFR<90 ml/min/1.73 m^2 [32].

Potential confounders for this study include CF liver disease; defined as the presence of one or more of the following: (a) ultrasound evidence of focal biliary or multilobular cirrhosis, hepatomegaly, splenomegaly, (b) portal hypertension or (c) previously demonstrated abnormal liver histology. Similarly, CF-related diabetes was considered a potential confounder and defined as a positive oral glucose tolerance test (1.75 g/kg glucose, maximum 75 g) with a 2-h glucose level >200 mg/dl (11.1 mmol/l).

As this was a descriptive study and thus lacked a control group, we chose to compare our GFR results to the largest normal pediatric nuclear GFR series published to date [33]. In this series, Piepsz et al. measured GFR via an exogenous plasma disappearance method ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA) clearance in 623 normal children. The mean mGFR in this group was 104±20 ml/min/1.73 m^2. Based on this data, we chose to define hyperfiltration in this study as a mGFR≥2 standard deviations above this mean (≥ 145 ml/min/1.73 m^2).

Data sources/measurements

Data were obtained from the CF clinic database, office charts, and the BCCH clinical laboratory and pharmacy systems.

Baseline demographic and clinical data collected included gender, ethnicity, age at CF diagnosis, genotype, and age at time of *Pseudomonas aeruginosa* acquisition. All other data were collected from within 7 days of the patients' first eligible mGFR study and included age, prior lifetime exposure to aminoglycosides, growth parameters, regular medications, administration of intravenous nutrition, serum creatinine, urea, albumin, urinalysis results, evidence of acute dehydration, sepsis, the known diagnoses of any congenital or acquired renal impairment, CF-related liver disease, or diabetes.

Nephrotoxin exposure was recorded as duration, not dose, of intravenous aminoglycoside therapy as doses were adjusted on an individual basis depending on drug-level monitoring. The initial doses used for intravenous tobramycin were 4 mg/kg/dose 8-hourly and 5 mg/kg/dose 8-hourly for amikacin. If an abnormal urinalysis result was found during this time, the next two consecutive urinalyses over the following 12-month period were reviewed to establish if findings were persistent. In addition, the most recent abdominal ultrasound result, from no more than 6 months distant to the mGFR, was also recorded.

The mGFR values were obtained by using two-point ^{99m}Tc-DTPA as an exogenous plasma disappearance marker; samples were obtained at 2 and 3 h. All studies were performed in the morning, thus minimizing the impact of diurnal variation. Nuclear medicine reports included height, weight, body surface area, and mGFR in ml/min and ml/min/1.73 m^2. Serum creatinine was measured by an enzymatic method on a Vitros 950/250. There were no significant changes in laboratory or nuclear medicine equipment or protocols used during this study period.

Bias

Missing data were reported as such, and all calculations and statistical analysis were performed on available data points only.

Statistical methods

Patient characteristics were analyzed descriptively; normally distributed data reported as mean and standard deviation, and skewed data as median and range. To explore the potential relationships between the demographic and clinical variables that were considered to be potentially important for the outcome of mGFR, several regression models were generated to identify potential predictors of outcome. Variables investigated were: genotype, age at diagnosis, gender, days of aminoglycoside therapy just prior to mGFR, lifetime aminoglycoside therapy (in days) prior to mGFR, age at time of mGFR, number of years post CF diagnosis, BMI percentile, IV nutrition, and IV lipid use at time of mGFR. Not all variables were entered into one model. For each regression, after entering a full model, the analysis was reduced until only significant relationships remained.

Results

A total of 67 children and adolescents were screened for inclusion, four were less than 2 years of age at the time of their mGFR and were therefore excluded, leaving a total of 63 patients for analysis. At the time of mGFR, the patients were aged 2.1-18.5 (mean 9.6±5.0) years. Thirty-three (52%) patients were female. The mean age at the time of CF diagnosis was 2.0±2.8 years. Fifty-eight (92%) patients were Caucasian. A CF mutation was known in 60 (95%) patients, with 33 being homozygous and 25 heterozygous for delta F508. Variables of interest at the time of mGFR are listed in Table 1. Data were complete for baseline characteristics, lifetime aminoglycoside exposure, *Pseudomonas* acquisition, growth parameters, and co-morbidities in all patients. A summary of the outcome data is shown in Table 2. Creatinine values were available for 98%, urea for 97%, albumin for 95%, and urinalysis for 95% of all

Table 1 Descriptive data at time of measured GFR

Variable	Result
Age (years) at time of mGFR; mean ± SD	9.6±5
Lifetime exposure (days) aminoglycosides; median (range)	20 (1-416)
Pseudomonas aeruginosa positive; *n* (%)	58 (92)
First *Pseudomonas aeruginosa* infection; *n* (%)	19 (30)
Age (years) at *Pseudomonas* acquisition; mean ± SD	6.4±4
Growth and nutrition parameters; mean ± SD	
Weight (kg)	34.6±15.9
Height (m)	136.6±26.9
BMI (kg/m^2)	17.3±2.5
BMI percentile	39±27
Serum albumin (g/dl)	3.9±0.4
Intravenous lipid, *n* (%)	25 (40)
Intravenous amino acid and lipid, *n* (%)	6 (10)
Co-morbidities; *n* (%)	
CF-related liver disease	7 (11)
CF-related diabetes	5 (8)

n number; *BMI* body mass index; *CF* cystic fibrosis. Conversion factors for units: serum albumin in g/dl to g/l multiply by 10

patients. Forty-five (71%) of the cohort had a previous abdominal or renal ultrasound result available within the pre-specified time frame. Regular medication data was complete for all patients. At the time of mGFR, no patients were dehydrated or septic, were receiving intravenous fluids, or were known to have congenital or acquired renal impairment. Four patients (6%) had evidence of renal dysfunction as per the NKF-K/DOQI definition, one with a reduced mGFR of 82 ml/min/1.73 m^2 and three who had persistent microscopic hematuria as per the study definition. Two of the three patients with hematuria were older (17.8, 14.8 years) and had mGFR results of 150 and 161 ml/min/1.73 m^2 along with substantial lifetime aminoglycoside exposure of 132 and 189 days, respectively. One patient has since transitioned to adult care and further information was not available. The younger patient unfortunately died of non-renal-related disease shortly after the mGFR. The third patient was only 4 years old, with an mGFR of 127 ml/min/1.73 m^2 and only 7 days of prior aminoglycoside exposure. This patient's hematuria completely resolved on follow-up testing 12 months later. The patient with the reduced mGFR did not have associated hematuria, and had never previously received aminoglycoside therapy. Subsequent urinalyses and serum creatinine measures were normal, and a repeat mGFR 13 months later was considerably higher and within the normal range at 124 ml/min/1.73 m^2. No patients were found to have proteinuria on urine dipstick analysis at any time. Formal testing for microalbuminuria was not done. All 45 renal ultrasound investigations were reported as normal by staff pediatric radiologists.

The mean mGFR for the entire group was 140±24 ml/min/1.73 m^2 (range 82-197 ml/min/1.73 m^2). Twenty-five patients (40%) had evidence of hyperfiltration, as defined by a mGFR≥2 SD above the normal pediatric population mean (i.e., ≥ 145 ml/min/1.73 m^2) [33] (Fig. 1).

The regression analyses showed no evidence of a statistical relationship between mGFR (whether corrected for BSA or not) and age at diagnosis, years since diagnosis, age at time of mGFR, gender, body mass index percentiles, lifetime days of aminoglycoside antibiotics, first growth versus chronic colonization with *Pseudomonas aeruginosa*, use of intravenous nutrition at time of mGFR or presence of CF-related liver disease or diabetes (data not shown). The only variables to show a strong relationship were lifetime use of aminoglycosides and age at time of mGFR. The correlation between these two variables is 0.39.

Discussion

The primary objective of this study was to establish the prevalence of renal dysfunction in a pediatric CF population. Our results demonstrate a low prevalence (6%) of renal dysfunction in this group of children, mean age of 9.6 years, who were an average of 3.2 years out from first

Table 2 Evaluation of renal function

Variable	Number evaluated	Result
mGFR; mean ± SD (range)	63	140±23.9 (82-197) ml/min/1.73 m^2
Laboratory evaluation; mean ± SD		
Creatinine	62	0.49±0.16 mg/dl
Urea	61	10.81±2.96 mg/dl
Urinalysis; *n* (%)		
Microscopic hematuria	60	3 (5)
Proteinuria	60	0
Use of antihypertensive medication	63	0
Renal anomaly on ultrasound	45	0

mGFR measured GFR; *eGFR* estimated GFR. Conversion factors for units: serum creatinine in mg/dl to μmol/l multiply by 88.4; serum urea nitrogen in mg/dl to mmol/l multiply by 0.357

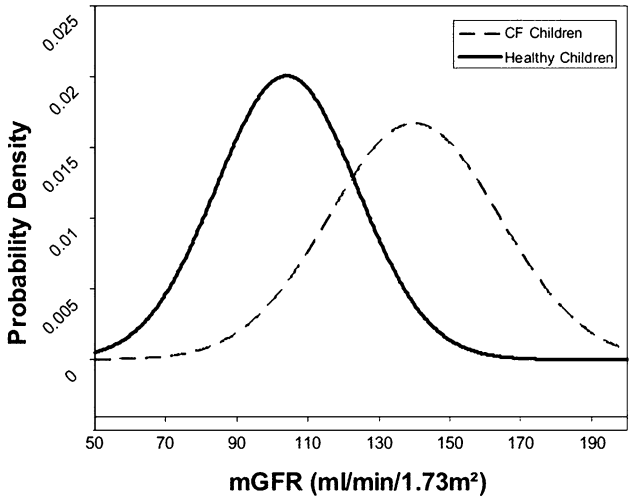

Fig. 1 Distribution of measured GFR: cystic fibrosis[a] versus healthy[b] children. [a]Study population (n=63) mGFR using ^{99m}Tc-DTPA; [b]Piepz 2006 Study (n=623) mGFR using ^{51}Cr-EDTA

acquiring *Pseudomonas aeruginosa*. We were unable to demonstrate any ultrasound abnormalities such as nephrocalcinosis or nephrolithiasis, as has been reported in previous smaller CF publications [3]. However, the mean mGFR of 140±24 ml/min/1.73 m^2 in this population is noteworthy.

In fact, whether glomerular hyperfiltration was defined as ≥ 2 SD or as > 90th centile for age, data from Piepsz et al. [33, 34], our results reveal that between 40 (≥ 2 SD definition) and 56% (> 90th centile definition) of our CF patients had evidence of glomerular hyperfiltration at the time of testing. These results are remarkably similar to those recently reported by an Australian group, who found a mean mGFR of 142 ml/min/1.73 m^2±27.2 in 27 children with a mean age 11.4 years±4.7. This study also used ^{99m}TcDTPA GFR methodology, with blood samples at 2, 3, and 4 h; however, had excluded any patient who received aminoglycoside antibiotics within the previous 8 weeks [35].

Glomerular filtration is maintained within narrow limits to prevent inappropriate fluctuations in solute and water excretion. Its regulation in healthy subjects is primarily achieved by alterations in arteriolar tone ("autoregulation") that influences both the hydraulic pressure in the glomerular capillary and renal blood flow. This phenomenon is mediated by at least three factors: stretch receptors in the afferent arteriole, angiotensin II, and tubuloglomerular feedback [36]. Within the CF population, increased proximal tubule sodium reabsorption has been demonstrated in the majority of studies [21, 22, 27, 29, 37]; perhaps due to essential fatty acid deficiency (EFAD), which plays a role in altering tubular sodium absorption secondary to changes in cell membrane composition and transport characteristics [37]. These changes would result in decreased sodium delivery to the distal tubule and an increase in GFR via tubuloglomerular feedback. Strandvik et al. [37] found that following essential fatty acid supplementation in patients with CF, there was both increased basal urinary sodium excretion and a reduction in GFR to normal values. Of note, basic science and clinical research suggests that EFAD is not due to nutritional deficiencies but rather stems from a relationship between the primary CFTR defect and altered essential fatty acid metabolism [38–41], meaning that all CF patients would be at risk of this, not only those with nutritional deficiencies.

Upon review of the GFR literature within the CF population we found a number of small studies over the past 30 years that have determined GFR by inulin or non-inulin radioisotope tracer techniques [20–30, 37] (Tables 3 and 4). The majority of these studies were done to evaluate drug clearance or examine the handling of sodium and water in the CF population. Although these studies were performed with a variety of salt and/or water loading protocols, it is striking that in seven of the eight studies, which included a strictly defined healthy control population, a trend towards or a statistically significant (p< 0.05) increase in the mean GFR was seen in the CF group [20–22, 24, 25, 28, 29]. In particular, if one restricts the data to the "gold standard" inulin measurement of GFR (Table 3) one can see a clear separation in the mean GFR in the CF (135 ml/min/1.73 m^2) versus control (115 ml/min/1.73 m^2) groups.

In adults, glomerular hyperfiltration has been shown to precede the development of microalbuminuria and subsequent nephropathy in two other chronic disease models, diabetes and hypertension [42–44]; and persistent microalbuminuria has been described in CF patients with and without co-existent diabetes [45]. While less clear in the non-diabetic CKD population, proteinuria reduction appears to play a role in slowing progression of CKD (reviewed by Kalaitzidis and Bakris [46]). If glomerular hyperfiltration precedes or contributes to the development of micro- or macroalbuminuria in CF patients, then its presence may predict an increased risk for progressive nephropathy in this population.

There are a number of limitations of our study including all those of a retrospective review. However, this study represents the largest single-center collection of measured GFR data in the pediatric CF population. The absence of a control group clearly makes interpretation of GFR values in our patients more difficult. This issue is compounded by the fact that the methodology used in our study differs from both the "gold standard" of inulin clearance, as well as the ^{51}Cr-EDTA values we chose to compare to from Piepsz et al.'s work [33]. Although inulin clearance during constant infusion is considered the reference method for measuring GFR, this

Table 3 GFR in the CF population—inulin methodology

Study (year)	*n*	Age range in years (mean)	Sex	Method	Patient state	CF GFR Mean ± SD	Control GFR Mean ± SD	Controls comments
Robson et al. (1971) [27]	8	8-16 (12)	3M 5F	Inulin	16-h fluid deprivation	120±14	-	No controls
Vogelstein et al. (1977) [30]	11	4-16 (9)	7M 4F	Inulin	IVF 100 ml/h/m^2 8 h prior	160±42	151±44	*n*=9 Unwell 7-15 years
Berg et al. (1982) [22]	16	5-19 (11.5)	7M 9F	Inulin	20 ml/kg water PO prior, 5 ml/kg during & Na load	127±18$^{\#}$	112±10	*n*=10 5 years–Adult
Arvidsson et al. (1983) [20]	5	(16.2)	6M 1F^{t}	Inulin	ND	142±38	102±15	*n*=5 Adults
Hedman et al. (1988) [24]	8	11-22 (17)	3M 5F	Inulin	IV antibiotic administered prior or infused concurrently	132±30$^{\#}$	103±8	*n*=10 10-46 years
Strandvik et al. (1989) [37]	10	5-26 (14)	5M 6F^{t}	Inulin	Standardized sodium intake 2 mmol/kg 4 days prior	133±18$^{\#}$	112±10	*n*=25 Some unwell Child-Adult
Hedman et al. (1990) [25]	6	15-23 (19)	4M 2F	Inulin	IV antibiotic infusion concurrently	136±8$^{\#}$	108±12	*n*=8 17-34 years
Summary	64	(13.1)	35M 32F^{t}	Inulin	Varied	135±26	115±19	*n*=67

ND not detailed; *IVF* intravenous fluid; *PO* per oral; *IV* intravenous; *IVF* intravenous fluid; *Na* sodium; *n* number; *M* male; *F* female; ^{t} total in study, some patients did not have GFR, * difference in GFR between CF and controls statistically significant ($p<0.05$)

is generally not suitable for routine clinical use due to its technical demands and in fact neither it nor ^{51}Cr-EDTA is available in North America for general use [47]. Fortunately, correlation between these three methods, ^{51}Cr-EDTA, ^{99m}Tc-DTPA and inulin clearance is excellent with a correlation of r=0.997 between ^{51}Cr-EDTA and inulin [48] and r=0.94-0.98 between ^{51}Cr-EDTA and our method of a two-point ^{99m}Tc-DTPA technique [49].

Although it could be postulated that patients with CF have increased extra-renal clearance of DTPA, resulting in an over-estimation of the GFR when utilizing such radioisotope tracer methodology, there is no convincing published literature in the last 40 years to support this. Even if one presumed an additional extra-renal DTPA excretion of 10%, our results would still have found a mean GFR>1SD above the normal population (126 vs.

Table 4 GFR in the CF population—non-inulin methodology

Study (year)	*n*	Age range in years (mean)	Sex	Method	Patient state	CF GFR Mean ± SD	Control GFR Mean ± SD	Controls comments
Spino et al. (1985) [28]	8	(17)	ND	^{99m}-DTPA	Overnight fast prior & 200 ml PO fluid 5× during	122±17	111±13	*n*=10 Mean 22 years
Assael et al. (1986) [21]	11	11-23 (16)	6M 5F	Polyfructosan S	PO water 20 ml/kg then urine replacement with water during	131±9	117±18	*n*=19 18–24 years
Stenvinkel et al. (1991) [29]	10	21-33 (25.6)	2M 8F	^{51}Cr-EDTA	200 ml water PO hourly during	110±19	99±10	*n*=10 20-36 years
Levy et al. (1984) [26]	12	8-23 (15.7)	6M 6F	Iothalamate	IVF 50 ml/h/m^2 2 h prior & during	148±29	141±20	*n*=6 Some unwell Child–Adult
Beringer et al. (2009) [23]	19	>18 years (29.3)	8M 11F	Iothalamate	Overnight fast, 600 ml PO fluid pre, 150-200 ml/h PO fluid during	104±32	105±30	*n*=19 Mean 28.6 years

ND not detailed; *IVF* intravenous fluid; *PO* per oral; *IVF* intravenous fluid; *n* number; *M* male; *F* female

104 ml/min/1.73 m^2) and 21% of patients demonstrating hyperfiltration.

In addition, measurement of GFR in a clinical rather than research setting may lead to variability or bias depending on the conditions of each patient (hydration status, protein intake) and study conditions (time of day, mGFR protocol). In this study, these concerns were lessened as the studies were performed on patients receiving standardized antibiotic therapy who were sedentary during the admission and received hospital prepared diets. The one possible uncontrolled dietary intake variable was administration of intravenous lipid and/or total parenteral nutrition at the time of the mGFR. However, analysis without these few patients did not substantially alter our results (mean GFR 140±26 versus±24 ml/min/1.73 m^2). Regression analysis also did not identify these factors as influencing the GFR. Finally, as only a small proportion of patients had multiple mGFRs to date, we were unable to evaluate change in mGFR over time in this population.

In summary, we were unable to document overt evidence of renal dysfunction in this pediatric CF population following limited lifetime aminoglycoside exposure. However, our GFR data, consistent with those from a recently published smaller pediatric CF study [35], when considered in context of published normal values in children and the published adult CF literature, demonstrate the presence of glomerular hyperfiltration in this CF population. Future studies should be directed toward confirmation of this finding via controlled studies and subsequently elucidating the underlying mechanisms of this hyperfiltration and its relationship to long-term outcomes of renal dysfunction in this at-risk population.

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