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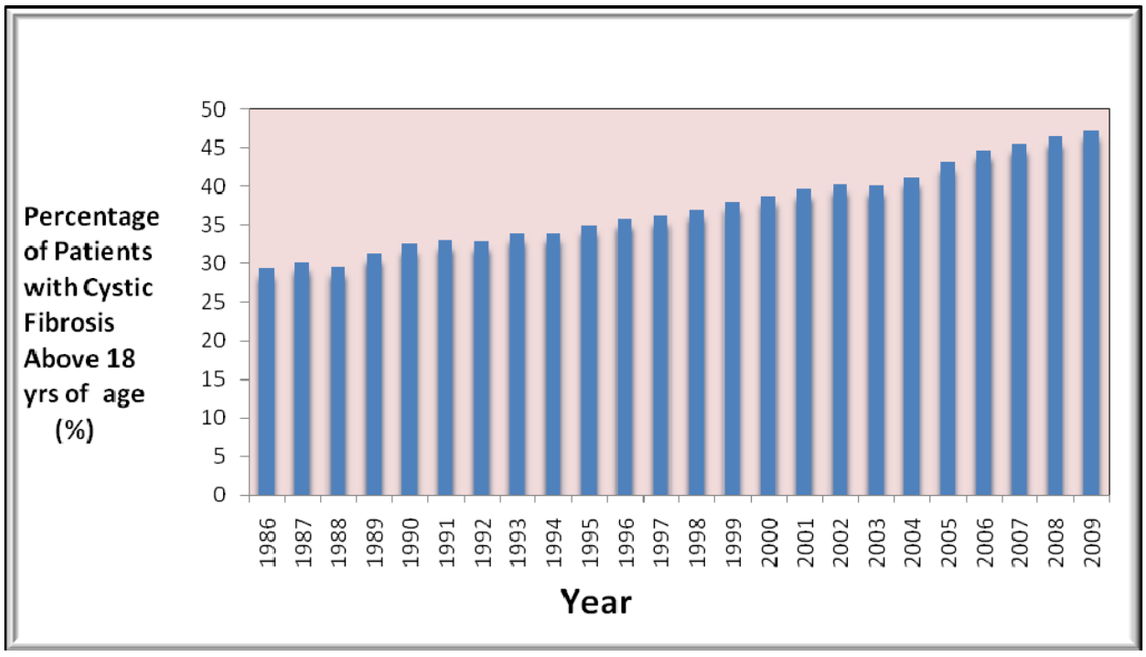
Glomerulonephritis and the Cystic Fibrosis Patient

Daniel Fischman,
Arvin Parvathaneni and Pramil Cheriyath
Pinnacle Health System-Harrisburg Hospital,
Harrisburg, Pennsylvania,
United States of America

1. Introduction

Cystic Fibrosis (CF) is a disease with an evolving definition. Through earlier diagnosis and newborn screening programs, as well as a robust world-wide research program, we are able to treat individuals afflicted with this life-threatening malady more aggressively and with earlier interventions. Despite our progress in extending the life expectancy of the typical CF patient, the disease is still viewed by the general medical community as one of childhood.

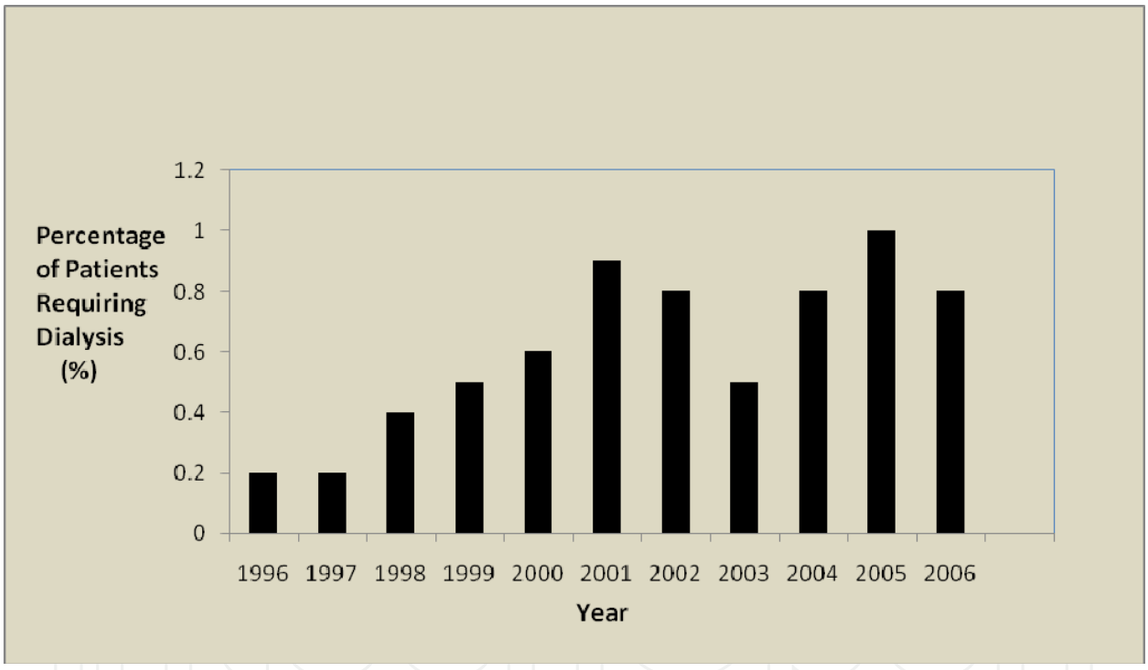


Source: Cystic Fibrosis Foundation Patient Registry Annual Data Reports, 1986-2009

Fig. 1. Prevalence of Cystic Fibrosis in North American Adults

This former "age constraint" on the natural history of CF is paralleled by other major developments, such as an expansion of the number of organ systems, which we now know are involved in this disease. We now know that this disease affects more than the pulmonary and gastrointestinal systems.

With the aging of the CF population (Figure 1), it has come to light that CF patients suffer from an increased risk of Diabetes Mellitus (Fischman & Nookala, 2008; Stecenko & Moran, 2010), Osteoporosis (Haworth, 2010), and malignancies (Hernandez-Jimenez et al., 2008). There is also a growing body of literature suggesting that as a result of treating other conditions associated with CF and as a result of the inflammatory and immunologic milieu associated with Cystic Fibrosis, these patients also suffer from renal disease (Stephens & Ridden, 2002; Katz et al., 1988) (Figure 2). In this chapter, we will discuss our current understanding of Cystic Fibrosis and review potential associations to renal disease with special attention to glomerulonephritis (GN).



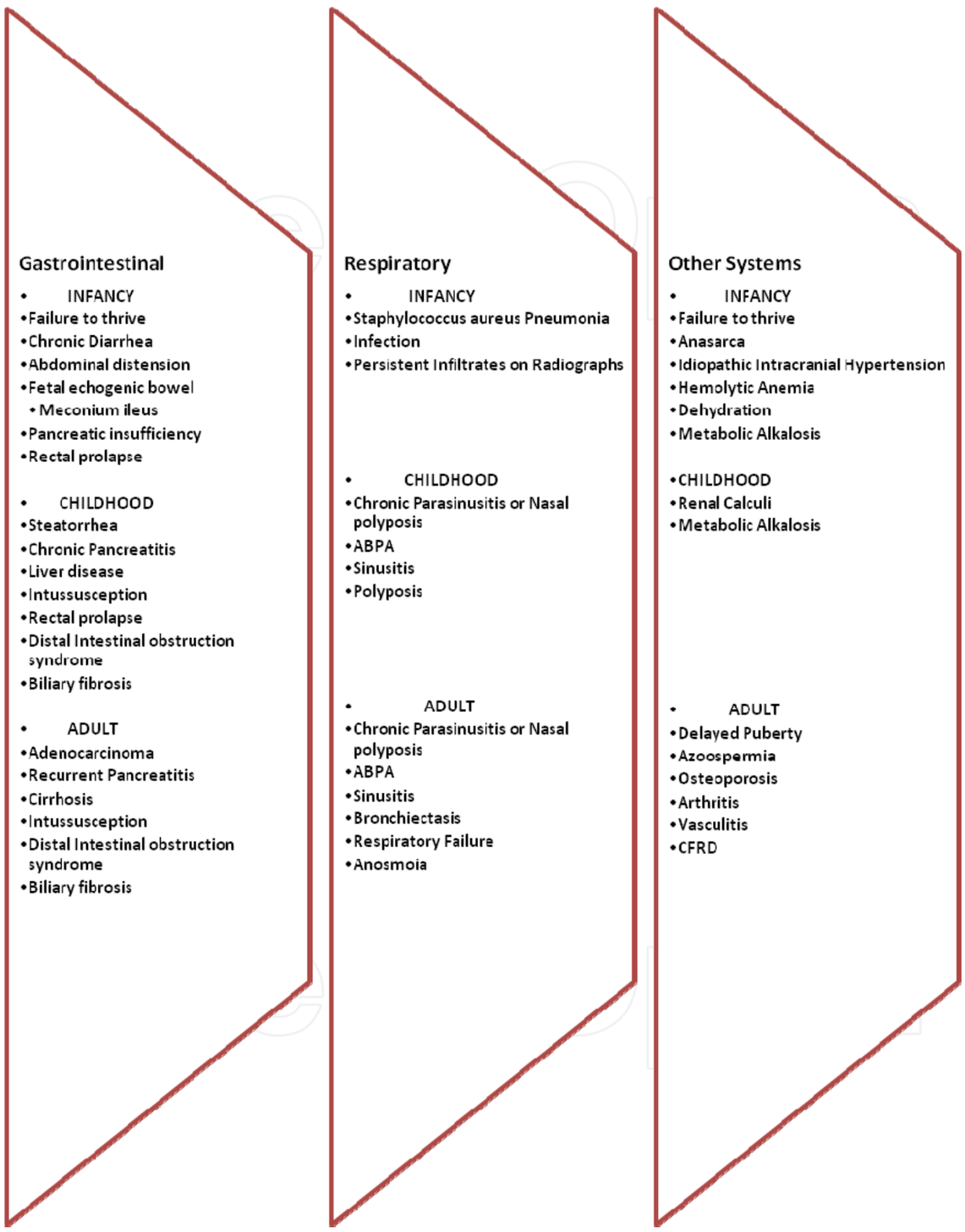
Source: Cystic Fibrosis Foundation Patient Registry Annual Data Reports, 1996-2006

Fig. 2. Prevalence of Cystic Fibrosis Patients Requiring Dialysis for Renal Failure

2. Background - Cystic Fibrosis

2.1 Genetics

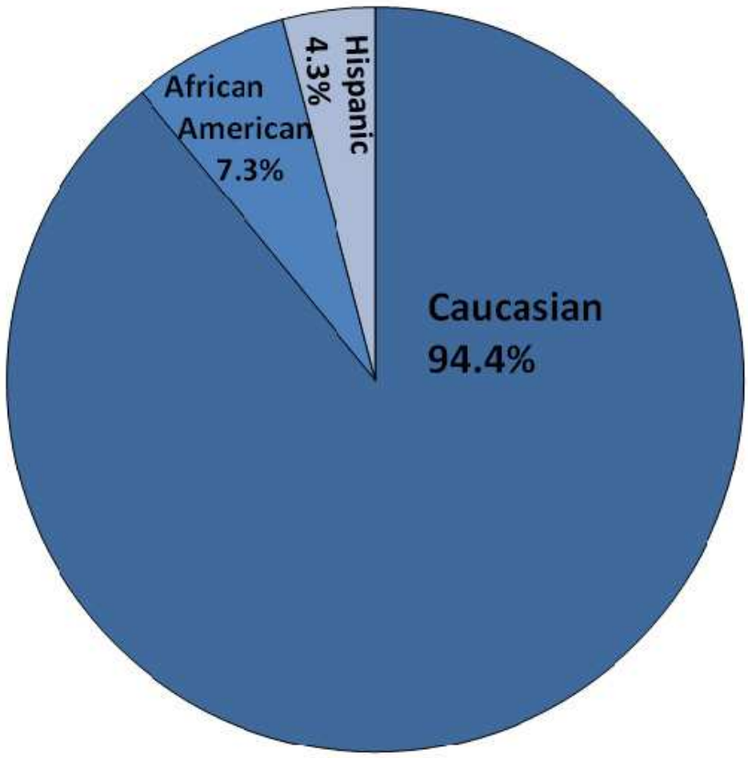
Cystic Fibrosis is the most common, lethal, autosomal recessive disorder seen among the Caucasian population. For this reason, its disease prevalence throughout much of the world is 1 in 2,000 to 1 in 3200 individuals. Among non-Caucasian populations, and those not living in North America or Western Europe, the prevalence is approximately 1 in 4,000 to



Legend: ABPA = Allergic Bronchopulmonary Aspergillosis,
CFRD = Cystic Fibrosis-Related Diabetes Mellitus

Fig. 3. Common Signs and Symptoms of Cystic Fibrosis, by Stage of Life

1 in 20,000 (Figure 4) (Sullivan & Freedman, 2009). Although we have known for decades of the association between salty sweat, obstructive lung disease, and pancreatic insufficiency, which comprise the hallmark symptoms of CF, and it was postulated as early as 1949 that a gene defect was the cause of CF, it was not until 1989 that the gene defect was localized to chromosome 7 (Rowe et. al., 2005). Since that time, more than fifteen hundred mutations have been identified that can lead to the cystic fibrosis phenotype (Boyle, 2007).



Source: Cystic Fibrosis Foundation Patient Registry Annual Data Report 2009

Fig. 4. Racial Demographics of Cystic Fibrosis Patients in North America

This specific gene encodes a protein called the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), which is found on many different types of cells. CFTR plays numerous regulatory roles throughout the body. The role most commonly associated with CFTR is that of chloride channel. However, the CFTR protein also plays a role in the inhibition of sodium transport, the regulation of ATP channels, and the inhibition of calcium-activated chloride channels. We now know that there are multiple types of CFTR gene mutations. They range in effect from complete lack of protein production (Class I Mutation), and defective protein processing and trafficking to the cell surface (Class II), to reduced production of normal-functioning CFTR protein (Class V) (Sullivan & Freedman, 2009) (Table 1). The F508del mutation, which accounts for two-thirds of Cystic Fibrosis in Northern Europe and North America, is a class II mutation, resulting in production of a defective CFTR protein.

Mutation Class	*Effect on CFTR Protein*	*CFTR Ability to Function*	*Pancreatic Exocrine Dysfunction*
I	Protein not produced	No	Severe
II	Protein trafficking defect with CFTR degraded in ER/GolB; CFTR does not reach cell membrane	No	Severe
III	Defective protein regulation; CFTR reaches cell membrane but not activated by ATP or cyclic AMP	No	Severe
IV	Reduced Cl transport through apical membrane CFTR	Yes	Mild
V	Splicing defect with reduced production of functioning CFTR	Yes	Mild
VI	CFTR reaches cell membrane, but more rapid CFTR turnover	Yes	Presumably Mild

Legend: CFTR = Cystic Fibrosis Transmembrane Regulator Protein, ER = Endoplasmic Reticulum, GolB = Golgi Body, ATP = Adenosine Triphosphate, AMP = Adenosine Monophosphate, Cl = Chloride ion

Table 1. CFTR Mutation Classes

Since Cystic Fibrosis is an autosomal recessive genetic trait, full expression of this disease requires that a defective gene be present on each chromosome. However, having one abnormal gene typically conveys a milder level of morbidity. As the level of CFTR metabolic regulatory function decreases below fifty percent, the chance of the individual developing sino-pulmonary conditions such as sinusitis, nasal polyps, or asthma increases. Men with the cystic fibrosis trait may experience infertility due to Congenital Bilateral Absence of the Vas Deferens (CBAVD). Despite the fact that it takes the presence of only one abnormal CFTR gene and fifty percent CFTR function for sino-pulmonary and genitourinary symptoms to occur; it typically takes CFTR function at levels less than five-percent of normal, usually seen with two mutations, before a patient's sweat chloride excretion rises to levels diagnostic of CF. Furthermore, it takes CFTR protein function to be decreased by ninety-nine percent for pancreatic insufficiency to occur (Strasbaugh & Davis, 2007). Moreover, despite our efforts to characterize the association between genetic defect and phenotypic disease, neither sweat chloride level nor pulmonary function test values correlate with number or type of CFTR mutation. In two studies looking at this association, the mutation known to lead to Cystic Fibrosis could be found in only three out of five patients (Groman et. al., 2005; Groman et al., 2002). However, it is interesting that a 2009 study of urinary protein excretion with regard to Cystic Fibrosis did find an apparent association between level of renal protein excretion and genotype, suggesting that although we cannot directly correlate gastrointestinal or pulmonary phenotype with a patient's genotype, we may be able to correlate renal phenotype with CF genotype (Cemlyn-Jones & Gamboa, 2009).

2.2 Pathophysiology

The pathophysiology of Cystic Fibrosis results from abnormalities localized to the CFTR gene site resulting in an abnormality in CFTR protein production or processing. Either

through this absence of CFTR protein, or through the production of abnormally functioning protein, an electrolyte imbalance occurs on luminal surfaces in multiple organ systems. The common result is the production of thick, tenacious secretions, which have impaired immunologic function and result in dysregulation of the patient's inflammatory response, leading to an imbalance between pro-inflammatory and anti-inflammatory chemokines. In addition, there has been some evidence to suggest that the abnormal CFTR protein may facilitate protein binding of bacteria, leading to CF-related lung disease involving such bacterial pathogens as Pseudomonas aeruginosa and Staphylococcus aureus (Sullivan & Freedman, 2009; Rowe, 2005).

2.3 Diagnosis

The diagnosis of Cystic Fibrosis is typically made based on a combination of clinical symptoms consistent with the disease along with confirmatory testing. Since 1959, the diagnostic standard for Cystic Fibrosis has been the measurement of sweat chloride levels, as stimulated through a process using Pilocarpine Iontophoresis. In children younger than six months of age, a normal concentration of sweat chloride is considered to be less than 30 mmol/liter. In patients older than six months, the normal range would be less than 41 mmol/liter. Regardless of age, any repeatable sweat chloride level greater than 59 mmol/liter is consistent with the diagnosis of Cystic Fibrosis, particularly if accompanied by symptoms of sino-pulmonary disease, a gastrointestinal malady such as fat-soluble vitamin deficiency, malnutrition, or intestinal obstruction, metabolic alkalosis, dehydration, or acute salt depletion (Figure 2) (Farrell et al., 2008).

Consistent with the phenotypic pancreatic insufficiency seen in 90-95% of Cystic Fibrosis patients, pancreatic enzyme levels may be measured to help confirm the diagnosis. As of 2010, fourteen European countries and all states in the United States have a process in place for screening newborns for this disease. Most of these testing programs, at least to some degree, rely on measuring levels of Immunoreactive Trypsinogen, a pancreatic enzyme found to be elevated in the first six weeks of life in infants with CF (Barto & Flume, 2010).

In the situation where the sweat chloride analysis is indeterminate or the symptomatic phenotype is subtle, genetic testing is often employed. If the patient is found to have two mutations known to be consistent with the cystic fibrosis phenotype, then the diagnosis can be made. If one mutation is found, and it is unclear if the patient has a second, less well-characterized mutation, then the patient is considered to have a possible diagnosis of Cystic Fibrosis. As noted previously, genetic testing may still be performed in the circumstance of confirmed disease, since the patient's specific mutations may have prognostic significance. Furthermore, as we attain a greater understanding of the myriad of ways that defective CFTR genes may lead to inadequate or defective protein production and function, we will be able to tailor our therapeutic regimens more effectively to the patient's genetic circumstance, in order to modulate or restore CFTR function (Ashlock et al., 2009).

2.4 Clinical manifestations

To date, it has been impossible to draw a direct link between the degree of genotypic abnormality and a particular patient's morbidity. However, there are some common clinical patterns and associations seen in cystic fibrosis patients. Based on these clinical findings, an all-encompassing definition of Cystic Fibrosis would be "a chronic and progressive, multi-system disease leading to sino-pulmonary disease, with probable exocrine pancreatic insufficiency, malnutrition, and gastrointestinal obstructive symptoms". Patients with

Cystic Fibrosis typically have some degree of obstructive lung disease and present with a distinguishing factor of early colonization and subsequent infection from organisms not typically seen except in immunosuppressed or severely bronchiectatic individuals, such as Pseudomonas aeruginosa, Burkholderia cepacia, or Stenotrophomonas maltophilia.

As a consequence of pancreatic insufficiency and associated malnutrition, many Cystic Fibrosis patients are deficient in fat soluble vitamins and suffer from a chronic, negative protein balance. Mouse studies have shown that the presence of CFTR gene defects leads to a heightened risk of Osteoporosis and subsequent bone fracture (Haworth, 2010). Along with this fracture risk, CF patients have an increased risk of kidney stones. One autopsy study of thirty-eight CF patients found that thirty-five had evidence of nephrocalcinosis, including one still-born and two neonatal infants (Katz et al., 1988). This predilection seems to be multifactorial and results from the interplay of 1) impaired vitamin D absorption leading to impaired calcium absorption, 2) chronic disease characterized by increased metabolic tempo, 3) immobility, 4) increased osteoclast activity, 5) inadequate caloric intake due to increase work-of-breathing, 6) an imbalance between protein anabolism and catabolism, and 7) loss of oxalate-degrading bacteria due to frequent, and often chronic antibiotic use (Stephens & Rigden, 2002). Furthermore, Andrieux et al., in their 2010 study, found that 75% of children in their study population had hypocitraturia and 70% had hyperoxaluria, both of which are risk factors for nephrolithiasis (Andrieux et al., 2010).

One interesting aspect of the renal expression of CFTR is that cystic fibrosis patients often have greater antibiotic excretion than their non-CF counterparts. This necessitates the use of higher-than-typical antibiotic doses. The classic example of this occurs with the use of aminoglycoside antibiotics for treatment of pseudomonal infections, where Tobramycin is dosed at 10 mg/kg, sometimes in conjunction with inhaled Tobramycin, instead of the usual 5-7 mg/kg (Barto & Flume, 2010, Bergman et al., 2007). Indeed, in one study of renal failure in children with Cystic Fibrosis, twenty of twenty-four cases of acute renal failure were associated with recent or concomitant aminoglycoside administration (Bertenshaw et al., 2007). As a result of this uncertain pharmacokinetic and pharmacodynamic profile encountered with cystic fibrosis patients, monitoring drug levels is critical to insure that therapeutic doses are being achieved for efficacy.

3. Renal disease and the CF patient

3.1 A broad picture of renal disease in Cystic Fibrosis

Since Dorothy Anderson first generated the term, “Cystic Fibrosis,” in 1938, we have known that kidney disease may be part of this malady (Abramowsky & Swinehart, 1982). However, the natural history of CF-related renal disease has been elucidated in few studies. In Abromowksy and Swinehart’s 1982 study, they found that all thirty-four of the patients studied had some form of glomerulopathy, with nineteen having glomerulosclerosis. Twenty-five had what was described as a “Mesangiopathy,”and twenty-six had tubulointerstitial disease. In this study, the authors concluded that a number of factors had led to the myriad of renal lesions observed: 1) lung disease with resultant cyanosis, 2) liver disease, 3) Cystic Fibrosis-Related Diabetes Mellitus, 4) the effects of nephrotoxic medications, and 5) an altered immune response. Of note, the authors report that sixteen of thirty-four patients studied had complement-3 (C3) deposits in their kidneys while thirteen had evidence of immunoglobulin–M deposits (IgM) (Abramowsky & Swinehart, 1982).

A more contemporary, 2010 study investigating renal disease in Cystic Fibrosis followed 112 children, starting in the first year of life. This study revealed the presence of microalbuminuria in fifty-eight percent of patients. This finding was attributed to the presence of chronic inflammation as a result of the malfunctioning or absent CFTR protein, repeated infections, and the nephrotoxicity of many medications commonly used in the treatment of CF (Andrieux et al., 2010). Furthermore, a 2009 study following five hundred ten adults with CF, median age of thirty-one years, found that 13 developed renal disease severe enough to warrant renal biopsy, with eight different types of nephropathies found on histologic analysis. Twelve of these thirteen patients were found to have glomerular lesions. In this study, the main types of renal disease found were AA amyloidosis and diabetic nephropathy (Yahiaoui et al., 2009).

In literature reviewed for their 2002 article on renal disease in Cystic Fibrosis, Stephens and Rigden report that IgA Nephropathy appeared to be the most common form of glomerulonephritis described in CF patients, though the occurrence of this condition appeared rare (Stephens & Rigden, 2002). With respect to all renal disease in CF patients, the most common renal pathology found has been nephrocalcinosis. Drug-related nephrotoxicity also continues to be a common cause of renal morbidity among CF patients. Among the various agents responsible medication-induced renal disease, aminoglycosides continue to play a prominent role. As a result of the pharmacodynamic and pharmacokinetic eccentricities of the cystic fibrosis patient, Acute Tubular Necrosis (ATN) remains a constant concern when treating pulmonary exacerbations in this patient population. This risk of ATN is amplified by pulmonary biofilm formation and the need to use a combination of intravenous, oral, and inhaled antibiotics to effect a decrease in pathogen levels, and potentially facilitate bacterial eradication. It is for this reason that current Cystic Fibrosis Foundation guidelines recommend once-daily dosing of aminoglycosides to optimize treatment benefit, yet minimize risk of renal injury (Flume et al., 2009). Furthermore, a 2010 review of aminoglycoside toxicity in cystic fibrosis patients suggested that use of once-daily Tobramycin, particularly when dosed in the morning, may be superior to use of gentamicin in preventing aminoglycoside-induced renal injury (Prayle & Smyth, 2010) (Figure 4).

3.2 Measurement of renal function in CF patients

Discussion of renal disease in CF patients is complicated by the fact that conventional methods of measuring renal function may not be accurate in this population (Prayle & Smyth, 2010). In Andrieux's 2008 study of renal disease in children with CF, his team observed that there was no correlation between a calculated Glomerular Filtration Rate (GFR), using the Schwartz Formula's manipulation of serum creatinine (SCr) values, and a urine creatinine-based (UCr) standard.

Schwartz Formula:

$$GFR(mL/min/1.73\ m^2) = ((k)(Height\ in\ cm)/(SCr\ in\ mg/dL)) \text{ where}$$

K = Constant as follows:

- 0.33 in premature infant
- 0.45 in term infants to 1 year-old
- 0.55 in children older than one, up to 13 years old
- 0.55 in adolescent females
- 0.65 in adolescent males

In one-third of children studied, the Schwartz Formula's serum-creatinine derived approach overestimated renal function (Andrieux et al., 2010). Furthermore, Yahiaoui's 2009 study investigating renal disease in thirteen adults with Cystic Fibrosis concluded that one of the reasons that renal disease is considered uncommon in CF patients is that measurements of SCr and calculations of GFR, using either the Cockcroft-Gault or MDRD equations, fail to adequately and reliably reflect a CF patient's true level of kidney function (Yahiaoui et al., 2009). To explain this apparent inadequacy in SCr-based evaluation of renal function observed in the CF population, it has been suggested that decreases in muscle mass seen among CF patients, and typically related to their underlying disease states, leads to decreased production of SCr. This would hinder the proportional rise in SCr levels in response to renal insufficiency, which has been observed in other studied populations. Recognizing this challenge of accurately measuring renal function in CF patients, methods that more directly measure kidney function have been proposed including methods using UCr collection, typically over twenty-four hours or using plasma levels of an inert tracer which is only excreted via the kidneys (Prayle & Smyth, 2010).

In recognizing the fallacies of SCr-based formulae, the difficulties of collecting urine accurately over an extended period of time, and the invasiveness of nuclear tracer-based measurements of renal function, Beringer and colleagues studied levels of the biomarker Cystatin C (Cys C) as a potential method of estimating GFR. Their study showed that measurement of Cystatin C clearance was a suitable alternative to measurement of SCr or calculated GFR in following a CF patient's renal function. Furthermore, Cys C levels were not affected by age, gender, muscle mass, diet, or level of physical activity. Moreover, the authors make specific mention of using this method to follow CFRD patients for evidence of renal disease (Beringer et al., 2009). Unfortunately, at this time, Cys C levels have not become widely employed.

3.3 Cystic Fibrosis-Related Diabetes Mellitus and Renal Disease

Since Cystic Fibrosis-Related Diabetes Mellitus (CFRD) is becoming an increasingly common complication in the natural history of Cystic Fibrosis, and can lead to significant renal pathology, we discuss this type of renal disease as an independent section. By the time CF patients reach their thirtieth birthday, 45-50% will have developed CFRD, with an associated increase in morbidity and mortality. This complication of Cystic Fibrosis was formerly the most dreaded of sequelae, as it was associated with a six-fold increase in mortality, particularly among women (Fischman & Nookala, 2008). However, through aggressive efforts to increase screening for evidence of impaired glucose intolerance and overt diabetes, as well as through early use of oral diabetic medications and insulin, the mortality disparity associated with CFRD has all but disappeared (Stecenko & Moran, 2010) (Table 2).

As with other forms of Diabetes Mellitus, CFRD may lead to microvascular changes in such structures as the Eyes, Kidneys, Stomach, and Nerves. A 2007 study of the microvascular complication of CFRD suggested that CFRD-related nephropathy occurred less commonly than renal complications seen in association with other forms of Diabetes Mellitus (Schwarzenberg et al., 2007). The results found in Schwarzenberg's study appear to be consistent with our current understanding of CFRD, which suggests that the increased mortality risk that CFRD conveys is due to accelerated progression of the patient's underlying lung disease, not due to vascular complications (Stecenko & Moran, 2010). Moreover, the microalbuminuria that we typically associate with microvascular damage to the kidney was only seen among CF patients who had fasting hyperglycemia (Schwarzenberg et al., 2007) (Table 3).

Characteristic	CFRD	DM I	DM II
Age at Onset	18-21 years	< 20 years	>40 years
Prevalence	22% of CFFR population (2% of children, 19% of adolescents, 45-50% over age 30[a])	7% of US population	7% of US population (NB: > 15% of population > 50 years)
Body Habitus	Thin	Normal	Overweight/Obese
Insulin Secretion	Decreased, Release delayed	Absent	Decreased relative to need
Insulin Resistance	Increased or Unchanged	Increased Slightly	Increased Dramatically
Ketoacidosis	No	Yes	No
Microvascular Complications	Yes	Yes	Yes
Macrovascular Complications	Extremely Rare	Yes	Yes
Nutritional Support	**High calorie diet:** (120-150%) of RDA **Fat**: 40% of dietary intake (No restrictions on type) **Protein**: 10-20% of calories, not reduced for nephropathy **Sodium**: > 4 grams per day **Vitamins**: Routine supplementation	**Calories adjusted for goal:** growth, weight maintenance, or loss **Fat Restriction**: <30% of total calories, <10% from saturated fats **Protein**: 10-20% of total calories; reduced for nephropathy **Sodium**: <2.4 grams per day **Vitamin**: Supplementation for diagnosed deficiencies	**Calorie restriction for weight loss** **Fat Restriction**: <30% of total calories, <10% from saturated fats **Protein**: 10-20% of total calories; reduced for nephropathy **Sodium**: <2.4 grams per day **Vitamin**: Supplementation for diagnosed deficiencies
Pharmacologic Therapy	Insulin therapy(currently SOC); oral anti-diabetic agents(controversial)	Insulin replacement; SC synthetic Amylin analogues	Oral antidiabetic agents; Insulin therapy; SC Incretin Mimetic and synthetic Amylin analogues

Legend: CFFR = North American Cystic Fibrosis Foundation Registry; DM I = Diabetes Mellitus Type I; DM II = Diabetes Mellitus Type II ; RDA = recommended daily allowance; SOC = standard of care; SC = subcutaneously administered.

Table 2. A Comparison of Cystic Fibrosis-Related Diabetes Mellitus to Types 1 and 2 Diabetes Mellitus

Glucose Tolerance Catergory	Fasting Serum Glucose (mg/dl)	Two-Hour Oral Glucose Challenge: One-Hour Value (mg/dl)	Two-Hour Oral Glucose Challenge (mg/dl)
Normal Glucose Tolerance	<126	>/= 200	<140
Indeterminate	<126		<140
Impaired Glucose Tolerance	<126		140-199
Impaired Fasting Glucose	100-125		
CFRD *without* Fasting Hyperglcemia (CFRD FH-)	<126		>/= 200
CFRD *with* Fasting Hyperglycemia	>/= 126		>/= 200

Table 3. Cystic Fibrosis-Related Diabetes Mellitus Diagnostic Categories

It is interesting that a subsequent 2008 study comparing microvascular changes found in CF patients to a matched cohort of patients with Type I Diabetes Mellitus (DM1) found that while retinopathy occurred more frequently in DM1, renal disease as measured through microalbuminuria occurred with greater frequency in patients with CFRD. The authors of this study explained this discrepancy in microvascular findings by speculating that other factors, such as deficient CFTR function, chronic inflammation, repeated exposure to nephrotoxic agents, or genetic predispositions may be the cause (van den Berg et al., 2008). While the results of these two studies may appear to be conflicting, a closer analysis reveals that van den Berg's study methodology does not distinguish patients with fasting hyperglycemia from those without; thus, if van den Berg's CFRD population had a preponderance of patients with fasting hyperglycemia, then the results of these two studies may be consistent.

Within the last decade, case reports have emerged suggesting that Nodular Glomerulosclerosis (NGS) in cystic fibrosis patients may mimic the findings of Diabetic Nephropathy (DN) (Westall et al., 2004). Since the histopathology of these cases appears to be misleadingly reminiscent of that seen in Diabetic Nephropathy, we have chosen to discuss these cases in conjunction with our discussion of CFRD-related renal disease. In their case report, Westall's team reports that all three patients had pathologic findings thought consistent with DN, including Kimmelstiel-Wilson Nodules, without any evidence of impaired glucose tolerance. The authors speculate that the Focal and Nodular Glomerulosclerosis observed (e.g. the Kimmelstiel-Wilson nodules) may be an idiopathic occurrence, may be the result of CFTR deficiency or abnormal function, or may be the result of accumulation of toxic molecules. The authors explain that these toxic molecules are generated as the byproduct of an inflammatory process or as a result of oxidative stress. Furthermore, they conjectured that these pathologic findings may be the consequence of undetected episodes of hyperglycemia, which would eventually become more persistent.

In an accompanying editorial to Westall's case series, Krous discusses the implications of Westall's work. In his commentary, Krous does raise the question of whether we should be

routinely screening cystic fibrosis patients for proteinuria, since renal pathology similar to DN has been described, even without evidence of hyperglycemia. Krous also calls for further investigation of the specific pathologic process that leads to the NGS seen in both CF and Diabetes Mellitus. In the end, the only answer that Krous leaves us with is that it may be prudent to screen CF patients for proteinuria (Krous HF, 2004).

3.4 Glomeulonephritis

3.4.1 An introduction to glomerular disease in Cystic Fibrosis

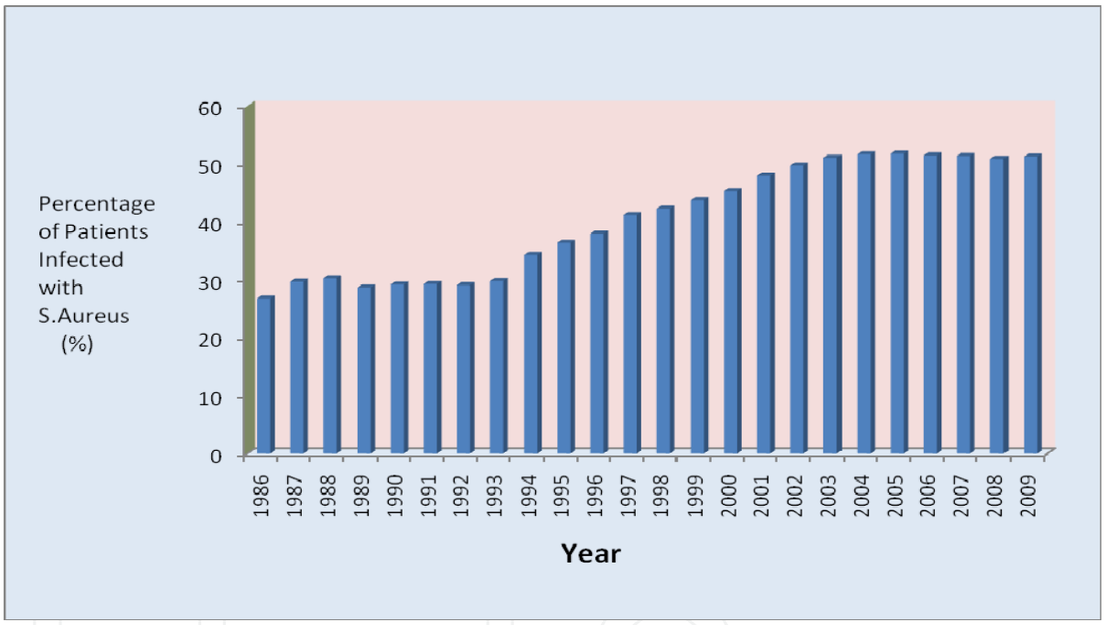
Despite the fact that renal pathology among Cystic Fibrosis patients was described from the time that CF's constellation of symptoms was first delineated, there still remains relatively little written on renal involvement in CF. There are many explanations as to why this may be the case: lack of a clear CF renal disease phenotype, difficulty measuring renal impairment due to inadequacy of SCr-based renal function tests, and, possibly, reluctance of cystic fibrosis center care teams to pursue the presence of renal pathology with potentially intrusive, and possibly invasive testing (Yahiaoui et al., 2009). However, with the aging of this patient population, an increasing number of case reports have suggested that renal disease is part of the CF phenotype. In 1972, Openheimer described the presence of glomerular pathology in autopsied CF patients (Openheimer, 1972). Abramowsky's 1982 study showed that a majority of patients studied not only had evidence of glomerular involvement, but also immunoflourescence findings of immunoglobulin and complement deposition in glomeruli, with localization to the mesangial regions and capillary loops (Abramowsky & Swineheart, 1982). A more contemporary study of thirteen adults with CF and renal disease, who underwent a renal biopsy, revealed that twelve had glomerular lesions (Yahiaoui et al., 2009). Thus, it is clear that, beyond a CF patient's very real risk of experiencing a renal injury as a result of a medication adverse drug reaction or toxicity, Cystic Fibrosis, itself, may be associated with renal pathology. In this section we will discuss the types of glomerular lesions that have been observed and current theories on the development of glomerular pathology in Cystic Fibrosis.

3.4.2 IgA Nephropathy

In Stephens and Rigden's review of renal disease in Cystic Fibrosis, they report that among the glomerulonephritides, IgA Nephropathy is the most frequently reported (Stephens & Rigden, 2002). In a 1999 case series reported by Stirati and colleagues, four out of the five CF patients who underwent a renal biopsy for proteinuria had findings consistent with IgA Nephropathy. It should be noted that the authors do admit that since IgA Nephropathy is a common type of GN in young adults, and the patients in their study ranged in age from twenty-two to thirty years, their findings may be a chance occurrence.

However, another plausible explanation for this association, put forth by the authors is that recurrent bacterial infections result in a robust immune response leading to increased levels of circulating immunoglobulins and immune complexes. These immune-mediating molecules may deposit in the kidney and lead to the histopathology and morbidity observed (Stirati et al., 1999). Interestingly, in Abromowsky and Swinehart's 1982 study, the explanation of chronic bacterial infection leading to a high level of immune activity resulting in glomerular pathology was also raised. Abramowsky and Swinehart conjectured that the proximate cause was chronic pseudomonas aeruginosa infection. However, contemporary immunologic investigations using pseudomonas antiserum did not reveal any antigens in the studied glomeruli.

If chronic pseudomonal infection is not the nidus for this robust immune response, then what is? The answer may actually lie in staphylococcal infection. Staphylococcus epidermitis bacteremia and staphylococcus aureus-asssociated endocarditits have long been known to cause glomerulonephritis. Furthermore, histopathology of staphylococcal-associated GN typically reveals glomerular immune complex deposits containing complement, particularly C3, and immunoglobulins, typically IgG and IgM. These findings are consistent with those described in CF-related Glomerulonephritis, and have even greater significance in light of the fact that staphylococcus remains a common colonizing pathogen (Figure 5), and a major cause of lung infection early in a CF patient's life, typically causing pneumonia before pseudomonas aeruginosa infections become common. Moreover, idiopathic IgA Nephropathy is known to occur within a few days of the patient experiencing an upper respiratory infection. Thus, there appears to be a viable association between staphylococcal colonization and IgA Nephropathy in cystic fibrosis patients (Satoskar et al., 2006).



Source: Cystic Fibrosis Foundation Patient Registry Annual Data Reports, 1986-2009

Fig. 5. Prevalence of Staphylococcus Aureus Infection/Colonization Among Cystic Fibrosis Patients

In a 2006 case series by Satoskar and colleagues, they report eight cases of staphylococcus infection-associated mesangial and/or intracapillary proliferative glomerulonephritis (GN) associated with IgA-laden immune complex deposition. In this study, seven of the eight patients described had infections other than endocarditis, and the eighth suffered from an epidural abscess which resulted in endocarditis (Satoskar et al., 2006). The reason why staphylococcal infections may lead to GN remains unclear. One theory proposed by Satoskar suggests that staphylococcus enterotoxins may behave as superantigens that bind Major Histocompatibility Complex Class II (MHC II) molecules on Antigen-Presenting Cells (APC). This complex of MHC II and enterotoxin then binds to T-cell receptors, resulting in widespread T-cell activation and a surge of cytokine release. These cytokines, in turn,

activate B-cells, which then produce IgA and IgG molecules. These immunoglobulins are then released, resulting in immune complex formation, and eventual deposition in the Kidney. Further elaborating on this mechanism of glomerular pathology, Koyoma's group described a specific staphylococcus aureus envelope antigen as a proximate cause for superantigen formation (Koyoma et al., 2004). Thus, research studying the association between staphylococcal skin and wound infections, as well as idiopathic IgA Nephropathy, may shed some light on the pathologic association between IgA Nephropathy and Cystic Fibrosis.

3.4.3 Membranoproliferative Glomerulonephritis

The occurrence of Membranoproliferative Glomerulonephritis (MPGN) in cystic fibrosis patients is not a new finding. Ambrowsky and Swinehart's 1982 autopsy study of thirty-four Cystic Fibrosis patients showed eighteen patients who had evidence of immune complex deposition in the Kidney, and, of those, sixteen had evidence of mesangial proliferation with two also having evidence of membranoproliferative histopathology. Thus, this autopsy study would suggest that MPGN is a major cause of renal disease in the CF patient.

However, more contemporary reviews of the subject do not find nor discuss MPGN in the CF patient (Stephens & Rigden, 2002; Yahiaoui et al., 2009). Indeed, the only recent report of this association was published by Soriano and colleagues in 2008 (Soriano et al., 2008). In this paper, the authors discuss multiple, plausible explanations for the natural history of renal disease in CF. One mechanism proposed, the Factor H Deficiency Model, is based on the observation that genetic knockout mice who are deficient in alternate complement pathway Factor H not only develop MPGN, but also experience higher mortality with pseudomonas aeruginosa infections than factor H sufficient mice. Furthermore, factor H deficiency has been found to lead to aberrant activation of Complement Factor C3 and higher serum levels of various chemokines and cytokines (Soriano et al., 2008). This pathologic explanation is supported by the work of Wisnieski's group, who reported in 1985 that mortality among their cohort of one hundred thirty-nine patients was highly associated with decreased alternate complement pathway function and the presence of circulating immune complexes (Wisnieski et al., 1985).

Separate from the immunologic explanation proposed above, a plausible link between Cystic Fibrosis and Membranoproliferative Glomerulonephritis lies in the function of Toll-like Receptors (TLR), which are part of the Innate Immune System. This family of receptor proteins is responsible for recognizing recurring structures on pathogens, including single-stranded DNA, lipopolysaccharides, and RNA molecules. Upon recognition of a structure known to be associated with a pathogen, the TLR initiates inflammatory and immune responses whose end result is meant to be destruction of the pathogen. By modulating immune responses, including regulating helper T-cell immunologic responses, aberrant TLR function is conjectured to lead to kidney inflammation and glomerulonephritis (Smith & Alpers, 2005). A 2004 study by Muir and colleagues showed that TLR-2 expression was up-regulated in the lungs of CF patients (Muir et al., 2004). Moreover, in 2006, Shuto and colleagues suggested that this TLR-2 up-regulation and prolonged activation was critical to the pathogenesis of CF lung disease (Shuto et al., 2006). Separate from the Factor H Deficiency or the TLR models for the development of glomerulonephritis in cystic fibrosis patients, the presence of staphylococcal superantigens has been conjectured to lead to MPGN in CF patients (Soriano et al., 2008).

3.4.4 Treatment

To date, there has been very little written on the treatment of glomerulonephritis in CF patients. One available case series details the diagnosis and treatment of two adult patients. In this article, it is reported that one of the patients experienced an improvement in his renal disease to the point where he could safely forgo hemodialysis after undergoing a double-lung transplant and starting his anti-rejection regimen (Soriano et al., 2008). This would suggest that the conventional immunosuppressant therapy typically employed in the treatment of glomerulonephritis would be appropriate in this population as well. However, given the known pharmacokinetic and pharmacodynamic intricacies of the CF patient, further study is warranted.

4. Conclusion

Cystic Fibrosis is a disease in evolution. Through wide-spread newborn screening programs, patients are diagnosed earlier. Through an aggressive, world-wide therapy development network, new and revolutionary treatments for the manifestations of Cystic Fibrosis are shepherded from the lab bench to the patient's home. As we develop a better understanding of how genetic mutation translates into phenotypic dysfunction and symptoms, we will be able to regulate and modify protein function to ameliorate the symptoms of Cystic Fibrosis. However, with these revolutionary changes to how patients experience the morbidity of Cystic Fibrosis, and with the aging of the CF population, new manifestations of CF may emerge. Kidney disease, particularly glomerulonephritis, may be one of the more plausible morbidities to afflict CF patients with growing regularity in the future. Thus, we must stay ever vigilant, and not become complacent that we have a complete understanding of this disease process. Cystic Fibrosis is no longer a disease of children. We must, therefore, continue to broaden our understanding of what it means to be an adult with Cystic Fibrosis.

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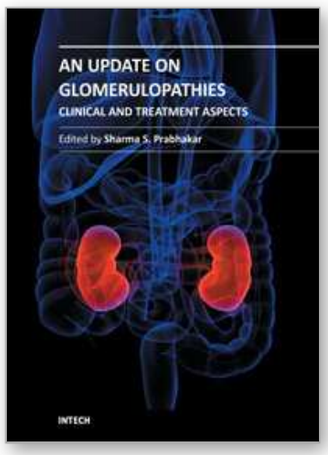

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