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REVIEW

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Cystic fibrosis lung disease: genetic influences, microbial interactions, and radiological assessment

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Abstract Cystic fibrosis (CF) is a multiorgan disease caused by mutation of the CF transmembrane conductance regulator (CFTR) gene. Obstructive lung disease is the predominant cause of morbidity and mortality; thus, most efforts to improve outcomes are directed toward slowing or halting lung-disease progression. Current therapies, such as mucolytics, airway clearance techniques, bronchodilators, and antibiotics, aim to suppress airway inflammation and the processes that stimulate it, namely, retention and infection of mucus plaques at the airway surface. New approaches to therapy that aim to ameliorate specific CFTR mutations or mutational classes by restoring normal expression or function are being investigated. Because of its sensitivity in detecting changes associated with early airway obstruction and regional lung disease, high-resolution CT (HRCT) complements pulmonary function testing in defining disease natural history and measuring response to both conventional and experimental therapies. In this review, perspectives on the genetics and microbiology of CF provide a context for understanding the increasing importance of HRCT and other imaging techniques in assessing CF therapies.

Keywords Cystic fibrosis · Genetics · Microbiology · Current therapies · Chest radiograph · High-resolution CT · Functional imaging

Introduction

Pediatric radiologists in Europe and North America are frequently called upon to assess patients with cystic fibrosis (CF), a fatal autosomal recessive disorder of the respiratory tract, gastrointestinal tract, male reproductive tract, and sweat glands that is caused by mutation of the CF transmembrane conductance regulator (CFTR) gene. CF is most common in Caucasian populations, with an incidence of about 1 in 2,500, but it occurs in all ethnic and racial populations [1]. The rate of neonatal diagnosis has increased, as CF screening has been added to newborn metabolic disease panels in some places, with 11.3% of new diagnoses suggested by positive newborn screening in 2003 [2]. As of October 2004, ten states in the USA had implemented CF newborn screening for all infants or for selected populations, and two other states had programs in the planning stage. However, newborn screening for CF has been deferred in many places, in part because such screening requires significant genetic counseling resources. Thus, most patients are still diagnosed based on clinical features related to gastrointestinal, nutritional, electrolyte, and respiratory pathophysiology (Table 1).

Several diagnostic tests with excellent specificity are available to evaluate patients in whom CF is suspected. Despite the advent of CFTR genotyping methods that are now widely available for molecular diagnosis, mea-

surement of sweat chloride concentrations (pilocarpine iontophoresis) remains a more sensitive test for definitive diagnosis of CF in most cases [1]. Measurement of transepithelial potential difference at the nasal mucosa (nasal PD) can detect ''sweat-test negative'' cases of mild CF, but is more laborious than sweat testing. Interestingly, some individuals with isolated recurrent pancreatitis [3, 4], isolated obstructive azoospermia caused by congenital absence of the vas deferens [5], isolated idiopathic bronchiectasis [6], or chronic rhinosinusitis [7], in whom sweat chloride and nasal PD are typically normal, have been found to have CFTR mutations, leading to the concept of CFTR-related disorders as a broader diagnostic category [8].

Identification of the CFTR gene in 1989 opened the way to a more detailed genetic understanding of and potentially a cure for this disorder [9–11]. However, this ultimate goal of CF research, the development of therapeutic methods to correct or bypass CF gene defects and thus to restore normal lifespan, has remained elusive. Current therapies are aimed at replacing deficient pancreatic enzymes and fat-soluble vitamins, promoting clearance of airway secretions, and suppressing chronic respiratory infection. One reflection of progress made in the treatment of CF is that the prognostic factor most closely associated with disease survival is the year of a patient's birth [12]. Median survival in this disorder, now about 33 years, has been improving since the 1950s, when pancreatic enzyme replacement therapy was introduced, with a significant increment in survival after the introduction of the current generation of antipseudomonal antibiotics in 1979 [2]. The implementation of comprehensive multidisciplinary CF care centers in population centers where the disease is relatively common has been another major factor contributing to improved survival. At present, the predominant cause of death is chronic respiratory failure caused by severe obstructive pulmonary disease, combined with progressive injury and destruction of airways and lung parenchyma. The incidence of pulmonary hypertension and cor pulmonale complicating late-stage CF lung disease has decreased significantly, probably because of more aggressive use of supplemental oxygen and more effective treatments for pulmonary exacerbations.

In addition to efforts to develop alternative strategies to ameliorate specific types of CFTR defects, investigators are developing new strategies to treat chronic CF lung infections, which are the primary cause of morbidity and mortality in this disorder. However, emerging microbial pathogens as well as the better-known CF bacterial opportunists challenge the current antibiotic formulary. Advances in diagnostic radiology are facilitating clinical research efforts, but the marked variations in CF lung disease severity and pattern pose significant challenges. This review summarizes recent progress in the molecular genetics, microbiology, and diagnostic imaging of CF and highlights directions in CF clinical research.

Table 1 Clinical features of cystic fibrosis and other CFTR-related disorders

Gastrointestinal tract, nutrition, and electrolytes
Meconium ileus and/or distal intestinal obstructive syndrome
Rectal prolapse
Malabsorption, steatorrhea caused by pancreatic insufficiency
Failure to thrive because of protein-calorie malnutrition
Hemolytic anemia and/or excessive bruising caused by fat-soluble vitamin deficiencies
Peripheral edema (secondary to hypoalbuminemia)
Neonatal biliary obstruction (might mimic biliary atresia)
Focal or multilobular biliary cirrhosis
Recurrent pancreatitis
Hyponatremic hypochloremic dehydration (salt depletion)
Salty taste of skin
Respiratory tract
Chronic nasal drainage and/or sinus disease
Nasal polyps
Acute or recurrent bacterial tracheitis during infancy
Chronic cough and sputum production
Chronic or recurrent wheeze, air trapping, and tachypnea
Delayed resolution of viral lower respiratory infections
Isolation of typical CF pathogens from throat or sputum culture, including (but not limited to) *Staphylococcus aureus*, nontypable *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and/or *Burkholderia cepacia*
Chronic obstructive lung disease
Bronchiectasis and other radiographic abnormalities
Allergic bronchopulmonary aspergillosis
Digital clubbing caused by chronic suppurative lung disease
Male reproductive tract
Obstructive azoospermia caused by congenital absence of vas deferens

Genetics of CF lung disease

The CFTR gene is located on the long arm of human chromosome 7 and spans approximately 250 kb of DNA sequence (Fig. 1). The 27 exons contained within its RNA transcript are spliced together to create a 6.5-kb mRNA, encoding a transmembrane protein of 1,480 amino acids that functions both as a chloride channel and as a regulator of other ion channels, such as the epithelium sodium channel [8]. CFTR is processed through the endoplasmic reticulum and Golgi apparatus prior to transport to the apical surface of various epithelial cells.

More than 1,100 disease-associated CFTR alleles and almost 200 additional sequence variations have been identified [13]. Most CFTR disease alleles have three or fewer altered nucleotides, reflecting predominantly nonsense, frameshift, single-codon deletion, missense, or splice-site mutations. Deletion of the amino acid phenylalanine at codon 508 (ΔF508) is the most common CFTR disease allele in Caucasians, representing approximately 70% of disease alleles. Accordingly, approximately 50% of Caucasian CF patients have a ΔF508 homozygous genotype. Diagnostic molecular testing for sets of more common alleles can detect two disease-associated alleles in about 85–90% of affected Caucasian individuals [14]. It is important to keep in mind when interpreting the results of such testing that approximately 1% of affected individuals will not have either of their CFTR disease alleles identified by these methods.

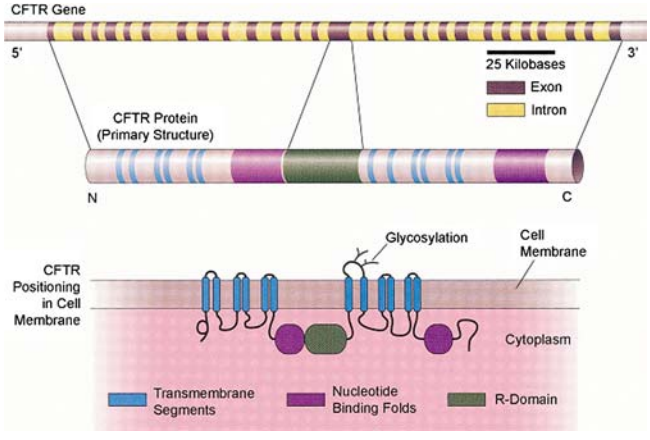

Fig. 1 The cystic fibrosis (*CF*) transmembrane conductance regulator (*CFTR*) gene and predicted protein domains. In humans the gene (*top*) is located on the long arm of chromosome 7 and contains 27 exons encoding a protein (*middle*) with a molecular weight of approximately 165 kDa after glycosylation. The CFTR protein consists of two sets of transmembrane domains, joined by a nucleotide-binding domain and a regulatory domain in tandem; a second nucleotide-binding domain follows the second transmembrane domain (*bottom*). CFTR is an ATP-binding cassette protein, and as such both the triphosphate and cyclic monophosphate forms of adenosine, as well as protein kinases A and C, regulate its activity through nucleotide binding and phosphorylation. CFTR functions both as an anion channel with selectivity for chloride and bicarbonate and as a regulator of other epithelial membrane channels. (Reprinted by permission from Ref. [180])

Classification of CFTR disease alleles and association with clinical phenotypes

CFTR disease alleles have been grouped into five classes [15] according to the functional effects of the mutation on the synthesis and maturation of CFTR protein (Fig. 2). Class 1 alleles have nonsense or frameshift

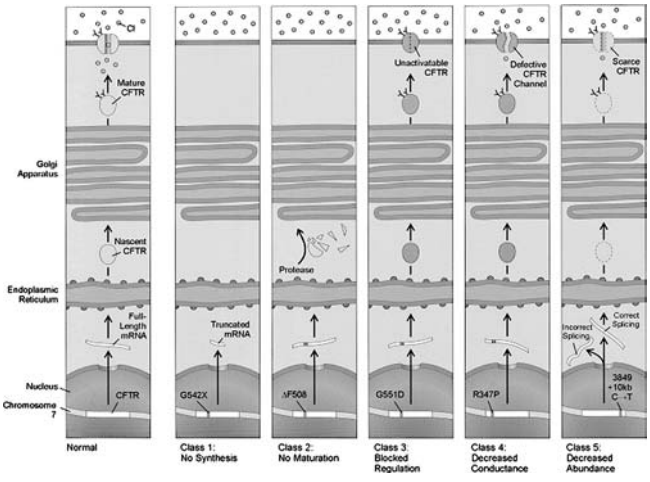

Fig. 2 Normal protein maturation and functional classification of CFTR mutant alleles. In its wild-type form (*left-most panel*), CFTR messenger RNA is transcribed in the nucleus and exported to the cytoplasm, where it is translated into protein at the endoplasmic reticulum. It then transits to the Golgi apparatus, where it is glycosylated prior to export of the mature protein to the plasma membrane. At the cell surface it functions as a chloride channel and also as a regulator of other membrane channels. Class 1 alleles (*second panel*), such as one with a nonsense mutation in codon 542 that normally encodes glycine (G542X allele), contain premature stop codons that result in truncated RNA messages. Class 2 alleles (*third panel*), such as the common ΔF508 allele (see text), result in misfolded proteins that are degraded by a quality-control mechanism termed the "proteosome" within the endoplasmic reticulum. Class 3 alleles (*fourth panel*) encode proteins that reach the cell surface, but contain missense mutations that render them incapable of being activated; replacement of glycine by aspartic acid at codon 551 (G551D allele) exemplifies this class. Class 4 alleles (*fifth panel*) reach the surface and can be activated but with decreased channel conductance and possibly also abnormal regulation of other membrane channels; they are exemplified by replacement of arginine by proline at codon 347 (R347P allele). Class 5 alleles (*right-most panel*), such as a single nucleotide transition from cytosine to thymine within a splice acceptor site (3849 + 10 kb C → T allele), result in decreased abundance of normal CFTR because of increased incorrect splicing of messenger RNA. Class 5 alleles are associated with a wide range of disease severity, including milder phenotypes, because of variability in the efficiency of RNA splicing between individuals as well as allele-specific differences of effect on splicing. (Reprinted by permission from Ref.[180])

mutations that result in unstable mRNA and no synthesis of CFTR protein. Class 2 alleles, exemplified by the ΔF508 mutation, encode misfolded CFTR proteins that are trapped and degraded in the endoplasmic reticulum. Class 3 alleles encode normally processed proteins with missense mutations that render CFTR incapable of being activated. Class 4 alleles encode activatable proteins with missense mutations that decrease chloride conductance. Class 5 alleles have mutations that lead to aberrant mRNA splicing or protein maturation and, thus, decreased cell surface abundance of CFTR proteins with normal channel activity. Thus, at the molecular level, class 1, 2, and 3 alleles are generally associated with absolute deficiency of CFTR activity, whereas class 4 and some class 5 alleles confer residual CFTR activity.

This classification scheme has proved useful for comparing different CFTR genotypes and determining epidemiological associations of specific CF clinical phenotypes [16]. People who have two class 1, 2, or 3 alleles usually display the full range of CF clinical features, including lung disease and pancreatic insufficiency, while those with at least one class 4 or 5 allele tend to have milder forms of CFTR deficiency, ranging from pancreatic-sufficient CF to atypical CF with much milder lung disease to isolated congenital absence of the vas deferens (CAVD) with minimal or no lung disease in males or complete absence of signs or symptoms in females (Table 2). These epidemiological patterns reflect the high rate of genetic penetrance of class 1, 2, and 3 CFTR alleles, especially with respect to their gastrointestinal, nutritional, and reproductive consequences. They also reflect the potential for non-Mendelian inheritance of CFTR-related disorders such as CAVD; moreover, because the spectrum of alleles associated with this disorder only partly overlaps that associated with classic CF, targeted CFTR mutation analysis for this disorder is less informative [17].

Secondary variations in the CFTR gene can modulate the clinical phenotype of certain mutations. For example, substitution of histidine for arginine at codon 117 (R117H) is a class 4 allele that is associated with variable length of a polythymidine tract at the intron 8 splice acceptor. When the R117H allele contains five thymidines at the intron 8 splice acceptor (the "5T" form of the acceptor site), it is associated with pancreatic-sufficient CF, whereas when it contains seven thymidines (7T), it is associated with much milder "atypical" CF lung disease or only CAVD [18–20]. The effect of the 5T mutation is itself influenced by the variable length of adjacent sequences upstream of the acceptor splice site [21, 22]. The 5T mutation in intron 8 can even influence the clinical phenotype in the absence of another mutation on the same allele, as illustrated by the association of the wild-type (5T) allele with CAVD and, in rare instances, with atypical CF lung disease [23]. Thus, wild type (5T) should probably be considered a class 5 allele. That the allele frequencies of R117H (7T) and wild type (5T) in the non-CF population approach or exceed the frequencies of these alleles in CF patients [24, 25] reflects the low rate of genetic penetrance of these alleles with respect to CF lung disease and indicates that some pedigrees with atypical forms of CFTR deficiency can exhibit non-Mendelian inheritance patterns.

Modifier genes as modulators of CF lung phenotype

Some ΔF508 homozygous individuals develop severe obstructive lung disease during the first and second decades of life despite maximal medical therapy, while others with the same genotype have little or no obstructive lung disease despite minimal therapy during

Table 2 Examples of disease-associated CFTR alleles

CFTR allele	Allele class	Usual clinical status (when compounded with a severe CFTR allele[a])	Allele frequency in Caucasians[b]		
			General population[c]	CF	CAVD
G542X (9T)	1	Pancreatic-insufficient CF	0.001	0.023	0.003
ΔF508 (9T)	2	Pancreatic-insufficient CF	0.012—0.016	0.694	0.20
G551D (7T)	3	Pancreatic-insufficient CF	0.001	0.022	0.01
R117H (5T)	4	Pancreatic-sufficient CF	0.0001	0.004	ND
R117H (7T)	4	CAVD or carrier	0.002—0.003	0.003	0.04
A455E (9T)	5	Pancreatic-sufficient CF	ND	0.001	ND
3849 + 10kbC → T	5	Pancreatic-sufficient CF	ND	0.007	ND
WT (5T)	5	CAVD or carrier	0.042	[d]	0.19
Other alleles[e]	1—5	Variable	0.002—0.006	0.247	0.55
WT (7T or 9T)	Wild-type	Carrier	0.935	[e]	[e]

[a]Severe CFTR allele is defined as a class 1, 2, or 3 allele.
[b]CFTR allele frequency data from [14, 16–18, 21, 22, 24, 25].
[c]Carrier frequency = 2× allele frequency.
[d]Case reports indicate that the WT (5T) allele might be associated with atypical CF, but allele frequency has not been determined.
[e]"Other alleles" includes alleles for which sequencing failed to reveal a CFTR mutation in people with CF or CAVD (i.e., apparent WT)

these years and experience significant progression only in their third or fourth decades. Considered longitudinally, this marked variability of lung phenotype among ΔF508 homozygotes reflects significant differences in the rate of disease progression. Although such differences might be attributed in part to environmental factors such as exposure to smoke [26–28] or opportunistic pathogens (as discussed in the next section), it has become clear that genes distinct from the CFTR locus also contribute to these phenotypic differences [29]. The difficulty has been defining the additional genetic loci (the so-called "modifier genes") that are responsible for modulating the typical course of disease. Most investigators have used a candidate gene approach, with negative or ambiguous studies more prevalent than positive ones [30, 31]. Genes encoding mediators of inflammation and host defense such as tumor necrosis factor (TNF) alpha and mannose binding lectin (MBL) have been implicated in studies of limited population samples [32, 33]. However, a much larger multicenter study with a more powerful statistical genetic design has cast doubt upon putative TNF and MBL associations and instead implicated variants in the transforming growth factor beta (TGFβ) gene as influencing disease severity, albeit in a minority of ΔF508 homozygotes [34]. It would appear that additional modifier genes remain to be identified. However, there could be relatively few loci, such as TGFβ, that represent "common" modifier genes for CF lung phenotype; instead, this phenotype might be influenced predominantly by a panoply of unique or "private" modifier gene variants that could be difficult to discover with the current genomic epidemiology toolkit.

Treatment strategies for specific CFTR allele types

A major goal of genetic disease research is the development of gene therapy, which could be applied in CF to correct the CFTR defect through delivery of a functionally normal gene to affected tissues. The identification and cloning of the gene for CF in 1989 raised hopes that this disease would quickly yield to the strategies of molecular medicine, and enabled investigators to attempt to deliver CFTR and other genes to respiratory epithelial cells using a variety of viral and non-viral vectors. Unfortunately, barriers such as mucosal immunity, limited selection of epithelial receptors, and gene silencing have hindered persistent or repeatable CFTR expression and phenotypic correction with these strategies. While some have continued efforts to overcome these obstacles, others have pursued alternative approaches targeted to specific CFTR allele types [35].

For example, aminoglycosides such as gentamicin bind to ribosomes and, for mutant mRNA molecules containing premature stop codons, hinder translational termination by promoting amino acid addition at such codons (translational "read-through") in a fraction of translation products. This suppression of translational termination might be of therapeutic benefit for genetic disease caused by nonsense mutations such as the CFTR Class 1 allele G542X [36–38]. Interestingly, gentamicin is a more potent suppressor of nonsense mutations than tobramycin, an aminoglycoside commonly used to treat CF lung infection. Clinical trials to evaluate the molecular efficacy of gentamicin, amikacin, and related compounds in affected individuals with CFTR nonsense mutations are now underway.

Because the ΔF508 mutation is present in at least heterozygous form in most people with CF, intensive pharmacological efforts are underway to identify more stable, potent, and effective lead compounds for the correction and potentiation of ΔF508 CFTR. Misfolded proteins such as that produced by the CFTR ΔF508 allele tend to be retained in the endoplasmic reticulum and delivered to the proteasome complex for degradation. Treatments such as reduced temperature and addition of glycerol or phenylbutyrate to the growth medium of ΔF508-carrying CF cells decrease the rate of protein misfolding, leading to increased apical translocation and some residual CFTR function. Phenylbutyrate is being tested for treatment of humans with this CFTR class 2 allele [39]; preliminary studies have shown that phenylbutyrate might partially restore nasal ion transport in CF patients. In addition, ΔF508 as well as class 4 alleles with missense mutations that impair chloride channel activity might respond to strategies aimed to potentiate chloride conductance. Genistein, a tyrosine kinase inhibitor, and other flavonoids have been shown to augment the chloride conductance of ΔF508 CFTR [40].

Microbiology and treatment of CF lung disease

CFTR deficiency and susceptibility to lung infection

Several models have been proposed to explain how CFTR deficiency alters airway epithelial cell function to increase susceptibility to lung infection. These models include altered epithelial surfaces that lead to increased bacterial adherence [41], exaggerated airway cell inflammatory responses [42], and altered epithelial ion transport that leads to inhibition of host antimicrobial peptides [43, 44] or impairment of mucociliary clearance of secretions [45]. Accumulating experimental evidence supports the last of these as the primary process linking CFTR deficiency to lung infection. Sophisticated epithelial cell culture methods have been used to demonstrate that impermeability to chloride ions and excessive absorption of sodium ions, attributable to CFTR deficiency and concomitant dysregulation of the epithelial sodium channel (ENaC), result in dehydration of the

periciliary liquid (PCL) and overriding mucus layer that normally coat the airway surface [45]. Depletion of PCL leads to dysfunction of cilia and increased adhesion of thickened mucus plaques at the epithelial surface (Fig. 3). Retention of mucus plaques might represent the sentinel event predisposing people with CF to airway infection by opportunistic bacterial pathogens. Hypoxic conditions can develop within these plaques that promote anaerobic growth and metabolism of CF pathogens [46]. Although CFTR-deficient mice do not develop a lower-airway mucus retention phenotype, investigators have recently simulated this phenotype by creating transgenic mice that overexpress a component of murine ENaC [47]. Lower-airway epithelial cells from these mice, like those from CF patients, display excessive sodium absorption and PCL depletion. Additional striking similarities to the human CF phenotype include the neonatal but not prenatal onset of airway secretory abnormalities, and impaired clearance of inhaled or instilled bacteria from the airway. Most strikingly, this work has suggested that retention of airway secretions, in and of itself, can be sufficient to trigger airway inflammation even in the absence of infection, lending support to earlier observations suggesting that airway inflammation, predominated by chronic infiltration of neutrophils, might precede infection in early CF [42, 48].

Microbial ecology and host response in CF lung infection

Over time, the airways of almost all people with CF become infected with one or more opportunistic bacterial pathogens [2]. In the first 5 years of life, the predominant organisms are *S. aureus* and *H. influenzae*, although some infants become infected with *P. aeruginosa* within weeks of birth. During later childhood, *P. aeruginosa* becomes the predominant organism, with 80% of CF patients infected by late teenage years (Fig. 4). Additional non-fermenting gram-negative bacilli such as *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* can also be identified. Infections with organisms classified within the *Burkholderia cepacia* complex also occur, with genomovar III (*Burkholderia cenocepacia*) associated with epidemic spread [49–51] and increased mortality [52, 53]. Non-tuberculous mycobacteria represent another category of less common CF pathogens. Species that can be found in CF secretions include *Mycobacterium avium-intracellulare* and *Mycobacterium chelonae* (some strains of which are designated *Mycobacterium abscessus*) [54, 55]; the latter is especially difficult to treat because of resistance and can be associated with relatively rapid progression of bronchiectasis and peripheral infiltrates on high-resolution chest CT (HRCT).

In the setting of persistent CF airway infection, *P. aeruginosa* displays adaptations, both physiological and mutational, that are distinct from those seen in acute infection. For example, *P. aeruginosa* can grow as a facultative anaerobe, as has been demonstrated in vitro [56] and in mucus plaques produced in CF cell culture models [46]. Moreover, most if not all CF pathogens have the capacity to form biofilms, a physiological adaptation in which communities or colonies of relatively slow-growing bacteria form multicellular structures, some elaborate, that promote bacterial survival under adverse environmental circumstances [57]. Biofilms, and slow-growing organisms in general, are notorious for resistance to antibiotics [57–63] and to endogenous antibacterial mechanisms such as phagocytosis [64, 65]. It has been proposed that *P. aeruginosa* biofilms within CF airway secretions serve as an antibiotic-resistant reservoir of metabolically quiescent bacterial cells from which actively dividing cell populations periodically emerge and bloom, promoting increased inflammatory responses at the epithelial surface on an intermittent basis that are clinically manifest as acute pulmonary exacerbations [66, 67]. To date, however, acute exacerbation onset has not been found to correlate with an obvious or consistent alteration in bacterial density or phenotype, and although sputum bacterial density can be significantly decreased by antibiotic therapy [68, 69], the onset and resolution of such exacerbations are still defined largely in terms of relatively nonspecific clinical features such as the patient's activity level, appetite, nutritional status, cough frequency, sputum production, and airway obstruction as measured by spirometry [70].

In CF as well as other chronic lung infections, mucoid forms of *P. aeruginosa* tend to emerge over time (Fig. 5). Mucoidy is a mutational adaptation that reflects increased secretion of alginate, a bacterial exopolysaccharide that serves as a protective barrier against both cellular and humoral components of host defense [71]. Mucoidy might enhance biofilm formation, although recent data suggest that *P. aeruginosa* biofilm formation primarily depends on production of secreted bacterial polysaccharides other than alginate [72–74]. Mucoidy is associated with inactivating mutations in a *P. aeruginosa* regulatory gene, *mucA*, that normally represses alginate synthesis [75, 76]. Motility, another phenotype that *mucA* regulates, is often decreased or completely lost in CF airway isolates of *P. aeruginosa* [77]. Additional adaptive mutations can increase production of certain pigments involved in scavenging nutrients such as iron [78, 79], and they can alter the bacterial envelope in ways that actually increase susceptibility to innate immune factors, such as complement [80, 81], but deter adaptive immune responses such as those mediated by opsonic antibodies [82]. Overall, these and other adaptations of *P. aeruginosa* contribute to its establishment and persistence in airway secretions, an environment that does not ordinarily promote bacterial growth.

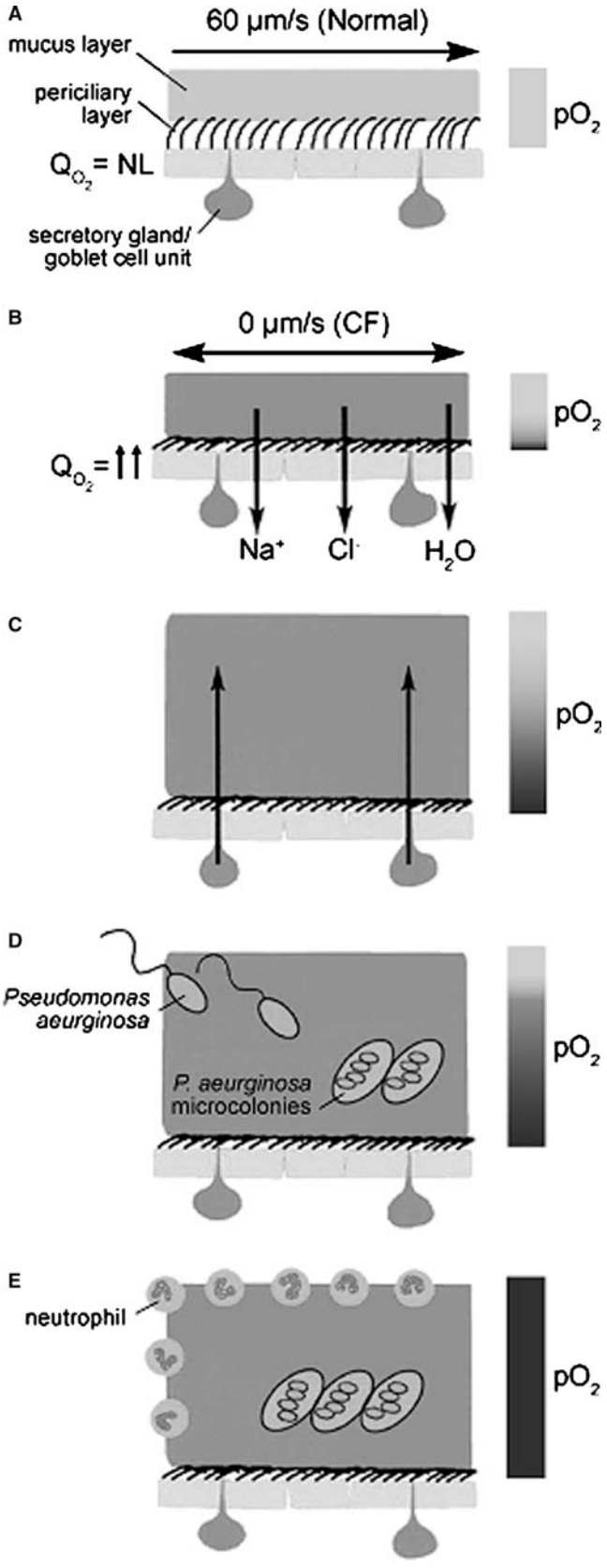

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Fig. 3 Proposed sequence of pathogenic steps leading to periciliary liquid (*PCL*) depletion, mucus plaque retention, and chronic *P. aeruginosa* infection within the CF airway. *Panel A* depicts proper regulation of PCL depth by intact epithelial ion transport mechanisms (secretion of chloride, inhibition of sodium absorption), resulting in normal mucus layer translocation under the influence of ciliary action, and ready diffusion of molecular oxygen to the epithelial surface. In the setting of CFTR deficiency (*panel B*), chloride is inappropriately absorbed (instead of being secreted via CFTR), and sodium is hyperabsorbed (because of dysregulation of epithelial sodium channels), which leads to decreased depth of PCL, impaired ciliary function, and adhesion of the overriding mucus layer to the epithelial surface. The mucus layer itself becomes dehydrated and more viscous (i.e., less fluid), resulting in impaired oxygen diffusion. In addition, mucus retention can promote inflammatory responses at the airway surface. As submucosal glands continue to secrete additional mucus (*panel C*), adherent mucus plaques thicken, further impeding oxygen diffusion. These retained mucus plaques offer a potential growth environment for opportunistic pathogens such as *P. aeruginosa* (*panel D*) that form biofilmlike microcolonies within it. *P. aeruginosa*, environmental forms of which are highly motile, is capable of anaerobic metabolism and might actually intensify hypoxic conditions at the airway surface. It also further stimulates inflammatory responses, including recruitment of neutrophils (*panel E*) and intensified mucus secretion. However, in this favorable milieu *P. aeruginosa* is often able to resist the phagocytic and other antimicrobial activities of neutrophils and other host defense mechanisms to establish a chronic airway infection. (Reprinted by permission from Ref. [1] as adapted from Ref. [46])

CF airways can be colonized with yeast such as *Candida albicans*, *Candida lusitaniae*, and *Candida glabrata*, which are usually regarded as innocuous commensals, but can be associated with candidal

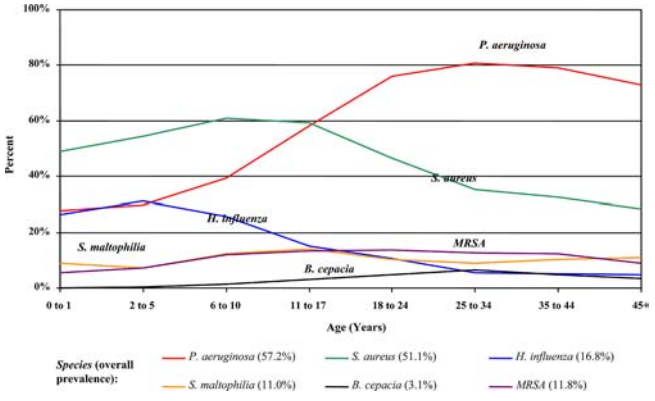

Fig. 4 Age-specific prevalence of CF pathogens, based on data reported to the US Cystic Fibrosis Foundation Patient Registry in 2003. Overall percentage of patients (all ages) who had at least one respiratory tract culture (sputum, bronchoalveolar lavage, or oropharyngeal or nasal swab) performed in 2003 that was positive for the following organisms: *P. aeruginosa* (*red line*), 57.2%; *S. aureus* (*green line*), 51.1%; *Haemophilus influenzae* (*blue line*), 16.8%; *Stenotrophomonas maltophilia* (*yellow line*), 11.0%; *B. cepacia* complex (*black line*), 3.1%; MRSA (*violet line*), 11.8%. Because some patients have more than one organism, the percentages indicated sum to >100%. (Reprinted by permission from Ref. [2])

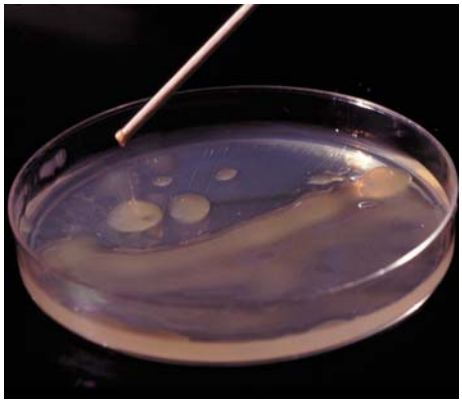

Fig. 5 Mucoid CF strain of *P. aeruginosa*. Mucoid strains secrete vast quantities of a viscous extracellular matrix containing alginate, a bacterial polysaccharide. Retraction of the tip of a wooden applicator from the surface of a single colony on a nutrient agar plate is used here to demonstrate the viscosity of this material. Such colonies are predominantly composed of exopolysaccharide, with much less cellular content than nonmucoid bacterial colonies of similar size. (Photograph courtesy of Adam Griffith and Jane L. Burns, M.D.)

fungemia via seeding of central venous catheters in patients on broad-spectrum antibiotic coverage for gram-negative organisms. In addition, airway secretions can harbor filamentious fungi such as *Scedosporium apiospermum* or *Aspergillus fumigatus*. In some patients who become colonized with the latter, a syndrome of fungal antigen sensitization termed "allergic bronchopulmonary aspergillosis" (ABPA) can develop [83]. This chronic allergic condition is associated with a constellation of immunologic findings, including peripheral blood eosinophilia, immediate cutaneous reactivity to *A. fumigatus* antigens, elevated total serum IgE (>1,000 IU/ml), and elevated *Aspergillus*-specific serum IgG and IgE. Patients often have scattered pulmonary infiltrates (sometimes only appreciated on chest CT), with little or no clinical response to antibacterial therapy, and might experience relatively rapid progression of central bronchiectasis. It is unclear whether more severe bacterial lung infection and the usual concomitant increase in antibiotic exposure represent risk factors for *A. fumigatus* acquisition and ABPA in CF patients [84, 85]; however, this condition does seem to correlate with overall allergic susceptibility (i.e., atopy) in affected individuals [86].

Additional host and environmental factors likely influence the onset and progression of CF lung infection. The human lung possesses a complex array of host defenses [87], including physical barriers (mucus), clearance mechanisms (cough reflex, mucociliary elevator), innate immunity (inflammatory cells and mediators), and adaptive immunity (e.g., lymphocytes). Defective mucociliary clearance and excessive airway inflammation have been strongly implicated in the pathogenesis of CF lung infection [87], but it is difficult to ascertain whether the degree of inflammation or mucociliary impairment corresponds to the probability of airway infection or severity of lung disease. People with CF appear to have normal adaptive immunity and to produce antipseudomonal antibodies appropriately. Titers of these antibodies correlate with duration and intensity of infection [88–90]. Some data suggest that antibodies specific for *P. aeruginosa* secreted exopolysaccharide (i.e., alginate) are associated with milder lung disease and a more indolent course [91]. Exposure to smoke, a powerful stimulus for mucus secretion, can exacerbate CF lung disease [26–28]. Although plausible, whether such secondary host and environmental factors modulate the long-term progression of CF lung disease has not been established unambiguously.

Treatment and control of CF lung infection

Antibiotics are the mainstay of therapy for CF lung infection. There is considerable variation in the style of CF lung infection treatment among CF clinicians worldwide [92, 93]. In the United States, many clinicians endorse an approach that has been termed "reactive therapy," i.e., initiation or escalation of antibiotics only in response to clinical findings consistent with pulmonary exacerbation, with discontinuation or minimization of antibiotics between acute symptomatic episodes. Although clinical experience strongly suggests that antibiotic therapy is an effective intervention for CF pulmonary exacerbation, few randomized controlled trials supporting this view have been published [69, 94], and one placebo-controlled trial failed to demonstrate that a 2-week course of intravenous ceftazidime was more effective than placebo [95], although this study might not have been adequately powered. In contrast, many clinicians in Europe and elsewhere practice what has been termed "pre-emptive therapy," in which patients are treated aggressively for their first positive culture for *P. aeruginosa*, and then are maintained on suppressive antibiotic regimens, by daily inhalation or intermittent intravenous administration (i.e., scheduled 2–3-week courses on a quarterly basis). The effectiveness of the latter approach has been evaluated only in relatively small trials, some of which have relied on historical rather than concurrent controls; moreover, a meta-analysis of these studies failed to demonstrate that such elective therapy was more effective than symptomatic treatment [96]. Conversely, the concern that continuous antibiotic use could result in more rapid emergence of bacterial resistance and diminished long-term antibiotic efficacy has not been rigorously examined, and in fact, clinicians in the USA often treat chronically infected patients with suppressive regimens of inhaled and/or oral antibiotics. Differences in

approach might be diminishing, especially in light of studies conducted in both Europe and the USA suggesting that aggressive antibiotic treatment of young children with first culture positive for *P. aeruginosa* can eradicate, at least transiently, early infection [97–103]. A large US multicenter randomized controlled trial termed EPIC (for Early Pseudomonas Infection Control) is now underway to test the long-term safety and clinical efficacy of this approach.

The choice of antibiotics to treat the predominant early CF pathogens (*H. influenzae* and methicillin-susceptible *S. aureus*) is relatively straightforward, with first- or second-generation cephalosporins, or amoxicillin in combination with the β-lactamase inhibitor clavulanic acid, as the most commonly used agents [1]. However, deciding whether to implement prophylactic or suppressive regimens for these organisms is less straightforward because of concerns that chronic suppressive antibiotics might hasten the acquisition of nonfermenting gram-negative rods (NF-GNR: *P. aeruginosa*, *S. maltophilia*, *A. xylosoxidans*, and *B. cepacia* complex), the treatment of which is more problematic [104, 105]. NF-GNR tend to be intrinsically resistant to most commonly used antibiotics and to develop high-level resistance readily upon exposure to any single agent at achievable serum concentrations [106]. It is, therefore, prudent to cover NF-GNR with combinations of at least two agents of different therapeutic classes, usually based on the results of antibiotic-susceptibility testing. Moreover, the goal of treating established NF-GNR infection is microbial suppression, because eradication is uncommon, and when achieved, usually transient [101, 102, 107]. First-line intravenous therapy for pulmonary exacerbations of *P. aeruginosa* endobronchial infection with susceptible organisms typically consists of an antipseudomonal beta-lactam such as ceftazidime in combination with an aminoglycoside such as tobramycin. The advent of inhaled antibiotics (e.g., aerosolized tobramycin or colistin) has enhanced the prevention and treatment of exacerbations, leading to less-frequent need for intravenous antibiotics [92, 108]. Inhaled antibiotics might also enhance the treatment of *S. maltophilia*, *A. xylosoxidans*, and *B. cepacia* complex, although their use for these organisms has not been rigorously evaluated. Because the nonpseudomonal NF-GNR are often resistant to beta-lactams and/or aminoglycosides, agents such as doxycycline and/or trimethoprim-sulfamethoxazole, to which they are more susceptible, are usually added to intravenous antibiotic regimens for these organisms. Interestingly, the efficacy of selecting antibiotics for CF airway infection based on susceptibility testing has not been evaluated prospectively, and the only retrospective study that has examined this issue failed to demonstrate a relationship between susceptibility results and clinical response [109]. Because of concerns that conventional antibiotic susceptibility testing poorly simulates the interaction of antibiotic combinations with slowly growing bacteria in vivo, alternative approaches to determining antibiotic susceptibility have been developed, including synergy testing [110–112] and biofilm-susceptibility testing [112, 113].

The US CF Foundation recently announced more rigorous infection-control guidelines aimed at decreasing the risk of transmission of respiratory pathogens among CF patients [114]. The vast majority of CF patients are infected with unique environmental isolates, but there are reports of patient-to-patient transmission of MRSA, *B. cepacia* complex, and to a lesser extent, multidrug-resistant *P. aeruginosa*. Some endemic or epidemic strains of multi- or pan-resistant organisms have been associated with poor outcomes and death and have spread rapidly through clinic populations. Moreover, differences in the age-adjusted prevalence of *P. aeruginosa* colonization between CF centers in the same geographic region have been offered as evidence that social interaction among patients increases the rate of *P. aeruginosa* acquisition [115] and used to justify more stringent infection-control guidelines. A focus is to minimize spread of these pathogens within the inpatient and outpatient environments, including the cleaning of hospital and clinic equipment. Standard precautions should be applied to all CF patients to contain their secretions. The revised guidelines recommend standard plus transmission-based precautions (contact, droplet, airborne) for patients with known *B. cepacia* complex, MRSA, and multidrug-resistant *P. aeruginosa* . For such patients, health care workers should wear gloves and a gown. Masks or eye protection are only necessary for patients unable to control secretions that might result in sprays during procedures. After procedures, the surfaces of equipment and examination rooms should be cleaned according to hospital policy with an EPA-registered hospital-grade disinfectant or detergent. It is also recommended that different CF patients (especially those with *B. cepacia* complex, MRSA, or multidrug-resistant *P. aeruginosa*) not be scheduled in succession for examinations or procedures that require exposure to a single workspace or piece of equipment.

Infection control is an emotional issue for patients and families, many of whom believe that the revised guidelines indicate that the hospital staff needs to adhere to stringent infection-control practices. Members of the CF team work with patients and families to balance quality-of-life considerations with anxiety associated with the idea of patient-to-patient spread of respiratory pathogens. Evidence suggests that such transmission is relatively rare.

There is general agreement regarding the use of nonantibiotic respiratory therapies for CF airway infection. Airway clearance techniques, which assist the patient in daily efforts to expectorate copious viscous

airway secretions, are among the most important interventions available [116–118]. These techniques include chest percussion with postural drainage, vibratory chest physiotherapy, oscillatory positive expiratory pressure (Flutter valve), and high-frequency chest-wall oscillation (vest therapy). They are augmented by the administration of beta-agonist bronchodilators such as albuterol, and mucolytics such as recombinant human DNase. The efficacy of the latter, an enzyme that decreases sputum viscosity by hydrolyzing neutrophil-derived DNA within airway secretions, has been demonstrated in a number of clinical contexts [119–123]. There is also support for the strategy of thinning CF airway secretions and enhancing mucus clearance through the administration of inhaled hypertonic saline, which might work by promoting rehydration of the airway surface [124, 125]; however, the data regarding this potential therapy are somewhat limited [126]. It should be noted that anti-cholinergic bronchodilators such as ipratroprium are contraindicated in CF because of the potential to worsen the dehydration and inspissation of airway secretions. Inhaled corticosteroids [127, 128], oral corticosteroids [129], and oral nonsteroidal anti-inflammatory medications [130] are sometimes prescribed with the goal of decreasing airway inflammation. However, many clinicians harbor concerns about the long-term safety and efficacy of systemic corticosteroids [131], and the effectiveness of inhaled corticosteroids has not been assessed by an adequately powered randomized controlled trial.

Imaging of CF lung disease: recent advances

The interpretation of the chest radiograph continues to be a key part of the evaluation and management of the patient with CF. Serial radiographs can be useful in detecting disease progression, and radiographs taken during disease exacerbations can detect complications and help direct therapy. The CF Foundation recommends chest radiographs every 2 years as part of standard care [132] and annually for patients with frequent infections or declining pulmonary function testing (PFTs) and during pulmonary exacerbations. Recent reviews of the chest radiographic imaging of CF and its complications are available [133–135]. This review will focus on recent imaging studies that provide insight into the pathophysiology and management of CF. During the last decade the approach to CF medical imaging has moved from descriptive evaluations to controlled population-based studies.

Chest radiography

From the earliest days of CF clinical care, physicians have used scoring systems to monitor patients for changes in clinical status and to evaluate treatment regimens. The chest radiograph has been incorporated in almost all of the major scoring systems, which use a variety of methods to assess the distribution and severity of linear opacities, hyperinflation, atelectasis, cysts, nodules, and larger opacities [136–141]. In a recent study, six chest radiographic scoring systems were compared by correlating clinical parameters of 30 CF patients (mean age 13.8 years ± 2.7 years) with chest radiographic scores determined by two independent observers [142]. For each scoring system, interobserver variability was low and showed good limits of agreement. All six systems had good correlation with pulmonary function tests, especially with the forced expiratory volume at 1 s (FEV_1) percent predicted, and with pulmonary exacerbation rates. The authors of this study favored the Crispin-Norman scoring system for its simplicity and low interobserver variability. In a study using the Wisconsin scoring system [139], Koscik et al. [143] urged that scorers be carefully selected and trained, and the researchers noted that pulmonologists and radiologists might differ significantly in scoring abnormalities [143].

In a review of more than 3,000 serial chest radiographs in 230 CF patients, Cleveland and coworkers [144] evaluated the Brasfield scoring system and demonstrated good intra- and interobserver variability and reliability. In this system, the severity of air trapping, linear markings, nodular cystic lesions, large lesions, and overall severity are each evaluated on a scale of 1–5, with 1 representing the most severe change and 5 representing the absence of pathologic change, so that the best achievable score is 25. This work demonstrated a gradual decline in radiographic score with age (Fig. 6).

Computed tomography

Although several publications have demonstrated greater sensitivity and specificity of CT than chest radiography in evaluating adults and children with CF [145–148], the method was used infrequently until the advent of faster spiral and multidetector machines that produced high-resolution thin-section images of the lungs with less motion [149], and changes in clinical practice that increased demand for more sensitive markers of disease [147, 148]. The clear superiority of CT in detecting disease in asymptomatic patients with normal radiographs and normal lung function [150] has alerted the clinical community to the potential power of this method in detecting early and mild disease and as a potential outcome surrogate in therapeutic trials.

The advent of sub 1-s scanners and isovoxel imaging coupled with physiologically synchronized ventilation now affords high-resolution imaging of the lung in infants and young children. Meticulous attention to the technical aspects of CT is essential to achieve the best and safest results. Low-dose techniques for single- and

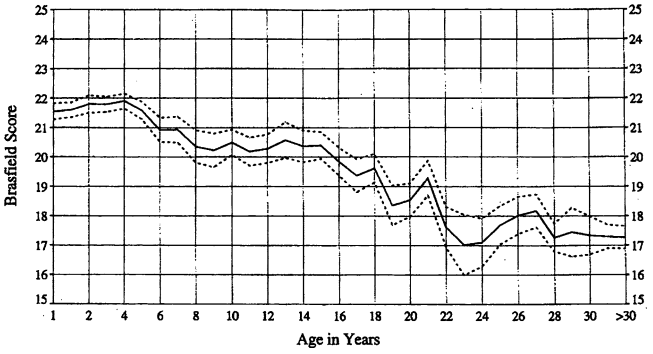

Fig. 6 Relationship between age and chest radiographic abnormalities in a CF population. Analysis of 3,038 chest radiographs and 230 patients with CF shows increasing severity of chest radiographic changes with age, as demonstrated by a reduction in mean Brasfield score [144]. The highest score of 22 corresponds to a normal chest. *Dotted lines* are ±2 SEM for each 1-year interval. (Reprinted by permission from Ref. [144])

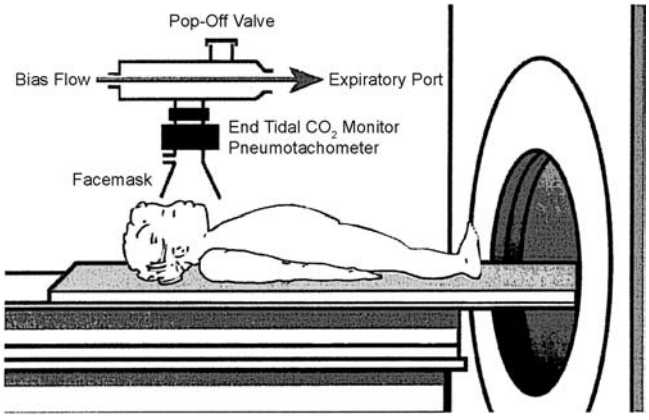

Fig. 7 Schematic of method to synchronize CT image acquisition with controlled ventilation of an infant or young child. Typically, one operator provides positive-pressure ventilation utilizing a face mask with a bias-flow device, while another applies gentle cricoid pressure to prevent overdistention of esophagus, monitors vital signs, and signals for CT scanning to begin. (Reprinted by permission from Ref. [156])

multidetector chest CT and HRCT are mandatory [151–154]. The use of breast shielding is recommended [155].

Investigators at Columbus Children's Hospital [156–158] and Lucille Packard Children's Hospital at Stanford University [159, 160] have successfully developed methods to standardize and control lung volume during chest CT. The Columbus group has focused on children younger than 5 years and has developed a controlled ventilation CT technique using a bias-flow device with face mask (Fig. 7) to obtain images at full inspiration (near-total lung capacity) and expiration in sedated patients (Fig. 8). Their method demonstrated a clear superiority of controlled ventilation HRCT in detecting bronchial abnormalities and air trapping in 20 young patients with CF compared with images obtained during quiet tidal breathing [161]. The Stanford group has developed a spirometric system to trigger the CT scanner at predetermined and standardized lung volumes [159]. This method utilizes an electron-beam scanner that is triggered by a portable spirometer at six transverse levels at near-total lung capacity and near-residual volume. These workers have developed software to measure air trapping in mild CF patients in an automated fashion [162]. Using this approach, the amount of air trapping measured by CT in 25 patients with mild CF and 10 age-matched controls was compared with PFT results. Air-trapping defect size was the best discriminator between patients and control subjects, and air trapping in mild CF cases did not correlate with global PFT results.

HRCT scoring systems

Just as different approaches to quantify severity based on chest radiographic findings have been devised (as discussed above), a number of scoring systems have been developed to quantify the results of HRCT in CF patients. The earliest system was devised by Bhalla et al. [147], is still frequently used, and scores results on a scale of 0 (absent) to 3 (severe), based on nine features (the first three factors count the number of lung segments involved): extent of bronchiectasis, extent of mucus plugging, extent of abscesses or sacculations, severity of bronchiectasis, degree of peribronchial thickening, bullae, emphysema, collapse, and consolidation. Several modifications of the Bhalla system, or alternative HRCT scoring systems, have been developed [146, 160, 163–168]. These scoring systems are compared in Table 3.

Comparison of five of these thin-section CT scoring systems [147, 163, 164, 167, 168] showed all of them to have good interobserver and intraobserver reproducibility and reliability and correlate with PFT results [169]. Accurate and reproducible HRCT scoring systems that can measure mild and localized CF lung disease are complementary to PFTs as an outcome surrogate [167, 170, 171].

Early detection of lung abnormalities

A retrospective autopsy study of CF infants published in 1976 showed that bronchiectasis and mucus plugging of airways can be present as early as the first 4 months of life [172]. Although such autopsy studies probably reflect selection bias toward more severe disease [171], such cases illustrate the importance of detecting and treating early changes before they become irreversible. The first imaging study to demonstrate structural abnormalities in the airways of infants and young children with CF [173] showed significantly greater mean airway wall thickness and mean airway luminal diameter in CF children ($n = 34$; mean age 2.4 years ± 1.4 years) than in

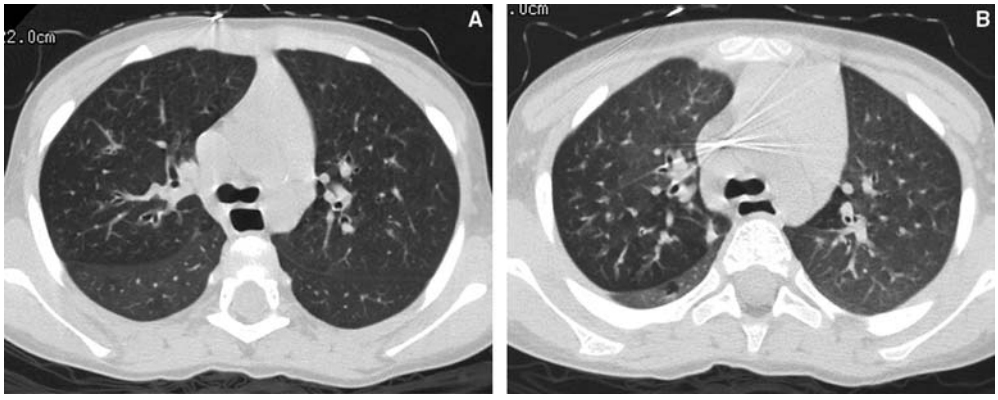

Fig. 8 The controlled ventilation technique as applied to CT imaging of the chest of a 2-year-old with CF. Inspiratory (**A**) and expiratory (**B**) views demonstrate excellent spatial resolution in this sedated young child. Mild airway thickening is noted in several airways. The expiratory view demonstrates air trapping in the posterior segment of the right upper lobe. (Reproduced courtesy of Frederick R. Long, M.D.)

controls ($n = 20$; mean age 1.8 years ± 1.4 years). These investigators measured multiple short-axis round airway/vessel pairs on four HRCT sections obtained at full inflation using a controlled ventilation technique. They found that the ratio of airway-to-vessel luminal diameter increased significantly with age in CF patients compared to controls.

Correlation of HRCT and pulmonary function testing

Several groups have studied the relationships between structural changes demonstrated on HRCT and global assessment of lung function in children old enough to have reliable PFT results. Helbich et al. [164] used a modification of the Bhalla scoring system to evaluate a group of 107 CF patients, each with two HRCTs performed 4 months to 4 years apart, and determined that morphologic changes in the lung were more conspicuous in patients with longer intervals between CT scans (i.e., greater than 18 months). The HRCT scores correlated best with PFT results such as FEV_1 and maximum expiratory flow, suggesting that imaging more sensitively detects changes in central airways than in peripheral airways. A prospective study of 47 CF patients by Oikonomou et al. [165] using a modification of the Bhalla system correlated loss of FEV_1 in patients from 6 to 23 years of age. The prevalence of HRCT features most commonly found included bronchiectasis (98%), atelectasis/consolidation (81%), bronchial wall thickening (77%), tree-in-bud appearance (74%), and mucus plugging (72%). The HRCT scores that correlated best with FEV_1 were bronchial wall thickening, tree-in-bud sign, extent of mucus plugging, and atelectasis/consolidation (Fig. 9). Bronchiectasis, the most prevalent feature noted, appeared to have little correlation with FEV_1, despite the fact that this pathologic change generally involves large- and medium-size airways and represents a potential source of increased airway secre-

Table 3 CF HRCT scoring systems (*AT* included air trapping in assessment, *BP* anatomical bronchopulmonary segments – 18 total (10 right, 8 left), *R* each lung divided into superior and inferior halves, *SL*/*sl* CT at six levels (SL) in "six" lobes (sl) with lingula of left upper lobe considered a separate lobe, *Z* each lung divided in upper, middle, and lower regions and then each region further divided into anterior and posterior areas)

Original system: first author (year) Modification of system: first author (year)	Reference	No. of patients	Age range (*M* mean, *m* median)	Clinical status	No. of HRCT parameters assessed	Regional weighting
Bhalla (1991)	[147]	14	5–42	Not stated	Nine	BP
Santamaria (1998)	[163]	30	6.75–24($M = 13.9$, $m = 13.2$)	Not stated	Eleven (AT)	BP
Helbich (1999)	[164]	107	2.8–32.3 ($M = 14.5 \pm 7.3$)	Stable / not infected	Ten	BP
Robinson (2001)	[160]	17	9–33($M = 17.3 \pm 7.2$)	During acute exacerbation	Six (AT)	SL/sl
Oikonomou (2002)	[165]	47	6.42–23.3($M = 13.6 \pm 4.8$)	During remission	Eleven	SL/sl and BP
Nathanson (1991)	[146]	28	0.5–35($M = 14.1 \pm 1.7$)	Not stated	Two	Z
Maffessanti (1996)	[166]	36	5–28($M = 13$)	Stable	Seven	R
Brody (1999)	[167]	8	5–16($M = 12.7$, $m = 13.3$)	During acute exacerbation	Seven	SL/sl
Castile (2000)	[168]	31	0.2–5.5($M = 2.3 \pm 1.3$)	Not stated	Eight (AT)	R

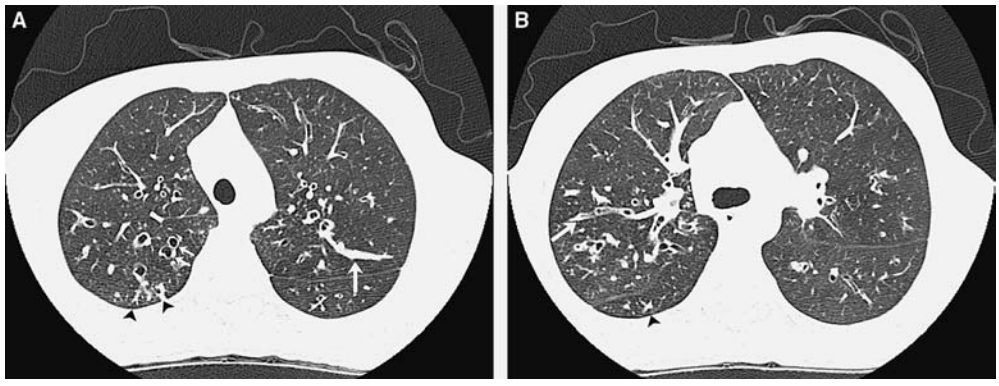

Fig. 9 HRCT images of the chest of an 11-year-old boy homozygous for the CFTR ΔF508 allele who has moderate obstructive lung disease. **A, B** These 1-mm images (2 cm apart) illustrate multiple bronchiectatic airways (*small arrows*), diffuse bronchial wall thickening, mucus plugging (*large arrows*) and tree-in-bud appearance in peripheral airway (*black arrowheads*)

tions and thus obstruction. This illustrates the important concept that lung function testing is not sensitive to regional airway disease and that CT will detect such regional disease well before any change in lung function is detected.

Dakin and colleagues [174] used a modified Bhalla scoring system that included assessment of mosaic perfusion pattern and extent of centrilobular nodules to assess the correlation between HRCT scores on the one hand and PFT results and sputum inflammatory markers on the other. The HRCT score correlated well with FEV_1 and with forced vital capacity, but it correlated only poorly with sputum inflammatory markers.

HRCT as an outcome surrogate in the evaluation of acute exacerbations and response to treatment of CF

Several recent studies have evaluated HRCT in the detection of disease exacerbations and in following response of CF to treatment.

Previously, only PFTs had been deemed a reliable outcome measure in CF clinical trials. The hypothesis that HRCT might correlate with short-term responses to therapy was retrospectively examined in eight patients for whom HRCT was performed at admission for CF pulmonary exacerbation and after hospital discharge ($n = 15$) [167]. The morphologic severity of CF changes was assessed by a modified Maffessanti HRCT scoring system. The study did not assess parallel changes in PFT results. The improvement in HRCT scores was statistically significant for 13 of 15 admissions. Admission and discharge scans demonstrated significant interval improvement in mucus plugging and peribronchial thickening. This is the first report to suggest that HRCT might be an important additional outcome surrogate in CF.

The ability of HRCT scoring systems and PFT results to detect progression of lung damage was studied in 48 CF children (mean age 11.05 years ± 3.3 years) with two HRCT and PFT assessments 2 years apart. All HRCTs worsened significantly, while PFT remained unchanged or improved. The HRCT parameters that significantly worsened were mucus plugging and the severity, extent, and peripheral extension of bronchiectasis [150]. The authors noted substantial structural lung damage in some children with normal lung function and suggested HRCT might be a useful outcome measure.

The relative insensitivity of chest radiography to detect CF pulmonary exacerbations prompted Shah et al. [148] to evaluate the utility of HRCT in evaluating reversibility of acute changes. Symptomatic ($n = 19$) and asymptomatic ($n = 8$) patients were prospectively evaluated by PFTs and HRCT utilizing a modified Bhalla scoring system. HRCT scores accurately reflected severity of disease and correlated with clinical improvement as determined by PFTs. They found that the presence of air-fluid levels, albeit rare, was the only HRCT finding specifically associated with CF pulmonary exacerbations.

Seventeen CF patients ranging in age from 9 to 33 years (mean age 17.3 years), prospectively studied before and after therapy for a pulmonary exacerbation utilizing spirometer-triggered HRCT and PFTs, demonstrated no interval change in markers thought to be irreversible, i.e., bronchiectasis and bronchial wall thickening. The total HRCT score and aspects of the score considered reversible, i.e., mucus plugging, atelectasis/consolidation, and air trapping, did significantly improve after therapy and correlated with slow vital capacity, FEV_1, and forced vital capacity. The mucus plugging subcomponent of the HRCT score demonstrated the greatest change [160].

Two recent prospective randomized clinical trials evaluating the efficacy of aerosolized DNase (Pulmozyme) incorporated HRCT in the experimental design. A study of 12 patients (mean age, 3.1 years) that used the Santamaria modification of the Bhalla scoring system demonstrated significant improvement in HRCT scores following DNase administration, despite the lack of difference in chest radiographic scores between the two groups [123]. In the second study, 25 children were randomized to daily treatment with either dornase alpha (Pulmozyme) or aerosolized normal saline and evaluated at 0, 3, and 12 months using PFTs, global HRCT

scoring, and composite scoring that incorporated both PFTs and HRCT [170]. The treatment effect noted at 12 months was 35.4% improvement measured by the composite score, compared with 13% improvement by the mean forced expiratory flow during middle half of FVC (FEF_{25-75}) and 6.2% improvement by the total global HRCT score. These two clinical trials strongly suggest an important role for HRCT as an outcome measure in evaluation of CF and its therapy.

Functional imaging in cystic fibrosis

Chest radiography and HRCT have primarily been used to detect and follow morphologic parameters. By scanning at two different lung volumes with faster CT techniques, air trapping can be detected and small airway disease inferred (Fig. 10). These techniques have been useful in the study of asthma [175] and have recently been used to study CF [161, 176]. Air trapping can be readily detected in infants and young children, utilizing a controlled ventilation chest CT technique [157]. Bonnel and coworkers [176] have recently examined ten children (mean age 11.7 years, range 7–17 years) with mild CF lung disease and have compared these patients with normal age-matched controls (mean 11.7 years, range 7–17 years). Utilizing an automated air trapping analysis method that measured expiratory lung density and the percent of segmented lung that demonstrated air trapping on expiration, the authors found that all CF patients had significantly lower lung density and significantly higher percent air trapping than was noted in controls. These measures better discriminated differences between the two groups than did PFT results.

Radionuclide and magnetic resonance methods have been infrequently used in the evaluation of CF patients. Three recent studies illustrate the potential of these methods in functional assessment. HRCT scores were compared to regional pulmonary perfusion scores derived from single-photon emission CT (SPECT) in eight young adult patients with mild-to-moderate CF [177]. Although morphologic changes depicted on HRCT correlated well with reduced perfusion on SPECT imaging in areas of severe or minimal disease, SPECT perfusion imaging was more sensitive in detecting mild-to-moderate disease areas.

Routine krypton ventilation scanning has been a component of CF clinical care of young children (younger than 6 years) at the Royal Brompton Hospital in London for the last 15 years. In a report of three separate studies [178], these workers concluded that ventilation scanning was a simple, noninvasive technique that augmented the clinical examination and chest radiograph, providing additional information useful in modifying clinical management.

The use of combined hyperpolarized ^{3}He and conventional proton MR imaging was explored in four young adult CF patients with moderate-to-severe lung disease [179]. The inhaled ^{3}He provides high signal intensity in the air spaces and can detect abnormalities in ventilation. This preliminary work demonstrated both extensive ventilation abnormalities and morphologic changes in their four patients.

The future of imaging in CF research

In conclusion, improved understanding of CF genetics and cell biology has led to innovations such as allele-specific strategies to augment the function of defective CFTR genes. Despite the hope that such approaches offer, the treatment of CF lung infection and its complications has advanced only modestly in the past 10 years. The short-term beneficial effects of new therapies such as inhaled DNase and inhaled tobramycin on airway obstruction and infection have been significant but individually mild, and their long-term effects on the trajectory of lung disease progression are not yet known. Because radically improving this trajectory will depend on initiating therapies as early in life as possible, the efforts of investigators are increasingly focused on early intervention trials. Despite its expense, these investigators are increasingly embracing HRCT as a means of

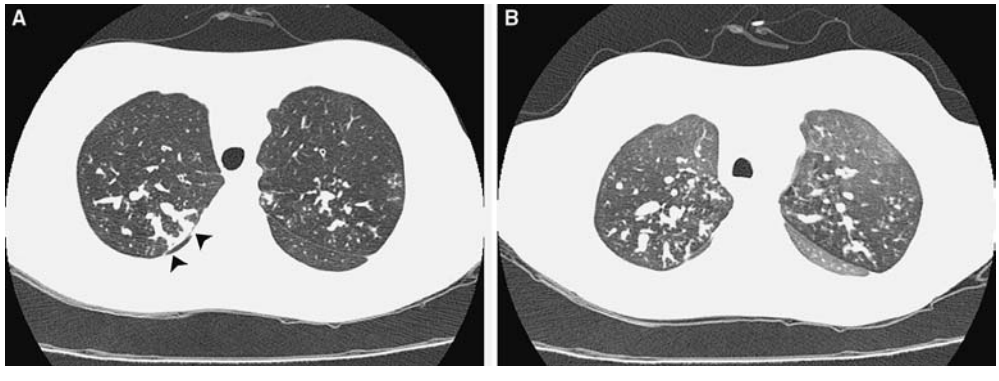

Fig. 10 Demonstration of air trapping by high-speed chest CT. The patient was an 8-year-old girl with a cough who was referred for evaluation of possible bronchiectasis. Inspiratory (**A**) and expiratory (**B**) views demonstrate mucus plugging in multiple medium and small airways, tree-in-bud appearance (*arrowheads*) and patchy air trapping in the mid-portion of both upper lobes

measuring the effects of early intervention, because conventional methods that measure air flow and lung volumes (i.e., PFTs) usually fail to detect the regionally heterogeneous airway obstruction that typifies early CF lung disease. The future development of hybrid imaging strategies that combine results from HRCT and functional imaging may provide even more sensitive and robust outcome measures for the evaluation of early CF intervention.

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