ABSTRACT OF ORIGINAL ARTICLE. This landmark article represents the first report of *Pseudomonas aeruginosa* as a significant clinical pathogen in patients with cystic fibrosis (CF). The authors summarize the case histories of four consecutive patients with CF admitted to a Chicago pediatric teaching hospital. In all four, *P aeruginosa* was the predominant organism cultured from tracheobronchial secretions. The histories were remarkably similar. The patients (two male, two female) were very young, ranging from 14 months to 5 years of age, and had previously been diagnosed with “pancreatic fibrosis” based on the absence of pancreatic digestive enzymes. The four patients had received pancreatic enzyme replacement (pancreatin) and prolonged antibiotics prophylaxis. The antibiotic regimens consisted of a variety of oral antibiotics, including sulfonamides, penicillin, aureomycin, and zephiran, as well as aerosol polymixin, prescribed as treatments for *Staphylococcus aureus* tracheobronchial infections.

The patients presented with acute respiratory distress and were diagnosed as having diffuse bronchopneumonia based on physical examination and chest radiography. Treatment consisted of intramuscular streptomycin (or terramycin) and penicillin. Repeated bronchial lavage was attempted to clear airway secretions. The two female patients did not respond to therapy and died within hours. The two males responded briefly, but subsequently died at 8 weeks and 1 year after initial culture of *P aeruginosa*. Similar postmortem findings in all patients included pancreatic fibrosis, suppurative bronchitis, multiple pulmonary abscesses, and bronchiectasis.

In their discussion, the authors emphasize several salient features of CF pulmonary disease. First, they raise the potential role of prolonged antimicrobial therapy in altering tracheobronchial flora. *S aureus*, the predominant pathogen in all initial descriptions of the illness, was being eliminated by antistaphylococcal antibiotic therapy. In its place, emerging *P aeruginosa*. This phenomenon of shifting bacterial flora had been reported recently in other illnesses, but not in CF. Second, the authors address the importance of *P aeruginosa* as an emerging opportunistic infection in the tracheobronchial tree, noting rapid development of antibiotic resistance attributable to its ability to “develop genetic mutations” and alter its “morphologic appearance”. Third and most important, the authors challenge the pediatric community to “critically examine” the clinical recommendation for prolonged antibiotic prophylaxis. Realizing the effectiveness of this regimen against *S aureus*, they suggested that physicians also weigh the risk of emergence of resistant strains of *P aeruginosa*. They recommended, “Effective antibiotics should be employed judiciously and changed when specifically indicated based upon cultures of tracheobronchial secretions. To minimize the appearance of resistant strains, combinations of two antibiotics having different mechanisms of action are desirable.”

**COMMENTARY**

When the authors reported their four case reports of *Pseudomonas aeruginosa* in 1951, did they understand the impact that this pathogen would have on patients with cystic fibrosis (CF)? At that time, CF had only been described as a clinical disease of the pancreas and lung for 13 years, and its genetic inheritance only understood at a rudimentary level. The median life span was ~5 years. Pancreatic enzyme replacement and antibiotic therapy were only palliative. *Staphylococcus aureus*, the major pathogen colonizing patients’ airways, led to overwhelming pneumonia and death in infancy. Early CF clinicians advocated liberal use of antistaphylococcal antibiotics in a desperate attempt to control the rapidly progressive bronchopulmonary disease. In this landmark article, Garrard et al, raise concern that prolonged antibiotic usage may be “altering the flora of the tracheobronchial tree”. They note that *P aeruginosa*, previously regarded as a “relatively harmless contaminant,” had become an in-

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creasingly important opportunistic infection with an “enlarging chemical and antibiotic armamentarium.”

Forty-seven years later, *P. aeruginosa* remains the most prevalent pathogen colonizing patients with CF worldwide and a major contributing factor to the morbidity and mortality of this illness. In the United States, ~60% of patients are chronically colonized with this pathogen.10 The CF lung is sterile at birth, but 23% of infants are colonized by 1 year of age, and almost 50% by school age (1996 CFF National Data Registry). *S. aureus* still remains the second most common pathogen, colonizing one third of patients throughout their lifetime. Yet, it is *P. aeruginosa* that is clearly associated with progressive obstructive lung disease and increased respiratory morbidity. For example, 45% of patients with normal lung function (FEV1 > 90%) are colonized with *P. aeruginosa*, whereas 87% of patients with severe disease (FEV1 < 40%) are colonized (1996 CFF National Data Registry). Is *P. aeruginosa* truly pathogenic or merely an epiphenomenon associated with an underlying progressive lung disease? Although *P. aeruginosa* infections remain localized to the endobronchial tree without systemic spread, there are several lines of evidence that *P. aeruginosa* is a significant pulmonary pathogen. First, chronic colonization is associated with an intense antibody response,11 suggestive of invasive disease. Second, appropriate antipseudomonal therapy is associated with improved pulmonary function and simultaneous decline in bacterial burden in the airway.12 Finally, patients colonized with *P. aeruginosa* have a shortened median survival even when correcting for genotype. Patients who have never been *P. aeruginosa*-colonized have a median survival of 36 years, whereas colonized individuals have a current survival of 27 years (CFF National Data Registry). By contrast, presence of neither *S. aureus* nor *Haemophilus influenzae* impacts on survival.

The cost of chronic *P. aeruginosa* infection to patients with CF is enormous in terms of medical care and lost days from school and work. More than half of all patients with CF with *P. aeruginosa* require intravenous (IV) antipseudomonal antibiotics annually. In the United States alone in 1996, these patients received >84 000 days of IV antibiotics in hospital and 34 000 days of home IV therapy (1996 CFF National Data Registry).

Were the authors correct that *P. aeruginosa* infection is an iatrogenic complication of oral prophylactic antibiotics? The selective force of antistaphylococcal antibiotics is likely a contributing factor. A large placebo-controlled prospective study comparing continuous antistaphylococcal antibiotics with intermittent therapy (placebo)13 in young healthy patients with CF showed that continuous therapy resulted in an increased incidence of *P. aeruginosa* colonization. At the end of the 7-year study, the group receiving continuous antibiotics had an *S. aureus* prevalence of 6.0% and a *P. aeruginosa* of 25.6% compared with a prevalence in the placebo group of 30.4% for *S. aureus* and 13.5% for *P. aeruginosa*. There appeared to be no difference in pulmonary function between groups. This explanation, however, may be too simplistic. With our current knowledge of the molecular basis of CF, we understand that chronic colonization with *P. aeruginosa* is a complex interaction between the pathogen and the unique environment of the CF lung. As we unravel this interrelationship, we will likely find a long-term therapeutic solution.

CF is caused by mutations in a single gene on chromosome 7 that encodes the CF transmembrane conductance regulator protein (CFTR).14 This protein has multiple functions that regulate salt and water balance across epithelial cells. The net effect appears to be altered hydration and salt content of the airway surface fluid (ASF) bathing the apical surface of these cells. CFTR also may impact on intracellular functions such as sulfation and sialylation of glycolipids that reside on the cell surface. There are several hypotheses regarding the relationship of dysfunctional CFTR to *P. aeruginosa* colonization of the airway. First, ASF contains salt-sensitive antimicrobial peptides that are an important first line of defense for bacterial pathogens. These peptides appear to be inactivated in the high salt content associated with CF ASF cells in vitro.15 The decreased sialylation of glycolipid on the cell surface of CF cells is associated with increased adherence by *P. aeruginosa*.16 Increased *P. aeruginosa* adherence also has been observed with buccal mucosa cells,17 where fibronectin, a glycoprotein that normally coats the buccal cells, is depleted. Thus, *P. aeruginosa* is able to take up residence in the respiratory tract.

What evolves subsequently is a unique host–pathogen interaction allowing coexistence, often for years, but eventually resulting in destruction of the CF airways. *P. aeruginosa*, an aerobic Gram-negative pathogen, is well suited to the moist environment of the respiratory tract. Once colonized, the pathogen is almost never eradicated and, in fact, patients with CF may harbor the same genetic strain throughout their life.18 Yet, this bacteria undergoes a characteristic morphologic change that is advantageous to its persistence. The majority of *P. aeruginosa* becomes mucoid because of production of a mucoid exopolysaccharide encasing the bacteria and forming microcolonies19 poorly permeable to aminoglycosides. Mucoid pathogens also are more resistant to opsonic and nonopsonic phagocytosis and opsonization by antibodies.20,21 The chronic infection is associated with an intense neutrophilic inflammatory response and high antipseudomonal antibody titers. The inflammation remains confined to the airway, but neutrophils perpetuate the inflammatory cycle by releasing chemotactic stimulants (eg, leukotrienes and cytokines) and proteolytic enzymes that lead to degradation of elastin and interfere with defense mechanisms.22 The result is bronchiectasis and pulmonary failure.

Have we made an impact on *P. aeruginosa* infection in CF? Clearly, CF is a very different illness in 1998 than 1951. As a CF clinician, I was shocked by the rapid death of the patients described in the four case reports. All patients were 5 years or younger at the time of presentation with *P. aeruginosa* and succumbed to pulmonary disease within hours to weeks. *P. aeruginosa* endobronchial infection has
evolved in CF from a fulminant to an indolent, chronic disease. The median survival has increased from 5 to 31 years. A child born today may expect to survive well into adulthood.

Which therapeutic interventions have made an impact? The development of more effective antipseudomonal antibiotics in the 1960s, 1970s, and 1980s, both aminoglycosides and β-lactams, probably had the greatest initial impact. A broader array of antibiotics also led to use of combination therapy (usually an aminoglycoside and β-lactam) to slow the emergence of drug resistance. This approach was advocated in the Garrard article and has become the mainstay of pulmonary management in CF. It is interesting to note that the 1997 National Clinical Practice Guidelines, published by the Cystic Fibrosis Foundation, are similar to the authors’ 1951 recommendations: “Intravenous antibiotics will be ordered based on the patient’s most recent sputum culture and sensitivity. The use of two antipseudomonal antibiotics is recommended to provide synergism and to slow emergence of resistance.”

There are many other therapeutic interventions that have impacted on the quality of life. These include earlier diagnosis, better pancreatic enzyme replacement therapy, improved nutritional and vitamin supplements, and improved mucolytic (Pulmozyme) and antiinflammatory therapies. Specialized care centers for patients with CF throughout North America and Europe have assumed an aggressive approach to patient management, with ongoing frequent monitoring using standardized outcomes, such as pulmonary function testing. Nutritional and pulmonary interventions are initiated early in life before significant clinical symptoms. Although this approach has changed the natural history of P aeruginosa infection in CF, it has not prevented colonization or eradicated existing infection.

Early administration with aerosol colistin may delay colonization with P aeruginosa. This intriguing observation has not been verified by prospective controlled studies. It is interesting that Garrard et al proposed use of aerosol polymyxin B, an antibiotic with a similar mode of action to colistin, in the 1950s. Unfortunately, the aerosol delivery systems available at that time rarely delivered a therapeutic dose to the lower airway.

The concern about the current aggressive antibiotic therapeutic regimens is the ongoing emergence of resistant P aeruginosa strains. A recent report from a large CF microbiology reference laboratory found the prevalence of tobramycin resistance among 5128 P aeruginosa isolates collected from 595 US patients to be 21% and the prevalence of multiresistant P aeruginosa isolates to be 9.9%. Thus, newer therapies are needed.

What lies in the future? The knowledge base that has evolved in CF in the past 15 years will now allow scientists and clinicians to develop therapies directed toward correction of the basic CFTR defect. Presumably, a normally functional CFTR will not provide the endobronchial milieu conducive to P aeruginosa colonization. Trials of human gene therapy have been initiated in patients with CF and have demonstrated both gene transfer and expression in airway epithelial cells. Additional studies are needed to overcome host immune responses and to improve gene transfer efficiency before this treatment modality will be practical. Several pharmacologic agents are currently being tested in phase I and II trials and will help bring the CFTR protein to the apical surface of the CF cell and improve function. Thus, even the mutated CFTR may become “functional” with some therapeutic support. Novel antimicrobial therapies also are being developed. One of the attractive approaches is development of salt-insensitive antimicrobial peptides that will be able to kill P aeruginosa, even in the environment of the CF ASF. Finally, improved aerosol delivery systems and formulations allow much higher antibiotic concentrations to be delivered directly to the airway without the risk of systemic toxicity. This approach has been studied most for aminoglycosides, such as tobramycin, but should be applicable to other antimicrobial therapies in the future.

In summary, the Garrard paper is the quintessential example of an astute clinical observation. These clinicians observed correctly that the microbial flora of their patients with CF were changing and that the change would impact care of this patient population. Just as acute salt loss and dehydration led to the diagnostic sweat test, recognition of the emergence of P aeruginosa has changed our management of the illness and led to significant improvement in longevity and quality of life.

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COMMENTARY


Comments by Rebecca H. Buckley, MD

ABSTRACT OF ORIGINAL ARTICLE. A hitherto unrecognized entity manifested by complete absence of gamma globulin with otherwise normal serum proteins and recurrent pneumococcal sepsis is described in an 8-year-old male. The patient appeared to be normal in other respects and, after extensive study, no structural or functional change could be demonstrated in any body system. He was unable to produce antibody to the pneumococcus with the four antigenic substances used; a positive Schick test persisted despite numerous attempts to reverse it with diphtheria toxoid. No antibody could be demonstrated following administration of typhoid vaccine in the usual manner, and his serum was negative for complement-fixing antibodies of epidemic parotitis after immune in the usual manner, and his serum was negative for complement-fixing antibodies of epidemic parotitis after

In the Discussion, [the author] concluded that there was a cause-and-effect relationship between the absence of gamma globulin and the repeated infections, based on the child’s dramatic improvement after beginning gamma globulin therapy. [The author] proposed two possible causes—congenital or acquired. While [he] felt that the patient’s good health for the first 4.5 years of life argued against a congenital cause, the persistence of the defect supported it.

COMMENTARY

This article is seminal, because it reports the very first described human host defect. Before that time, it had always been assumed that infections were attributable to excessive exposure to infectious agents or to changing or unusual properties of the organisms involved. This recognition of the first human primary immunodeficiency disease 4½ decades ago set the stage for an exponential increase in information about the functions of the various components of the immune system. Since then, >70 primary immunodeficiency disorders have been recognized, and this has obviously had a profound effect on the health care of children.

The condition described in this landmark article is now referred to as Bruton’s or X-linked agammaglobulinemia (XLA). Boys with this condition remain well during the first few months of life by virtue of maternally transmitted IgG antibodies. Thereafter, they repeatedly acquire infections with extracellular pyogenic organisms such as pneumococci, streptococci, and haemophilus unless given prophylactic antibiotics or gammaglobulin therapy. Chronic fun-

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