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Summary

Bacteria infect the respiratory tract early in the course of cystic fibrosis disease, often fail to be eradicated, and together with an aggressive host inflammatory response, are thought to be key players in the irreversible airway damage from which most patients ultimately die. Although incompletely understood, certain aspects of the cystic fibrosis airway itself appear to favor the development of chronic modes of survival, in particular biofilm formation; this and the development of antibiotic resistance following exposure to multiple antibiotic courses lead to chronic, persistent infection. In addition to the common cystic fibrosis pathogens, such as Staphylococcus aureus, Haemophilus influenzae, and Pseudomonas aeruginosa, several newer species are becoming more common. Furthermore, new molecular techniques have led to the identification of multiple different organisms within respiratory secretions, many of which are not cultured with conventional tools. Future work should aim to develop clinically applicable methods to identify these and to determine which have the potential to impact pulmonary health. We outline the basic tenets of infection control and treatment. Key words: cystic fibrosis, biofilm, antibiotic resistance. [Respir Care 2009;54(5):628–638. © 2009 Daedalus Enterprises]
to evade host defenses; other organisms that infect the CF respiratory tract; new diagnostic techniques; and the tenets of prevention and treatment.

Why the Propensity For Bacterial Infection? Lessons Learned From Pseudomonas aeruginosa

P. aeruginosa, an environmental pathogen found in moist areas such as sinks and drains, is of low virulence in the majority of clinical situations. In the healthy host, bacteria that enter the lungs are cleared rapidly, without the initiation of an inflammatory response; this involves a variety of innate host defense strategies, both mechanical (mucociliary clearance) and immunological (resident macrophages and antimicrobial peptides). In certain clinical situations this first line of defense fails, and these normally harmless bacteria survive, multiply, and lead to organ damage. Such conditions are encountered in mechanically ventilated patients in intensive care, in those with defective immunity or severe burns, and in patients with CF.

The mechanisms underlying the early acquisition of infection in CF are complex, incompletely understood, and were recently reviewed. Briefly, hypotheses include impaired mucociliary clearance related to low airway surface liquid volume (the low-volume hypothesis); increased availability of cell surface receptors; and impaired ingestion of bacteria by epithelial cells. Once within the airway, conditions such as hypoxia within mucus plugs may attract motile organisms capable of anaerobic survival and encourage biofilm formation. In addition to the biofilm matrix, P. aeruginosa has evolved a huge armamentarium of strategies by which it evades host defenses and ensures its survival within the CF respiratory tract.

Acquisition of Infection

The first of these mechanisms, the low-volume hypothesis, is the focus of another article from this conference and will not be discussed in detail here. The hypothesis is premised on the concept that the defective cystic fibrosis transmembrane regulator (CFTR) fails to inhibit sodium absorption through the epithelial sodium channel. Hyperabsorption of water results, which depletes the airway surface liquid, impairs mucociliary clearance, and allows inhaled bacteria to remain within the airway. This mechanism is considered by most to be key in CF pathogenesis, although some have questioned the exact nature of its role, given the very different manifestations in another disease with impaired mucociliary clearance: primary ciliary dyskinesia. Retained cough clearance and/or differences in inflammatory response in primary ciliary dyskinesia may be explanations. Additionally, the low-volume hypothesis alone does not appear to adequately explain the relatively narrow range of pathogens characteristically associated with CF (if indeed this is true—more later).

Bacteria use specific adhesins to bind to receptors, either on secretions or the cell surface. P. aeruginosa possesses several classes of adhesins, including pili (fine, hair-like unipolar structures) and flagella, which are also used for motility (Fig. 1). Murine studies have confirmed the importance of these structures, as deficient mutants cause significantly milder disease. The majority of pseudomonas strains isolated from recently infected patients with CF are piliated, which supports a role for adherence at this stage. Once chronic infection has been established, the pilin genes are down-regulated, which leads to loss of the structures. The receptor for both pili and flagella has been identified as a disaccharide, Galβ1-4Gal, contained within several asialylated glycolipids. One of these, asialoGM1, is present in increased abundance on the surface of CF respiratory epithelial cells, and many authors have reported greater adherence of P. aeruginosa to CF cells than to those of wild-type (healthy, non-CF) origin. This may be related to the abnormal function or distribution of sialyltransferase enzymes within the CF cell, and is partially correctable with CFTR gene transfer. Furthermore, pseudomonads produce an enzyme, neuraminidase, that cleaves sialic acid off glycolipids. Is the organism capable of increasing its foothold in the CF airway in this way?

It is unknown whether this mechanism, which has largely been observed in vitro in experimental models, is relevant in vivo. Against it, postmortem studies have clearly described an absence of bacteria in direct contact with airway cells; rather, those studies found large colonies within
led to an NFκB-mediated increase in expression of pro-inflammatory cytokines such as interleukin-8. This is one of the major neutrophil attractants in the CF airway and is present in high levels in both sputum and bronchoalveolar lavage samples. The complex pathway through which this process occurs has now been described, which led to the suggestion that bacteria in the airway may provoke inflammation without actually adhering to the cell surface, by shedding of bacterial components such as pili and flagella, which then bind to αGM1 and promote interleukin-8 release.\(^{11}\)

The adherence hypothesis supports the notion that inhaled pseudomonads have a natural niche on the CF airway surface. It would go some way to explaining the high prevalence of this organism (and \textit{S. aureus}, which also binds to this receptor), as opposed to other common respiratory organisms (such as \textit{S. pneumoniae}, which is surprisingly rarely cultured), and explaining the exaggerated inflammatory response observed. However, as with the airway-surface-liquid hypothesis, it seems unlikely to be the sole explanation. These 2 hypotheses are in no way mutually exclusive, and the predisposition to pseudomonas infection may relate to a combination of these 2 mechanisms, or others in addition.

Several years ago, a study by Pier et al reported that respiratory epithelial cells are capable of ingesting \textit{P. aeruginosa}, and suggested that this, followed by sloughing off of these cells, could be a pulmonary defense mechanism.\(^{8}\) They showed that cell lines expressing mutant CFTR were less capable of ingestion and hypothesized that this was the basis for the relationship between pseudomonas and the CF lung. They have since reported that the mechanism for uptake into the cell involves binding to the CFTR protein itself.\(^{12}\) These studies remain controversial, as the levels of uptake were extremely low, and applicability to the clinical situation has not yet been demonstrated. The levels of nasal and exhaled nitric oxide (NO) are low in CF, which is a surprising finding given the fact that NO levels are usually high in inflammation. This is accompanied by low levels of inducible nitric oxide synthase (NOS2),\(^{13}\) and there is accumulating evidence that expression of this enzyme is regulated by CFTR. NO has certain antibacterial properties, so a low NO level could play a part in the predisposition to infection. Similarly, the antioxidant glutathione is normally secreted via CFTR, and is therefore deficient in the CF airway;\(^{14}\) the link between the low glutathione level and predisposition to infection is as yet incompletely understood.

**Establishing Chronic Infection**

Once the initial foothold has been gained, the bacteria must survive despite host defenses, both innate and acquired, and repeated courses of both systemic and topical antibiotics. The bacteria’s armamentarium of immunoevasive strategies includes the secretion of exoproducts, antibiotic-resistance proteins, and phenotypic changes that render them virtually unrecognizable from the bacteria that were first on the scene. The physical and immunological protection provided by the biofilm structures they form is probably key in their long-term survival.

Both elastase and alkaline protease protect against immune destruction by cleaving immunoglobulins, complement components, and cytokines. Exotoxin A inhibits phagocytosis and suppresses the cell-mediated immune response. The siderophores, such as pyocyanin, which has been detected in CF sputum,\(^{15}\) break down intercellular tight junctions, slow ciliary beat frequency, and thereby may further impair mucociliary clearance.

Our understanding of antibiotic resistance mechanisms is growing rapidly, aided in part by new molecular tools, and the sequencing of the \textit{P. aeruginosa} genome. High levels of resistance relate to a poorly permeable outer membrane, efficient multidrug efflux pumps, and \(β\) lactamases. The details of this complex topic are outside our scope here, but the interested reader is referred to the paper by Hancock and Speert\(^{16}\) for a detailed review.

One interesting property of the \textit{P. aeruginosa} strains found in the CF lung that differentiates them from strains found in other clinical settings is that they are unusually hypermutable.\(^{17}\) They can react promptly to their environment, not only by switching genes on or off, but by an increased frequency of mutation events within the genome. One such mutation event triggers conversion to a mucoid phenotype (Fig. 2), which is almost pathognomonic for

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**Fig. 2.** A: The mucoid phenotype of \textit{Pseudomonas aeruginosa} growing on MacConkey agar. B: Compared to the clearly defined borders and matt appearance of non-mucoid colonies. (Courtesy of Nick Madden MD, Microbiology Department, Royal Brompton Hospital, London, United Kingdom.)
In response to environmental triggers such as nutritional stress or the hypoxia within a CF mucus plug, mutants are selected that over-produce mucoid exopolysaccharide (alginate), which surrounds them and protects them from external challenges such as mucociliary clearance, the host immune response, and antibiotics, and is highly pro-inflammatory. Cohort studies found worse lung function in patients infected with mucoid strains than in those with non-mucoid strains.

Another highly successful survival strategy involves the formation of biofilms. Many bacteria protect themselves in this way: on biological surfaces in diseases such as bacterial endocarditis and osteomyelitis; on synthetic materials such as indwelling catheters; and on environmental structures such as the rocks in ponds and rivers. Over the last decade it has become clear that *P. aeruginosa* (and possibly other chronically infecting organisms such as *Burkholderia cepacia* complex) exist in biofilms within the CF lung. Initiation of biofilm formation is dependent on a process of “quorum sensing.” Bacteria produce molecules such as acyl homoserine lactones, which diffuse freely in and out across the bacterial membrane. Due to this free diffusibility, the concentration within the organism reflects the concentration outside, which is a direct read-out of the bacterial number. Thus, bacteria “sense” other bacteria in the vicinity. Once a critical mass is achieved, the quorum-sensing molecules induce the expression of genes vital to biofilm production. In this state, micoccolonies of bacteria are surrounded by a dense matrix that protects against phagocytosis and prevents penetration by antibiotics (see Fig. 3). This phenotypic change probably plays a major role in the persistence of pseudomonas infection in the majority of CF patients, despite best medical attempts at eradication.

**Infection With Other Organisms**

*S. aureus* is relatively common in early childhood and is often the first bacterial infection to be isolated from the respiratory tract. Opinion differs as to whether attempting to prevent infection with antibiotics is useful (more on this below). Small colony variants have been described in the more recent literature and are commonly associated with persistent infection and co-infection with other pathogens, particularly *P. aeruginosa*. Resistant strains, in particular, methicillin-resistant *S. aureus*, pose substantial logistical problems in CF clinics. Additionally, recent data suggest a poorer prognosis in patients infected with these organisms, although whether this relates to preexisting factors or is a consequence of the infection is incompletely
understood. *H. influenzae* is also commonly isolated in early disease and in childhood. Compared to some of the other organisms discussed in this article, there is a relative paucity of research and literature on *H. influenzae*.

**Burkholderia cepacia complex**

*B. cepacia* complex (initially referred to as *Pseudomonas cepacia*) led to severe outbreaks in CF subjects worldwide during the 1980s, with substantial morbidity and mortality. The prevalence of *B. cepacia* complex has remained relatively stable among CF patients in both the United States and the United Kingdom during the past several years; approximately 3–4% of patients are infected, although prevalence is much higher in certain centers. Since the introduction of effective infection-control measures, the numbers of patients in such centers has stabilized or fallen.

Currently, there are 11 species in what is now collectively referred to as the *B. cepacia* complex. Within CF, *B. cenocepacia* (genomovar III), *B. multivorans* (genomovar II), and *B. vietnamiensis* (genomovar V) account for the majority of isolates: approximately 50%, 35%, and 5%, respectively, although *B. dolosa* (genomovar VI) has also come to prominence in recent years. Identifying *B. cepacia* complex species can be difficult. These species are easily confused with other non-fermenting Gram-negative bacteria such as *Stenotrophomonas*, *Alcaligenes*, *Pandoraea*, and *Ralstonia*. In some studies as many as 10% of CF sputum isolates initially identified as *B. cepacia* were in fact misidentified. Clinical microbiology laboratories that handle specimens from CF patients must be aware of this issue and have specific measures in place to ensure correct identification.

Several specific features of certain *B. cepacia* complex organisms cause particular concern in the context of CF: the potential for transmissibility; antibiotic multi-resistance and host-defense survival strategies; and the association with adverse clinical outcomes, including systemic spread, which makes it almost unique among CF airway pathogens.

Early recognition that several members of the complex were highly transmissible and were the cause of outbreaks in CF communities led to the closure of all CF summer camps in the United States and Canada and recommendations for cohorting CF patients based on their bacterial pathogens. Numerous CF-associated *B. cepacia* complex epidemics have now been described. One particularly transmissible strain that has spread both within and between CF centers on both sides of the Atlantic is *B. cenocepacia* strain ET12. It carries the cblA gene, which encodes for the major structural subunit of unique cable pili, which are key structures that mediate binding to mucin components and respiratory epithelial cells. These enormously long pili (2–4 μm) are peritrichously arranged and intertwine to form cable-like structures (Fig. 4).

*B. cepacia* complex species are intrinsically resistant to a broad range of antibiotics and non-oxidative killing by human phagocytic cells. Some strains can invade and survive within respiratory epithelial cells or macrophages, thus potentially evading host defenses. Further, they possess an array of virulence factors, including proteases and highly inflammatory lipopolysaccharide structures, which elicit brisk, exaggerated, and potentially detrimental host responses. As with *P. aeruginosa*, it appears that *B. cepacia* complex organisms produce biofilms in vivo. Features, including its nutritional versatility and adaptability, and the development of antibiotic resistance, are probably at least in part due to its unusually large, complex, and variable genome. Typically, these organisms are resistant to aminoglycoside and polymixin antibiotics due to the unusual lipopolysaccharide component of their cellular membrane. In addition to intrinsic resistance these species can also acquire resistance during therapy due to β-lactamase production.

*Fig. 4. Transmission electron micrograph of Toronto/Edinburgh epidemic clone of Burkholderia cepacia expressing cystic fibrosis mucus-binding Cbi adhesin pili. High-resolution was achieved with a JEOL 100CX electron microscope and negative staining. (From Reference 31, with permission.)*
regulation of antibiotic efflux pumps,\textsuperscript{49} and alteration of antibiotic targets. Inducible resistance is a particular problem in CF patients, who often receive multiple prolonged courses of antibiotics.

Infection with \textit{B. cepacia} complex is an independent negative prognostic indicator in CF. Individuals who acquire these organisms, however, fall into different clinical groups: they may be asymptomatic; experience rapid respiratory decline; or, as is observed in a minority, develop the “cepacia syndrome,”\textsuperscript{50} in which organisms invade systematically and cause endotoxmic shock, multi-organ failure, and, in many cases, death. The individual’s clinical response to infection probably relates both to bacteria-specific and host-specific features, although as yet this area is not fully understood.

### \textit{Stenotrophomonas maltophilia}

\textit{S. maltophilia} is an aerobic Gram-negative motile rod with multitrichous flagella. The prevalence of \textit{S. maltophilia} in CF increases with age and appears to relate to antibiotic exposure history. Prevalence rates of 4–30\% have been reported in various studies.\textsuperscript{51-53} The incidence of infection in patients who do not have CF has increased steadily in recent years, although single or intermittent isolation of \textit{S. maltophilia} is common. Broad-spectrum antibiotic therapy and selective pressure that could promote emergence of multi-resistant bacteria has long been implicated as a risk factor for \textit{S. maltophilia} acquisition. Among patients who do not have CF, the use of carbapenem antibiotics, especially imipenem, to which \textit{S. maltophilia} are uniformly resistant, has been widely believed to increase the risk of infection. However, there has been a similarly high rate of \textit{S. maltophilia} acquisition in patients treated with the \textit{\beta} lactam ceftazidime.\textsuperscript{54} In CF the use of steroids or antipseudomonal agents, including quinolone antibiotics and inhaled aminoglycosides, has been implicated as risk factors, although the findings have not always been consistent among studies. Epidemiological studies suggest that the majority of \textit{S. maltophilia} infection in CF results from independent acquisition, most likely from environmental sources, rather than from cross-infection. Several studies in CF have produced convincing evidence that acquisition of this organism \textit{per se} is not detrimental.\textsuperscript{55-58} Although patients who acquired \textit{S. maltophilia} had more advanced disease than those who did not, detection of this species in sputum culture did not independently affect the rate of deterioration or survival. To what extent these observations reflect the severity of underlying lung disease, as compared to the more frequent use of broad-spectrum antibiotics in this group of patients, remains to be determined.

### \textit{Achromobacter (Alcaligenes) xylosoxidans}

Although \textit{A. xylosoxidans}, a motile, Gram-negative bacillus, has been recognized for many years as being capable of causing infection in persons with CF, the proper nomenclature of this species has presented an ongoing challenge. Its incidence in CF differs between centers, and the organism usually coexists with other airway pathogens. Because infection is so often transient, detection and the reported infection rate are strongly influenced by the frequency of sputum culture. A recent study by Tan and colleagues indicated that 13 (2\%) of 557 patients in their pediatric and adult CF units were chronically infected with

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**Table 1. \textit{Burkholderia cepacia} Complex Virulence Factors and Their Functions**

<table>
<thead>
<tr>
<th>Virulence Factor</th>
<th>Protein/Gene</th>
<th>Species (strain)</th>
<th>Function</th>
<th>First Author, Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteases</td>
<td>\textit{zmpA}</td>
<td>Many, not \textit{Burkholderia multivorans} or \textit{B. dolosa}</td>
<td>Proteolysis of extracellular matrix</td>
<td>Gingues\textsuperscript{33} 2005</td>
</tr>
<tr>
<td></td>
<td>\textit{zmpB}</td>
<td>Many, not \textit{B. multivorans} or \textit{B. dolosa}</td>
<td>Proteolysis of extracellular matrix</td>
<td>Kooi\textsuperscript{36} 2006</td>
</tr>
<tr>
<td></td>
<td>\textit{mgTC}</td>
<td>\textit{B. cenocepacia} (K-562)</td>
<td>Survival in macrophages; virulence rat lung-infection model</td>
<td>Maloney\textsuperscript{37} 2006</td>
</tr>
<tr>
<td></td>
<td>HtrA protease</td>
<td>\textit{B. cenocepacia} (K-562)</td>
<td>Growth under osmotic or thermal stress, survival rat-infection model</td>
<td>Flannagan\textsuperscript{38} 2007</td>
</tr>
<tr>
<td>Lipases</td>
<td>Lipase</td>
<td>Multiple species</td>
<td>Role in invasion</td>
<td>Mullen\textsuperscript{40} 2007</td>
</tr>
<tr>
<td></td>
<td>Phospholipase C</td>
<td>\textit{B. cenocepacia}, \textit{B. multivorans}, \textit{B. vietnamiensis}, \textit{B. ambifaria}</td>
<td>Digestion of phosphatidylcholine of lung surfactant; no correlation with virulence yet</td>
<td>Carvalho\textsuperscript{41} 2007</td>
</tr>
<tr>
<td>Exotoxin</td>
<td>LPS</td>
<td>Many species</td>
<td>Cytokine secretion, inflammatory response</td>
<td>Reddi\textsuperscript{42} 2003</td>
</tr>
</tbody>
</table>

(Adapted from Reference 43.)
this organism; a further 31 (6%) patients were intermittently colonized.\textsuperscript{59} With regard to acquisition, there is little evidence that it is acquired by patient-to-patient cross-infection.\textsuperscript{60} Persistence seems to be variable once the lung is infected, from transient to up to 6 years in one patient. Based on the available evidence it does not seem that infection with \textit{A. xylosoxidans} contributes greatly to clinical deterioration in CF patients.

\textbf{Pandora\textit{e}, Ralstonia, Inquilinus, and other species}

Although CF patients have been identified as being chronically infected with \textit{Pandora\textit{e}} species, the prevalence and pathogenic role of these species in CF is unknown. At present \textit{Pandora\textit{e}} species are most noteworthy and troublesome in CF insofar as they are generally misidentified as other species,\textsuperscript{61} particularly \textit{B. cepacia} complex. The genus \textit{Ralstonia} was named in 1995, and \textit{R. insidiosa} and \textit{R. respiracu\textit{l}} have been identified from isolates recovered from CF sputum culture. The frequency and clinical impact of \textit{Ralstonia} species infection in CF have not been systematically studied.\textsuperscript{62} Organisms in the genus \textit{Inquilinus} are \textalpha\text{-protoprobacteria. \textit{Inquilinus} is a Gram-negative, non-fermentative bacterium but is not related to \textit{P. aeruginosa} or \textit{B. cepacia} complex.\textsuperscript{63} It is slow-growing and can be difficult to culture and identify. There are insufficient data to determine how pathogenic this organism is for CF patients.

\textbf{Nontuberculous Mycobacteria}

Patients with CF have long been recognized as having an increased predisposition for non-tuberculous mycobacteria, including \textit{Mycobacteria abscessus}, \textit{M. avium intracellularare}, and \textit{M. chelonae}. The majority of patients harbor unique strains acquired from the environment, as opposed to via patient-to-patient spread. The prevalence range is 2–20\%, and one of the largest studies reported that 13\% of patients had at least one of 3 cultures positive.\textsuperscript{64} The rates are increasing, although whether that reflects the increasing age (a significant risk factor for infection) of surviving patients or a true increase in acquisition is uncertain. As with some of the organisms discussed above, determining the significance of a single isolation can be difficult; many infections are transient and not associated with clinical decline. Evidence suggests that infection with \textit{M. abscessus}, in particular, may be more likely to be associated with clinical decline.\textsuperscript{64} Whereas imaging is useful in patients who have the infection but do not have CF, the appearances typical of CF can make distinguishing any additional features of non-tuberculous mycobacteria disease extremely difficult. Heavy or persistent isolates, or those associated with clinical symptoms not explained by other organisms, should arouse suspicion. It has recently been reported that otherwise healthy adults who have pulmonary atypical mycobacteria (with or without bronchiectasis), have a high prevalence of unrecognized CF or are CF carriers.\textsuperscript{65} Although the association of atypical mycobacteria with isolated bronchiectasis had been thought to be caused by a weak or ineffective cough, this appears to be unlikely. It has been suggested that all patients with pulmonary non-tuberculous mycobacterial infections and no apparent immunodeficiency be tested for CF.

\textbf{New Non-Culture-Based Diagnostic Techniques}

Conventionally, organisms are identified from sputum, cough (or oropharyngeal) swabs, or bronchoalveolar lavage, via culture on agar plates. Specific agars can be used, tailored toward the commonly recognized organisms, but all rely on culture. Visible colonies are tested for accurate identification and for antibiotic sensitivity. More recently, however, molecular techniques have been used on similar samples. These techniques do not rely on culture but instead use specific probes to search for bacterial DNA and/or RNA. The technique is based on the fact that different organisms possess different (and mostly well-described) DNA sequences, so identification is accurate. Some techniques can also quantify different bacteria, at least in relative values. These studies showed an unexpectedly wide range of organisms, including numerous anaerobes, for which most laboratories do not search with conventional culture.\textsuperscript{66,68} Interestingly, the healthy non-CF airway, which is often described as sterile, has also been shown to harbor DNA from multiple organisms, which raises important questions as to how pathogenic these organisms are in the disease setting. Several ongoing studies are addressing that issue. Both culture and molecular techniques rely on the availability of lower-airway secretions, which can be a problem with many patients with milder disease, particularly children. Experimental strategies focused on volatile bacterial products in exhaled breath may offer an advantage.\textsuperscript{69} “Electronic noses” and mass-spectrometry-based techniques have shown success in other airway infections and could be applicable to the non-expectorating CF patient, although further work is clearly required.

\textbf{Prevention and Treatment}

Infection-control measures are discussed in greater detail in O’Malley’s paper for this conference.\textsuperscript{70} In brief, cross-infection can be substantially limited by simple measures such as handwashing between patients, and the use of disposable equipment such as spirometer mouthpieces. The incidence of \textit{B. cepacia} complex infection has decreased since most clinics have adopted a cohorting policy and stopped mingling of CF patients outside the center, for
example in summer camps and conferences. However, routine widespread cohorting of patients based on airway cultures is a controversial issue. While most would agree that cohorting of patients with highly transmissible or multi-resistant pathogens is advisable, opinion differs with regard to specific organisms. Two areas of particular disagreement are whether to separate patients with and without antibiotic-sensitive *P. aeruginosa*, and whether patients with some of the organisms listed above (eg, *S. maltophilia*), which appear to pose little clinical disadvantage to the patient, should be isolated.

When considering the potential benefits of patient segregation, several disadvantages need to be addressed. First, each patient can be segregated only on the basis of previous culture results, which may not reflect current infection status, and which may be difficult to obtain, for example from children. Second, as it is becoming clear that within a species, some strains may be significantly more detrimental than others, cohorting all patients with these organisms together may pose a risk for those infected with the more benign strains. This could be the case, for example, in many *B. cepacia* complex clinics. Third, cohorting on the basis of multi-resistance may be hindered by the continuously changing susceptibility patterns of many of these organisms. Fourth, there may be a stigma attached to patients within certain of these infection groups. This has already been described for patients with *B. cepacia* complex organisms. Finally, cohorting creates a substantial logistical burden on CF centers. Perhaps in view of these concerns it is not surprising that there are no world-wide standard procedures for cohorting such patients. The majority of clinics separate patients with *B. cepacia* complex and methicillin-resistant *S. aureus*, while others will go further. Whichever model is favored, basic infection-control guidelines should always be followed.

**The Basic Tenets of Antibiotic Treatment**

Specifics of therapy have been well reviewed. Rather than dealing with organisms individually here, we address some basic principles underlying clinical management, starting with early childhood and progressing through the usual disease stages:

1. **The Role of Prophylaxis for *S. aureus* Is Unclear.** In the United Kingdom at least, many clinics use antistaphylococcal prophylaxis (most commonly fluclouxacinillin or amoxicillin/clavulanic acid) in young children, from the time of diagnosis. Although studies have demonstrated reductions in the incidence of *S. aureus* infection with this strategy, no benefits on lung function in the medium term have been conclusively demonstrated. Concerns have been raised that such a strategy may increase the incidence of *P. aeruginosa*, although this finding was limited to studies that used oral cephalosporins, which are not used in the United Kingdom. A definitive study to confirm or refute the benefits of this strategy is urgently needed.

2. **P. aeruginosa Can Clearly Be Eradicated If Identified Early.** One of the major developments of the last decade has been the recognition of the benefits of early identification and aggressive treatment of *P. aeruginosa*. Successful eradication has been reported with regimens that included systemic (oral ciprofloxacin or intravenous agents) and topical, nebulized treatments. The optimal regimen and duration remain unclear. However, the importance of careful, frequent surveillance cannot be overemphasized; any eradication protocol is useless if the infection is not identified.

3. **Long-Term Suppressive Treatment of *P. aeruginosa* Is Advantageous.** Nebulized antibiotics, in particular colomycin, have been used for decades in many parts of Europe, although, in the main, this practice evolved in an era when “evidence-based” medicine was less rigorous that it is today. Wider acceptance of this strategy has come with the development of inhalable tobramycin, and with the well-conducted trials that established the role of long-term suppressive therapy in maintaining lung function in patients with chronic *P. aeruginosa* infection.

4. **In Vitro Sensitivity Testing Has Substantial Limitations.** As any clinician well knows, certain patients fail to respond to an antibiotic regimen that is based on in vitro sensitivity testing, whereas others appear to respond well to a combination that should theoretically be useless. This probably reflects the very different growth modes of the organisms in the airway versus on a culture plate. Attempts to perform sensitivity testing on organisms grown in biofilms in the laboratory have been somewhat disappointing. Further work is needed, as we urgently require a better method of predicting optimal treatments.

5. **Doses Are Often Different Than Those Used in Patients Who Do Not Have CF** Patients with CF handle drugs differently than patients who do not have CF; in general, higher doses are required. The action of the antibiotic on the organism should be borne in mind when designing a dosing regimen, as exemplified by the switch to once-daily aminoglycoside antibiotics, which achieves a higher peak (concentration-dependent killing) and longer post-antibiotic effect than conventional 3-times-daily dosing.

6. **Monotherapy Should Be Avoided When Treating With Intravenous Agents.** Many organisms in CF are prone to becoming multi-resistant. Monotherapy (eg, with intravenous cephalosporins) greatly encourages multiple-
drug resistance. Use combinations of ≥ 2 antibiotics from different groups.  

7. The Benefits of Synergy Testing for Multi-Resistant Organisms Is Unproven. One is often faced in the clinic with a heart-sinking row of “R’s” on the antibiogram—a problem that increases with advancing age of the patient. In vitro, combinations of agents that alone are ineffective may be synergistic, although evidence for this translating into clinical benefit is largely lacking.87

8. There May Be Problems in the Longer Term. The aggressive use of antibiotics is no doubt one of the major reasons for the improving prognosis of today’s CF patients. This does, however, come at a price. Subclinical renal impairment associated with repeated doses of aminoglycosides is increasingly recognized in adult patients.88 Drug allergies are common and often further impair our therapy choices. The extended life expectancy of patients today means that much more focus is now required on the medium to long term.

Summary

Bacterial infections are a major clinical burden and are key in the deterioration of respiratory function in CF. In addition to the conventionally associated bacteria, many others are emerging, in part related to antibiotic pressure. New diagnostic techniques are increasing awareness of yet unidentified organisms, although the clinical relevance of many of these remains to be determined.

The best therapy is prevention, which can be aided by infection-control measures. Simple precautions to prevent carrying bacteria from one patient to the next are extremely important and, for the most part, easy, whereas strict cohorting is challenging and has substantial disadvantages. Appropriate and judicious use of antibiotics is critically important to limit the development of resistance and adverse effects in patients who undergo multiple courses of antibiotics.

REFERENCES


72. Ramsey BW. To cohort or not to cohort: how transmissible is *Pseudomonas aeruginosa*? Am J Respir Crit Care Med 2002;166(7):906-907.


77. Duff AJ. Psychological consequences of segregation resulting from chronic *Burkholderia cepacia* infection in adults with CF. Thorax 2002;57(9):756-758.


**Discussion**

**Rubin:** I hope I’m not stealing any of Catherine O’Malley’s thunder, because I know she’s going to talk about infection control and cohorting right after lunch. I do have a question related to the respiratory therapist. There’s really a concern about this killer bacteria, MRSA [multiply-resistant *Staphylococcus aureus*]. It sells a lot of newspapers here in the United States. We’ve had concerns, not only with cohorting, but what is the risk to the caregiver who does a lot of hands-on care if they’re immuno-nocompetent? Are any of these things that respiratory therapists should be concerned about? Should we be routinely looking at caregivers’ flora in their nose or in their oropharynx?

**Davies:** That’s an important point. At my institution and many others in the United Kingdom, we routinely screen patients but completely ignore the staff who interact with the patients. Perhaps people do not want to face the possibility that the staff might be benignly colonized with these organisms. It’s strange that there’s so much infection-control strategy from the patient’s perspective but very little from ours. Bruce, I don’t think the data are there to provide an answer, but it’s something that we should not “duck,” and we are ducking it at the moment.

**Geller:** You gave a wonderful presentation of how smart the *Pseudomonas* organism is in avoiding our
attempts to kill it. Of the others organisms that you spoke about early on, I know there is little evidence, but which do you think are also doing harm and should be our next point of attack?

Davies: **Burkholderia cepacia** complex is extremely concerning. Fortunately, it affects only a small portion of the CF population, but the effects can be quite devastating. And I think it is the most devastating infection because of the stigmatization and the terrible septicemic death it can cause.

I’ve seen relatively little evidence that the newer organisms I mentioned are either well understood or terribly detrimental, but that might just be because we’re only just starting to identify and understand them. For the majority of them I think there’s not a lot of evidence that they’re devastating.

We’ve been looking at *S. maltophilia* for many years now, and my interpretation of the data is that it’s “piggybacking” on patients who are not doing very well, as opposed to causing decline. So *S. maltophilia* is not causing terrible anxiety in our institution.

We have a very interesting group of patients who don’t appear to have chronic pseudomonas but who are chronically and heavily infected by *S. aureus* and who do rather badly. I don’t understand the particular mechanisms in those patients, and many of our treatment strategies seem to be futile. We shouldn’t ignore *S. aureus*, because, though for many patients it seems to be a relatively benign infection, for others it can be quite serious.

**REFERENCES**


**Rubin:** We’ve seen the same with staphylococcus, and we’ve been looking now for virulence factors, particularly *Panton-Valentine leukocidin*, and have seen a very high prevalence in those who are doing very poorly with staphylococcus.

**Davies:** That’s very interesting.

**O’Malley:** In response to the increasing incidence of MRSA, my institution started testing clinicians to determine how many are harboring it.

**Davies:** The first few centers to do that could create a wave of momentum, because once we start to hear reports—particularly if the reports are not as we would like them to be—I think other institutions may take that on as well.

**O’Malley:** I suspect we will find that many clinicians have it. The question is, what do we do about that?

**Ratjen:** If you have a high rate in the community, of course you will find it in clinicians. But the question of what to do with that information is very difficult. The issue we struggle with for many of the bacteria—other than pseudomonas, with which we usually have this relatively simple situation that it is or isn’t chronically present—but with many of the other microorganisms, they tend to be there for a shorter period, and then it’s difficult to sort out the patients in whom these organisms are actually relevant, versus the patients who just transiently have the organism and clear it spontaneously.

Data from Johns Hopkins University indicated that in patients who seem to be more persistently infected you can see an effect on their rate of decline, and the detrimental effect may tell us something that we should probably look for other organisms such as *Achromobacter*, to see if there is a subgroup that has a more chronic type of infection; that might give us a different story.

*S. aureus* is very relevant. About a decade ago, Sharma et al found that patients who were clear of pseudomonas still had a rapid rate of deterioration. There was a small group of patients who were only positive for staphylococcus. So there seems to be a group of patients who are clear of pseudomonas but have a problem with staphylococcus, and I think that we need to learn more about that. In our database, in patients who had pseudomonas before and are free of pseudomonas, their rate of decline seems to be higher than those who continue to have pseudomonas; we don’t understand that yet. It’s an interesting signal that we haven’t paid much attention to yet.

**REFERENCES**


**Marshall:** What about anaerobic bacteria? Are they important?

**Davies:** I don’t know. I think that we should take notice of them, and I
think that it’s about time we started looking at the whole “zoo,” as I would call it, rather than just the organisms we think are relevant. But I don’t think we have the data to say whether they are detrimental or just innocent bystanders. I can envision a situation in which they could go down as the more pathogenic bacteria went up, so you could get very spurious information from the various fingerprints, but we don’t have the data yet. But we shouldn’t ignore them.

Rosenblatt: If it’s the bacteria in the milieu in the biofilms, why is it that in some patients it seems there’s such a discrepancy between the sinuses and the lungs? I expect there to be the same destructive process going on in the sinuses, but there’s this disconnect in some patients.

Davies: That’s a good point. I have never thought about sinuses very much, but I wonder if biopsy of the sinus epithelium would show the same destructive processes as in the lower airways? The sinuses are sort of walled by bone, so they can’t develop the same sort of bronchiec-tatic changes as lower airways, so maybe they don’t develop symptomatically in the same way.