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Early Eradication of Pseudomonas aeruginosa in Patients with Cystic Fibrosis

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Abstract

Pseudomonas aeruginosa (Pa) is the predominant organism infecting the airways of patients with cystic fibrosis (CF). This organism has an armamentarium of survival mechanisms that allows it to survive in the CF airway. Since colonization and chronic infection with Pa is associated with poorer lung function and increased morbidity and mortality, therapies that can prevent infection could significantly improve the lives of patients with CF. Numerous studies have examined the effects of treatment on the eradication of Pa as a means to ameliorate disease. This article outlines the pathophysiology and clinical implication of Pa acquisition, and reviews the existing treatment regimens aimed at early eradication of Pa in patients with CF.

Keywords

Pseudomonas aeruginosa; cystic fibrosis; inhaled tobramycin; eradication therapy; colonization

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder of chloride transport that occurs in approximately 1 in 3,200 Caucasian individuals. Since the first detailed description of CF in 1938 by Dorothy Andersen, much has been elucidated regarding this disease.[1] The subsequent discovery of disease causing mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in 1989 ushered in a revolution in the understanding of the pathophysiology of CF.[2] However, our understanding of the interplay between the chloride transport defect in CF airway epithelium and development of chronic bacterial infection is limited.

Although CF affects many organ systems, patients with CF experience the most morbidity and mortality from manifestations of obstructive pulmonary disease. Although a myriad of organisms have been implicated in disease progression, *Pseudomonas aeruginosa* (Pa) is the predominant organism infecting the airways of patients with CF. This organism is thought to be a significant cause of respiratory complications. Once the airways of CF patients become

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colonized, Pa cannot be eradicated. Therefore, any therapy that delays the colonization of CF airways with Pa has the potential to preserve lung function. It is hypothesized that patients with CF become transiently infected with Pa before they become colonized with this organism, thereby providing a window of opportunity to eradicate this organism before it gains a foothold towards colonization (Figure 1)[3]. Hence, numerous studies have examined approaches to eradication of early Pa infection as a means to ameliorate disease. Here, we discuss the pathophysiology and clinical implication of Pa acquisition, and review the existing treatment regimens aimed at early eradication of Pa in patients with CF.

PSEUDOMONAS AERUGINOSA IN CYSTIC FIBROSIS

The interaction between an individual CF patient's lung environment and immune response and the invading bacteria's defence mechanisms determines if the airway will become colonized with Pa. In a normal, healthy lung, inhaled bacteria are cleared through a combination of mechanical and immunological defence mechanisms. In CF, the defective CFTR results in impaired chloride secretion and hyperabsorption of sodium, thereby leading to a dehydrated airway surface liquid layer.[4] This environment allows bacteria to flourish, as the diseased airway is depleted of surface fluid and thick mucus is retained leading to impaired mucociliary clearance. Additionally, the activity of antimicrobial peptides, which are important in innate immunity, is altered in the CF airway.[5] The role of CFTR in clearance of Pa from the airway remains obscure. However, it is known that epithelial cells expressing the CFTR F508del allele demonstrate less uptake and ingestion of Pa.[6] While neutrophils, the predominant cell type in CF airways, are involved in fighting off infection, they also play an important role in the inflammatory process. Neutrophils in the CF airway have been shown to have increased adherence and subsequently increase interleukin-6 and interleukin-8 levels which contribute to prolonged inflammation.[7,8]

In addition to having a suitable growing environment, Pa is a resourceful organism that has evolved multiple mechanisms to enhance its survival in the CF airway. Initially, Pa uses flagella to navigate and pili to adhere to respiratory epithelium.[9] Once infection has been established, Pa utilizes several mechanisms to evade the host immune system. Pa secretes many products to aid in its survival including: elastase (ELA) and alkaline protease (AP) that cleave immunoglobulins, cytokines, and complement; exotoxin A (ExoA) that inhibits phagocytosis; and pyocyanin that impairs mucociliary clearance by slowing ciliary beat frequency.[10] *P. aeruginosa* has also been shown to downregulate the transcription of flagellin, an important inducer of pro-inflammatory markers such as interleukin-8 and stimulator of the host immune response via Toll-like receptor 5, after colonization.[11,12] As Pa is exposed to various antimicrobials over time, it accumulates mutations that help establish chronic infection and convey antibiotic resistance. Among these mutations is the loss of function mutation in *mucA*, a negative regulator of exopolysaccharide alginate production. The resulting increased alginate production is thought to confer additional protection for Pa against host defences such as mucociliary clearance and antimicrobial penetration, and it has been associated with an attenuated inflammatory response.[12] The production of alginate gives Pa a mucoid phenotype when grown *in vitro*.

Finally, biofilm formation represents another important survival mechanism that allows Pa to establish chronicity in the CF airway. Studies show that Pa colonies attach, form, and expand into structured communities of bacteria surrounded by a polymeric matrix within the thick mucus of the respiratory airway.[13,14] *P. aeruginosa* growing in a biofilm are rendered more difficult to remove by mucociliary clearance, and develop increased antibiotic resistance.[15,16] Biofilm formation is preceded by bacterial attachment and multiplication on the lung epithelium. Once a certain bacterial density is reached and growth slows, biofilm production is signalled by a process of quorum sensing, in which extracellular signals herald the differentiation of Pa bacterial cells into complex multicellular structures.[13,14]

DETECTION OF *PSEUDOMONAS AERUGINOSA*

Identifying initial Pa infection is challenging since it often occurs in young patients who cannot expectorate sputum. Several methods are employed to detect the presence of Pa in the lower respiratory tract. However, no gold standard exists for diagnosis, as each technique has its advantages and disadvantages. Ideally, lower respiratory tract Pa would be detected by bronchoscopy with bronchoalveolar lavage (BAL); however, this procedure is invasive and requires deep sedation or general anaesthesia. Sputum induction is used in older children and adults, due to ease of procurement and accurate representation of organisms in the lower respiratory tract. However, young children are frequently unable to coordinate sputum expectoration, even with the aid of hypertonic saline. Thus, in this population, oropharyngeal (OP) cultures are the mainstay for diagnosis of Pa infection in clinical practice.

The usefulness of OP cultures to identify Pa in the lower respiratory tract has been examined, comparing OP culture results to those from simultaneous BAL (Table 1).[17–20] Ramsey and colleagues initially concluded that positive OP cultures are highly predictive of lower airway disease.[20] In three subsequent studies, however, negative OP cultures were found to more reliably predict absence of infection.[17–19] Culture results from OP swabs must, therefore, be interpreted carefully. Despite their limitations, results from OP cultures in patients unable to yield adequate induced sputum samples are used by many clinicians as a surrogate marker for detection of Pa in the lower respiratory tract.

The use of serologic markers of the immune response to Pa antigens has also been proposed as a method to detect Pa colonization. Several techniques, including crossed immunoelectrophoresis, radioimmunoassay (RIA), and enzyme-linked immunosorbent assay (ELISA) have been utilized.[21] Several studies demonstrate the presence of anti-Pa antibody titres may help distinguish early infection from chronic colonization. In a 1987 prospective study of 62 patients, increasing anti-Pa titres were found only in patients who developed chronic Pa colonization. Elevated titres against phospholipase C (PLC) were found in 100% of patients with chronic Pa colonization, while 58% had increased titres to AP and ExoA. Titres against ELA were higher in 15% of Pa colonized patients.[22,23] Furthermore, anti-Pa antibodies have the potential to reveal the presence of Pa infection before the bacteria are obtained by culture. In a study of 33 patients in Leeds, UK, 24 patients demonstrated increasing IgG titres against Pa as early as 2 years before initial isolation of the organism.[24] Similarly, Danish investigators found that increasing anti-Pa IgG titres were detectable up to

3 years prior to infection.[25] Though not yet widely used, molecular techniques such as PCR are highly sensitive for detecting Pa (93–100%).[26–29] Indeed, the combination of serologic markers with PCR evidence of infection can successfully identify more patients with chronic Pa colonization than serology, sputum or nasopharyngeal culture, or PCR alone, according to a 2007 study.[23]

CLASSIFYING *PSEUDOMONAS AERUGINOSA* "INFECTION"

Organisms that predominate in the respiratory tract vary with time. Early in CF airway infection, *Staphylococcus aureus* and *Haemophilus influenza* predominate. *P. aeruginosa* becomes a main culprit later in life, with a mean age of acquisition of 45 months.[30] A prospective, longitudinal cohort study of infants enrolled at 3 American CF centres showed that over 97% of the patients had serologic or microbiologic evidence of Pa infection by age 3.[17] Female sex, homozygosity for the F508del mutation, and continuous therapy with anti-staphylococcal antibiotics are among the risk factors for early acquisition of Pa.[31,32] The prevalence of Pa infection steadily increases with advancing age. Data from the CF Foundation Patient Registry demonstrate that as many as 20–25% of infants and 25–50% of children age 2–10 years have had Pa obtained from at least one airway culture. According to the 2008 CF Foundation Patient Registry, the shift to Pa as the predominant organism occurs between ages 25–34 years in the United States. Approximately three-quarters of adults with CF and one-third of children with CF had cultures which grew Pa. This peak incidence occurs at a later age than what has been reported in previous years.[33]

Precise classification of Pa infection remains problematic. The timeline of harbouring Pa can be regarded in terms of initial acquisition of the organism, early intermittent infection, and chronic infection (Figure 1). In published work, the terms "colonization" and "early infection" are sometimes used interchangeably when describing the presence of Pa in the respiratory tract. The first definition of chronic infection introduced in 1974 by Professor Høiby in the Copenhagen CF centre was based on monthly microbiological examination of sputum and was later modified to include the antibody response to Pa.[34,35] Many centres do not obtain monthly microbiology samples nor do they measure Pa serologies; thus, in 2000, a European Consensus Committee convened by the European CF Society published a consensus definition for chronic infection.[21] Perhaps the most comprehensive criteria to date for categorizing Pa infection comes from Leeds, UK, where airway cultures from a 12 month period were evaluated and used to group patients into four categories (Table 2).[36] Despite these efforts, no universal definition of chronic infection has been widely accepted, a factor that may complicate early treatment recommendations.

CLINICAL IMPLICATIONS

The significance of early detection and the rationale behind early eradication of Pa has important implications on clinical outcomes in children with CF. Early colonization with Pa has been associated with poorer lung function, lower weight percentiles, and increased morbidity and mortality.[37–40] In one particular prospective, observational cohort study involving 56 children, infection with Pa resulted in lower average FEV^1 values, worse disease severity as measured by NIH scores and prolonged hospitalization stays for

respiratory illness. Furthermore, all of the patients who died in this study had acquired a multi-resistant, mucoid strain of Pa.[30] The production of alginate as a mechanism for evading the host immune system gives Pa "mucoid" phenotype, which is associated with chronic infection, antibiotic resistance, and more rapid decline in lung function. Studies have suggested that the conversion from the non-mucoid to the mucoid phenotype occurs over a relatively short time period of about 1.8 years.[30,41] These findings clearly indicate that early detection and early eradication of Pa can have important implications for clinical outcomes in children with CF.

ERADICATION OF *PSEUDOMONAS AERUGINOSA*

Studies Support Benefit of Early Therapy

Studies dating back to the 1980's have investigated the effects of early treatment for patients known to harbour Pa (Table 3). Several investigators have addressed the hypothesis that early eradication of Pa may lead to decreased number of patients with chronic Pa colonization. Table 3 summarizes the results from many of these studies, emphasizing the anti-pseudomonal regimen employed and the efficacy of Pa eradication. Caution must be taken when comparing these studies, as the method of Pa detection and definitions of infection and chronic colonization are not consistent between reports. Despite these differences, when taken together, this evidence supports the use of early therapy to prevent chronic colonization with Pa. Still, the best regimen(s) remains to be determined. An optimal treatment plan would be one that is well-tolerated with few side effects, shows maximal effectiveness in eradicating Pa as well as maintaining eradication, and would be based on results from a large study group, ideally, from a randomized, controlled trial.

The concept of early eradication was first reported by Little-wood et al who noted decreased frequency of cultures with Pa growth after initiation of colistin in a case study of 7 patients.[42] The first published randomized, controlled trial performed by Valerius et al in 1991 showed in patients treated with inhaled colisitin and oral ciprofloxacin, 86% remained free of chronic colonization versus 42% of untreated patients (at mean follow up time of 17.4 months).[43] These authors specifically evaluated time to chronic colonization rather than elimination of Pa after treatment. They rigorously defined chronic colonization as Pa growth in monthly sputum cultures for 6 consecutive months and/or precipitating antibodies against Pa.[21] Other groups report similar findings comparing inhaled anti-pseudomonal antibiotics and oral fluoroquinolones with historic controls.[44,45]

The next reported randomized, controlled study published in 1998 evaluated the efficacy of inhaled tobramycin for one year by a "time to event" analysis, looking for conversion to cultures without Pa.[46] The authors acknowledge the weakness of the study, largely secondary to patient dropout rate; still, 88% of treated patients cleared Pa from their cultures, while none of the 4 patients completing placebo treatment successfully cleared the infection. Ratjen et al also evaluated this regimen in an open label, uncontrolled study and found that 93% of patients successfully eradicated Pa and the same number remained culture and precipitin antibody-negative at one year of follow up[47]. Sixty percent of patients treated were still culture and antibody negative after 2 years. In 2003, Gibson et al randomized 21 patients to inhaled tobramycin or placebo therapy and determined eradication rates in the

two groups based on cultures from bronchoalveolar lavage.[48,49] They found that Pa was cleared from 100% of the treatment group, compared to only 7% of the controls. Seventy-five percent of those treated continued to be free of Pa two months later. Indeed, this trial was stopped early due to the significant microbiological effect revealed in the treatment group. These investigators expanded the duration of inhaled tobramycin to 28 or 56 days and found that 75% of patients treated for 28 days and 82% of patients treated for 56 days had no Pa growth in BAL cultures at 112 days.[49] Further, they showed inhaled tobramycin had a more robust antimicrobial effect on lower airway Pa by comparing cultures from oropharyngeal samples with those taken from BAL.

Perhaps the most thoroughly evaluated treatment combines inhaled and oral anti-pseudomonal therapies, first described by Valerius, as discussed above.[43] Several groups report the efficacy of this regimen by different outcome measures, mostly in studies using historical controls.[44,45,50,51] Vazquez et al found significantly fewer cultures with Pa growth ($p < 0.001$) from patients treated with inhaled colistin and tobramycin plus oral ciprofloxacin for 14 days.[44] Frederiksen and colleagues evaluated a group three times the size of the Valerius study by the same outcome measure: time to chronic colonization.[45] Using the same definition of chronic colonization, they found 84% of patients treated with inhaled colisitin and oral ciprofloxacin were not chronically colonized at 3.5 years compared with 28% of historical controls. Additional studies showed 81% (median) of treated patients continued to have cultures free of Pa for 18 months after initial eradication.[50] Indeed, in the 51% of patients recolonised during this study's 7 year follow-up period, genotypically novel Pa strains were identified in 73% of cases, providing evidence of eradication with subsequent infection with a genetically different organism. Most recently in 2008, Hansen et al showed treatment with inhaled colistin and oral ciprofloxacin for 3 weeks or 3 months led to longer duration until Pa acquisition: 5 months in the 3 week group and 10.4 months in the 3 month group (not statistically different from those treated for 3 weeks) compared to 1.9 months in the untreated group (statistically significant difference from the treated groups).[51] These patients were also evaluated for development of chronic infection, according to criteria from both Copenhagen and Leeds. Anti-pseudomonal therapy delayed time to chronic infection to 3.7 years in 12 of the 99 patients who were treated. Eighty percent of all treated patients were protected from chronicity up to 15 years. Though time to chronic infection varied a few years depending on the definition used, all 12 patients ultimately met criteria from both Copenhagen and Leeds, demonstrating good agreement between the definitions of chronicity from the two centres.

A recent article from the Cochrane Database of Systematic Reviews addressed the issue of antibiotic therapy for eradication of Pa in patients with CF.[52] The authors included randomized, controlled trials evaluating combinations of inhaled, oral or intravenous antibiotics versus placebo, usual treatment, or other combinations of inhaled, oral or intravenous antibiotics. Twenty-five studies were initially identified; four met inclusion criteria and were conducted in paediatric patients only. The authors concluded inhaled antibiotics, alone or in combination with oral antibiotics, successfully eliminated Pa from CF patients more often than no treatment. Further, they noted some lasting effect of the antibiotic treatment in maintaining eradication. Even with this systematic evaluation,

however, they were unable to determine the best regimen for Pa eradication based on the published data available.

Studies Underway—Any Treatment Guideline in Sight?

Several large, randomized, multicenter trials are currently underway to further evaluate widely used anti-pseudomonal regimens (Table 4). The European ELITE study assigned patients to 28 or 56 days of inhaled tobramycin, with a follow up period of 27 months.[53] Preliminary reports show no significant benefit to continuing therapy beyond the 28 day period, with both groups showing approximately 90% eradication of Pa after one month of treatment. In the United States, investigators are comparing cyclic anti-pseudomonal treatment with culture-based therapy in the EPIC study.[54] Three hundred and six patients were enrolled and treated upon first acquisition of Pa. Subsequent treatment was either scheduled quarterly or based on results from respiratory cultures taken every 3 months. To examine the benefit of additional oral anti-pseudomonal therapy, each group was further randomized to receive oral ciprofloxacin or placebo in addition to inhaled tobramycin. Preliminary results presented at the North American CF Conference in October, 2009 suggested that all the approaches to Pa eradication were effective. However, the preventative approach did not appear to be more effective than culture-based therapy. Furthermore, the addition of ciprofloxacin did not confer additional benefit over inhaled tobramycin alone (www.cff.org). Another smaller study underway in Belgium randomized patients with newly isolated Pa (from sputum or cough swabs) to treatment with either inhaled tobramycin or inhaled colistin plus oral ciprofloxacin.[55] Early analysis has shown that both regimens have comparable rates of immediate and lasting Pa eradication, though only half of patients treated in either arm remain free of Pa at 6 months without additional antibiotic treatment. Finally, 168 infants diagnosed with CF by newborn screening in Australia and New Zealand were recruited to a 5 year prospective, randomized trial of BAL-directed therapy.[56] Patients in one arm of the trial were treated based on clinical symptoms and results of cough suction specimens while therapy for the other arm was based on BAL results from routine bronchoscopy or BAL performed during exacerbations. Treatment consisted of IV therapy, followed by inhaled and oral anti-pseudomonal medications. In patients followed for two years thus far, 100% have successfully eradicated Pa in both groups, bolstering the evidence for Pa infection early in life and the ability to successfully eradicate the organism when diagnosed.

For early eradication of Pa, the utility and efficacy of inhaled colisitin or tobramycin have clearly been demonstrated. Parenteral antibiotics may be beneficial as additional therapy, as their use alone has resulted in Pa elimination in some studies.[57] Results from the ELITE and EPIC trials will be valuable in refining an early eradication regimen for patients with Pa. Specifically, duration of treatment and the usefulness of oral antibiotics may be readily ascertained once these studies are complete. We eagerly await the results of these trials for further treatment recommendations.

A Note about Drug Delivery

While the benefit of inhaled antibiotic therapy for Pa eradication is clear, treatment guidelines must also account for mode of delivery of these medications, recently reviewed

by Kesser and Geller.[58] The use of nebulised drugs presents multiple challenges to patients with CF and the clinicians caring for them. First, the drug-containing particles must be of an appropriate size to reach the target destination in the lung. This issue is particularly challenging in young children, who have small calibre airways and small tidal volumes and are limited to tidal breathing and mask interfaces.[59,60] Medication administration time also presents a difficulty for patients striving to be compliant with multiple therapies. Nebulisers that deliver therapy more quickly are available and have already been used with some CF therapies, including vibrating-mesh nebulisers such as the eFlow (PARI Pharma) and the Aerogen AeroNebGo (Nektar Therapeutics, now part of Novartis). Nebulisers must be cleaned and sterilised on a regular basis to ensure accurate drug delivery, another factor adding to the already time-intensive daily schedule of CF patients. Portable, low maintenance models that deliver medication quickly are currently under development to facilitate patient adherence to treatment.

Ensuring accurate dosing of inhaled antibiotics is perhaps the most concerning aspect of nebuliser use for Pa eradication. Initial pharmacokinetic (PK) studies performed on sputum from patients using the UltraNeb 100 (DeVilbiss) ultrasonic nebuliser showed tobramycin was delivered well with this machine.[61] Follow up studies using the LC Plus (PARI Pharma) jet nebuliser showed the same high sputum levels of tobramycin could be achieved with half the nominal dose, indicating that drug dosing is device-specific.[62–64] New nebulisers have been designed to deliver medication with decreased residual volumes, resulting in more complete dose delivery. The eFlow is one such model, though a second eFlow version (eFlow Rapid) was designed according to delivery efficiency parameters seen with the use of the PARI LC jet nebuliser.[58] The eFlow Rapid has a larger residual volume and a smaller aerosol chamber, resulting in more drug loss during exhalation; thus, the two eFlow models cannot be used interchangeably. Other novel nebulisers are designed to control patient breathing during drug delivery to prevent medication waste, including adaptive aerosol delivery systems such as I-neb (Respironics/Philips) and the Akita device (Activaero).

As newer, ultrafast nebulisers enter the market, clinicians must caution patients against indiscriminate use of nebuliser machines for different therapies. In 2008, an expert panel convened by the European CF Society agreed that: “Every drug-device combination should be tested in clinical studies for efficacy and safety, especially for drugs with a small therapeutic window.”[65] Indeed, many therapies based on the results of clinical trials are only approved for a specific drug-nebuliser combination. Off-label use of these nebulisers may result in insufficient dosing of the drug as was seen with use of the Sidestream (Respironics) nebuliser to administer inhaled tobramycin; pharmacokinetic studies showed the lung dose of tobramycin was half of that seen with use of the on-label nebuliser the Pari LC Plus.[62] The off-label use of these machines may also have toxic side effects (e.g., tachyarrhythmia with unit-dose albuterol); thus, care must be exercised and instructions must be specific regarding nebuliser use for control of Pa in CF patients.

Future Directions

Early eradication therapies against Pa have been shown to be effective based on microbiologic data. How this treatment affects the clinical course of CF, however, remains

unclear. As early as 1989, Steinkamp et al demonstrated some improvement in weight for height ratio and overall clinical status following eradication therapy.[66] Those with poor lung function at the beginning of therapy showed significant improvement. Almost a decade later, Frederiksen and colleagues also showed improvement in pulmonary function (FVC and FEV^1) in patients treated with inhaled colisitin and oral ciprofloxacin.[45] Conversely, other studies have shown no change in lung function after treatment.[46,47] In spite of these findings, the association of Pa chronic infection with worse outcome is well-established.[67–69] Thus, protecting patients with CF from becoming chronically colonized with Pa remains a priority to clinicians and researchers alike.

Several alternative strategies are under investigation, including the use of a daily mouthwash containing anti-pseudomonal IgY and vaccination against Pa (recently reviewed by Johansen and Gotzsche).[70,71] Unfortunately, confounding therapy in the Nilsson et al study and the frequency of adverse events in one of the largest vaccination trials have prevented recommendation of these treatment modalities at this time.[70,71] Other therapies such as nebulised antibodies against Pa, new antibiotic formulations (including liposomal and dry-powder inhaled preparations) and more effective delivery devices are under development. Ultimately, preventing chronic colonization of Pa remains an important goal for maintaining quality of life and longevity in patients with CF.

NOTE IN PROOF

Since submission of this paper, the results of the European ELITE study have been published.[72] This study was a large, randomized, multicenter trial undertaken to examine the safety and efficacy of 28 or 56 days of inhaled tobramycin in the eradication of Pa. Cystic fibrosis patients 6 months or older were enrolled from November 2003 to January 2008 and given 28 days of inhaled tobramycin solution. At the end of this period, participants were randomized to either stop treatment or continue for an additional 28 days. Recently published results from this trial showed eradication of Pa (by either deep throat swab or sputum culture) was similar in both groups, with 93% and 92% free of Pa one month after the end of treatment in the 28- and 56-day groups, respectively.[72] The median time to recurrence was 26.12 and 25.82 months in the 28- and 56-day treatment groups, respectively, not a statistically significant difference. The ELITE trial demonstrates that a 28-day regimen of inhaled tobramycin is effective in treating early Pa infection and extending the treatment to 56 days does not provide any additional benefit. Given the scale of this study, clinicians should consider a shorter course of inhaled tobramycin effective in early eradication of Pa.

Abbreviations

Pa	Pseudomonas aeruginosa
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
BAL	bronchoalveolar lavage

OP	oropharyngeal
PCR	polymerase chain reaction

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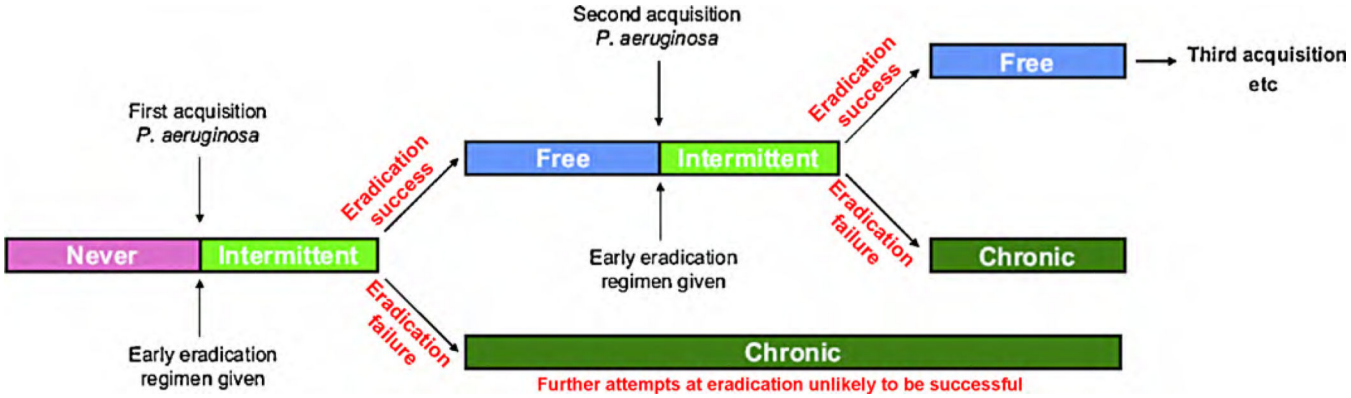

Figure 1.

Illustration of the time course of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis using Leeds definition of infection and colonization[36]. Taken with permission from Lee[3].

Table 1

Diagnostic values of OP cultures for *Pseudomonas aeruginosa*.

Authors	Year	Sensitivity	Specificity	PPV	NPV	Conclusions
Ramsey *et al*[20]	1991	46%	93%	83%	70%	OP+ cultures are highly predictive, but cultures lacking organisms do not rule out the presence of pathogens in the lower airways.
Armstrong *et al*[18]	1996	71%	93%	57%	96%	OP cultures do not reliably predict the presence of lower airway pathogens.
Rosenfeld *et al*[19]	1999	44% (≤18 month old)68% (>18 month old)	95% (≤18 month old)94% (>18 month old)	44% (≤18 month old)76% (> 18 month old)	95% (≤18 month old)91% (> 18 month old)	OP− culture indicated that isolation of Pa was unlikely, while OP+ culture did not reliably predict lower airway Pa infection.
Burns *et al*[17]	2001			69%83% (using 2 OP cultures, drawn 3 months apart)	85–95%97% (using 2 OP cultures, drawn 3 months apart)	Use of 2 OP cultures (separated by 3 months) in nonexpectorating patients could be a useful surrogate marker.

Pa-*Pseudomonas aeruginosa*, OP-oropharyngeal, OP+ oropharyngeal cultures with growth, OP− oropharyngeal cultures without growth, PPV-positive predictive value, NPV-negative predictive value.

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Table 2

Classification of *Pseudomonas aeruginosa* Infection

	Copenhagen[34]	Leeds[36]	European Consensus[21]
Chronic infection	6 consecutive monthly sputum samples with growth of Pa, or a rise in Pa-specific antibodies	Pa cultures were positive in 50% or more of the 12 months	Presence of Pa for at least 6 months, based on 3 positive cultures at least 1 month apart
Intermittent infection	At least 1 isolate of Pa with normal Pa antibody levels	Pa cultures were positive in 50% or less of the 12 months	
Free of infection		No growth of Pa during the previous 12 months, having had a previous Pa positive culture	
Never		Pa never cultured from sputum or cough swab	

Pa-*Pseudomonas aeruginosa*

Table 3

Pseudomonas aeruginosa Eradication Studies

Investigators	Pt. No.	Method of detection	Type of study	Regimen (*drug/duration*)	Success of eradication; Duration of eradication	Other comments/ conclusions
Littlewood[42]	7	OP or Sp	Case study	INH colistin	NANA	Decreased frequency of Pa+ after initiation of drug
Steinkamp[58]	14	OP or Sp	Open, no control	INH tobramycin, variable time (mean 20 months)	NANA	Efficacious and safe Patients were chronically infected.
Steinkamp[57]	28	OP or Sp	Open, no control	IV tobramycin + IV azlocillin × 14 days	Pa-: 64% 2 d after tx end. Pa-: 35%–3mo, 18%–6mo, 47% 14 mo. to study end.	Safe; some still Pa+ at tx end, most Pa + by 3–6 months after therapy.
Valerius[43]	26	Sp	RCT with untreated control	INH colistin + PO ciprofloxacin × 21 days	NA; Not chronically colonized: 86% of tx, 42% of ctrl group mean 17.4 months	Endpoint: time to chronic colonization using the Copenhagen criteria*
Vazquez[44]	16	OP or Sp	Historic control group	INH colistin and INH tobramycin + PO Ciprofloxacin × 14 days	NA Mean follow up: 27.4 months (tx), 24.2 months (ctrl)	Based on number of Pa+ cultures, not patients, Pa+ in 4.6% tx vs. 86% ctrl group ($p<0.001$)
Frederiksen[45]	91	OP or Sp	Historic control group	INH colistin + PO ciprofloxacin × 3 weeks-3 months	Pa- (until onset of chronic Pa): 86% tx vs. 75% ctrl; Not chronically colonized: 84% of tx, 28% of ctrl group at 3.5 years	Endpoint: time to chronic colonization using the Copenhagen criteria*
Wiesemann[46]	22	OP or Sp	RCT with placebo control	INH tobramycin × 1 year	NANA	Analyzed by “time to event” (conversion to Pa- culture); only assessed in tx group: 1.89 months (mean); Large pt. dropout rate.
Ratjen[47]	15	OP or Sp (*very specifically defined-no Ab hx, no Pa+ hx*)	Open, no control	INH tobramycin × 1 year	Pa-: 93%Pa- AND Ab-: 93% at 1 year, 60% still Pa- and Ab- at 2 years	Early Pa+ patients, also supported with serological data.
Munck[64]	19	OP or Sp(*also <2 precipitin antibodies*)	Open, no control	IV ceftazidime or imipenem × 2–3 wk then INH colistin × at least 2 months	Pa-: 100% at end of tx Pa-: 3–25 months	Unrelated strains of Pa seen in all pts, though 5 pts. had some isolates with identical genotypes.
Nixon[30]	24	BAL/Sp, tracheal aspirate	Prospective, observational cohort (Patients identified by newborn screening)	IV timentin/tobramycin (or other) × 2 weeks, then PO ciprofloxacin and/or INH tobra × 3 months	NA at >12 mos, 25% still Pa-.	Following Pa acquisition prospectively with BAL, tx undertaken when Pa+.
Heinzl[65]	28	OP/Sp	Retrospective analysis of prophylaxis policy for “high-risk” CF Patients	INH gentamycin: continuous vs. intermittent tx Mean: 6.5 years	NAPa-: 100% in continuous tx group, 44% in intermittent group within 9–53 months	Endpoint: time to Pa acquisition$^{\theta}$
Gibson[48]	21	BAL	RCT with placebo control	INH Tobramycin × 28 days	Pa-: 100% tx, 7% ctrl Pa- at 2 mo: 75% tx	First RCT showing eradication in lower airways

Investigators	Pt. No.	Method of detection	Type of study	Regimen (*drug/duration*)	Success of eradication; Duration of eradication	Other comments/ conclusions
Taccetti[**50]	47	"respiratory secretions"	Sequential cohort study with historical control group	INH colistin + PO ciprofloxacin ×3 wks (extended to 3 months if still Pa+)	81%[*]18 month eradication (median)	51% recolonised (and retreated) during the 7 year study period; new strains in 73% of strains genotyped
Gibson[49]	31	BAL	Open label, sequential cohort, multicenter	INH tobramycin × 28 or 56 days, variable follow up	75% in 28/56 cohort, 63% in 28/84 cohort; 82% in 56/112 cohort; 75% in 28/112 cohort	Of patients with negative exotoxin A titres, ALL had successful eradication. Inhaled tobramycin more robust anti-microbial effect on lower airway Pa.
Hansen[51]	146	LRT/sputum	Descriptive, retrospective cohort study, historical controls	INH colistin + PO ciprofloxacin × 21 or 90 days	Pa- at 6 months: 21 day tx: 50%; 90 day tx: 81% Time to Pa+: 21 day tx: 5 months, 90 day tx: 10.4 months, ctrl: 1.9 months Time to chronic infection: 3.7 years in 12% of Pa+ 80% protected from chronicity up to 15 years	Endpoints: time to Pa acquisition and time to chronic colonization by both Copenhagen[*] and Leeds[**] criteria

[*] Copenhagen criteria[24];

[**] Leeds criteria[26];

θ Defined as 2 or more Pa+ bacterial cultures from respiratory secretions obtained within a 3 month time span.

OP-oropharyngeal, Sp-sputum, BAL-bronchoalveolar lavage, LRT-obtained by endolaryngeal suctioning, RCT-randomized controlled trial, INH-inhaled, IV-intravenous, PO-oral, Pa-Pseudomonas aeruginosa, NA-not available, tx-treatment, ctrl-control.

Table 4

Ongoing Studies of *Pseudomonas aeruginosa* Eradication

Investigators	No. Pts.	Type of study	Treatment Arms	Preliminary Results
ELITE (European)	88	Multicenter, Open-label, RCT	INH tobramycin × 28 or 56 days	~90% eradication in both groups 1 mo after end of treatment (conference presentation) — awaiting publication
Ratjen et al[53]		Primary endpoint: median time to recurrence of Pa		
EPIC (US)	306	Multicenter, RCT	INH tobramycin × 28 days + PO ciprofloxacin × 14 days	Preliminary results show all approaches are effective; the addition of ciprofloxacin does not appear to add any benefit (conference presentation)— awaiting publication
Treggiari et al[54]		Cycled therapy based on first Pa+ culture versus culture-based therapy after initial treatment	OR PO placebo × 14 days	
Belgian Study	50, 32 analyzed thus far	Single centre, RCT	INH tobramycin × 28 days	Initial Pa clearance in 82% in patients on INH tobramycin, 93% on colisitin+ciprofloxacin; 41% on INH tobramycin and 46% on colistin+ciprofloxacin remained Pa- at 6 months
Proesmans et al[55]		Comparison of two antibiotic regimens in patients with new Pa+ cultures	OR INH colisitin+PO ciprofloxacin × 3 months	
Australasian BAL	168 infants	Multicenter, Prospective, RCT	IV tobramycin +timentin or ceftazidime, followed by	100% eradication in all pts followed for 2 years thus far, regardless of BAL or cough suction as culture source
Wainwright et al[56]		Evaluation of BAL versus non-BAL directed therapy	INH tobramycin × 2 months +PO ciprofloxacin × 1 month	

RCT-randomized controlled trial; Pa-*Pseudomonas aeruginosa*, Pa+-Pa positive culture, Pa- -Pa negative culture, BAL-bronchoalveolar lavage, INH-inhaled, PO-oral.