Cystic Fibrosis Foundation Pulmonary Guideline*

Pharmacologic Approaches to Prevention and Eradication of Initial *Pseudomonas aeruginosa* Infection

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Abstract

Description: The Cystic Fibrosis (CF) Foundation developed clinical care guidelines for the prevention of *Pseudomonas aeruginosa* infection, the treatment of initial *P. aeruginosa* infection, and the use of bronchoscopy to obtain routine airway cultures in individuals with CF.

Methods: A multidisciplinary committee developed questions about the prevention and treatment of initial *P. aeruginosa* infection and the use of bronchoscopy to obtain routine airway cultures. The outcome measure of interest was cultures without *P. aeruginosa* growth. Systematic reviews of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials were conducted in May 2012 and August 2013. Searches combined controlled vocabulary terms and text words for CF and terms relevant to each question. The entire committee reviewed the evidence, and final recommendation statements were graded using the U.S. Preventive Services Task Force system.

Recommendation 1: The CF Foundation strongly recommends inhaled antibiotic therapy for the treatment of initial or new growth of *P. aeruginosa* from an airway culture (certainty of net benefit, high; estimate of net benefit, substantial; grade of recommendation, A). The favored antibiotic regimen is inhaled tobramycin (300 mg twice daily) for 28 days.

Recommendation 2: The CF Foundation recommends against the use of prophylactic antipseudomonal antibiotics to prevent the acquisition *P. aeruginosa* (certainty of net benefit, moderate; estimate of net benefit, zero; grade of recommendation, D).

Recommendation 3: The CF Foundation recommends routine oropharyngeal cultures rather than bronchoalveolar lavage cultures obtained by bronchoscopy in individuals with CF who cannot expectorate sputum to determine if they are infected with *P. aeruginosa* (certainty of net benefit, moderate; estimate of net benefit, moderate; grade of recommendation, B).

Keywords: inhaled antibiotics; bronchoscopy; oropharyngeal culture; antipseudomonal vaccine; airway infection

(Received in original form April 18, 2014; accepted in final form October 5, 2014)

*These guidelines were developed and supported by the Cystic Fibrosis Foundation and are not official guidelines from the American Thoracic Society (ATS). They have not been reviewed or endorsed by the ATS Board of Directors.

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Author Contributions: All authors and committee members participated in review of the literature and development of recommendations and review of the manuscript. P.J.M., E.T.N., K.A.R., C.B., M.G., T.L., L.L., J.M., F.R., M.R., C.M.O., R.H.S., L.H., K.S., and B.C.M. formed a writing subcommittee to compose the manuscript. P.J.M., and E.T.N. were primarily responsible for editing the manuscript. K.A.R. was responsible for conducting the systematic review.

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This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Ann Am Thorac Soc Vol 11, No 10, pp 1640–1650, Dec 2014

DOI: 10.1513/AnnalsATS.201404-166OC
Internet address: www.atsjournals.org

Abnormal ion transport in epithelial cells residing on the cystic fibrosis (CF) airway surface and in submucosal glands alters antimicrobial airway defenses and promotes chronic endobronchial infection with bacteria such as *Pseudomonas aeruginosa*. This infection is associated with an enhanced inflammatory response in the airways (1). Clinically, the acquisition of *P. aeruginosa* is associated with more parenchymal damage, a more rapid decline in lung function, and earlier mortality (2–7). For example, Emerson and colleagues found that the presence of *P. aeruginosa* was associated with a 2.6-fold increase in the 8-year mortality in children with CF (4). Therefore, an effective strategy to prevent chronic infection could have a significant impact on individuals with CF.

It is hypothesized that *P. aeruginosa* infections initially occur transiently before progressing to chronic infection. Over time, *P. aeruginosa* adapts to the airway by developing a "mucoid" phenotype that exists within a biofilm, which contributes to the development of persistent, difficult-to-eradicate infection (8). However, early antibiotic therapy has the potential to clear or "eradicate" initial *P. aeruginosa* infection and to postpone chronic infection with this organism. Early evidence that the aggressive approach to prevention and treatment of *P. aeruginosa* could lead to a substantial reduction in the prevalence of this organism and improved survival was demonstrated in Denmark (9, 10). In addition, many retrospective and uncontrolled studies suggest that antibiotic therapy can prevent progression from a transient infection to a persistent or chronic infection (for review, *see* Reference 11). More recently, prospective randomized controlled trials (RCTs) have demonstrated the effectiveness of inhaled antibiotics in clearing *P. aeruginosa* infection when it is first identified. Although these studies focus primarily on microbiologic outcomes, there is evidence that effective treatment of *P. aeruginosa* infection will lead to better clinical outcomes (12, 13). Because the optimal approach to eradication of initial *P. aeruginosa* infection is unclear, we undertook a systematic review of the medical literature to develop guidelines for effective prevention and eradication strategies (Table 1).

Table 1. Summary of recommendations

Disease	Cystic fibrosis (CF)
Target audience	Physicians and other clinicians
Target population	Individuals with CF
Interventions	Inhaled and oral antibiotics Bronchoscopy Vaccines against *Pseudomonas aeruginosa*
Outcomes	Cultures without growth of *P. aeruginosa*
Recommendations	Recommendation 1: The CF Foundation strongly recommends inhaled antibiotic therapy for the treatment of initial or new growth of *P. aeruginosa* from an airway culture (certainty of net benefit, high; estimate of net benefit, substantial; grade of recommendation, A). The favored antibiotic regimen is inhaled tobramycin (300 mg twice daily) for 28 d. Recommendation 2: The CF Foundation recommends against the use of prophylactic antipseudomonal antibiotics to prevent the acquisition *P. aeruginosa* (certainty of net benefit, moderate; estimate of net benefit, zero; grade of recommendation, D). Recommendation 3: The CF Foundation recommends routine oropharyngeal cultures rather than bronchoalveolar lavage cultures obtained by bronchoscopy in individuals with CF who cannot expectorate sputum to determine if they are infected with *P. aeruginosa* (certainty of net benefit, moderate; estimate of net benefit, moderate; grade of recommendation, B).
High-value care	Antibiotic therapy is effective for eradicating newly acquired *P. aeruginosa* infections; however, routine prophylaxis to prevent infection is not effective. Bronchoscopy for the routine monitoring for *P. aeruginosa* airways infection is not recommended.
Clinical considerations	Individuals infected with *P. aeruginosa* who have significant symptoms or those who are experiencing an exacerbation may require additional therapies beyond inhaled tobramycin. Although bronchoscopy is not recommended for obtaining routine cultures, it can be a valuable tool in individuals who fail to respond as expected to therapy and in other clinical settings.

Recommendations

1. The CF Foundation strongly recommends inhaled antibiotic therapy for the treatment of initial or new growth of *P. aeruginosa* from an airway culture (certainty of net benefit, high; estimate of net benefit, substantial; grade of recommendation, A). The favored antibiotic regimen is inhaled tobramycin (300 mg twice daily) for 28 days.
2. The CF Foundation recommends against the use of prophylactic antipseudomonal antibiotics to prevent the acquisition *P. aeruginosa* (certainty of net benefit, moderate; estimate of net benefit, zero; grade of recommendation, D).
3. The CF Foundation recommends routine oropharyngeal cultures rather than bronchoalveolar lavage cultures obtained by bronchoscopy in individuals with CF who cannot expectorate sputum to determine if they are infected with *P. aeruginosa* (certainty of net benefit, moderate; estimate of net benefit, moderate; grade of recommendation, B).

Methods

An 18-member multidisciplinary committee developed a series of questions about the effectiveness of prevention and eradication strategies for *P. aeruginosa* infection and the use of bronchoscopy to obtain routine airway cultures. The outcome of interest was cultures without growth of *P. aeruginosa*. The key questions were as follows. (*1*) What is the best eradication therapy for a newly acquired *P. aeruginosa* infection? (*2*) Can prophylactic antibiotic therapy prevent *P. aeruginosa* infection? (*3*) What is the role of bronchoscopy in obtaining routine airway cultures?

Systematic reviews were commissioned from The Johns Hopkins University. Searches of PubMed, EMBASE, and the Cochrane Central Register of Controlled

Trials (CENTRAL) were conducted in May 2012 and updated in August 2013. The searches combined controlled vocabulary terms and text words for CF and terms relevant for each question to create comprehensive search strategies. Reference lists of relevant Cochrane reviews were also scanned, and references of eligible articles were examined. All identified citations were imported into a database maintained in reference management software (ProCite; ThomsonReuters, New York, NY). A custom workform was used to track the search results. Citations were uploaded into a web-based system (DistillerSR; Evidence Partners Inc., Ottawa, ON, Canada) to complete and track the screening process. Two reviewers independently screened citations for eligibility, first using title and abstract. Citations determined to be potentially eligible were subsequently screened using the full text or full article. Predefined eligibility criteria were applied during the screening process. However, additional criteria were added for the full-text screen based on feedback from the chairs of the committee to remove studies of individuals with chronic *P. aeruginosa* infection. Specifically, studies with a population defined by authors as chronically infected with *P. aeruginosa* or articles stating that subjects had two or more positive *P. aeruginosa* cultures in previous 12 months were excluded from consideration. Disagreements concerning eligibility were resolved by consensus or by a third reviewer.

Data abstraction forms were developed based on the forms from prior projects. Using the forms, two reviewers abstracted information about study and participant characteristics and about outcomes from each eligible article. Information from completed forms was entered into a custom designed database (Access; Microsoft, Redmond, WA). Evidence tables were created from the database and provided to the committee members as Excel spreadsheets (Microsoft).

The committee met in October 2012 and October 2013 to review the evidence and to make recommendations. Committee members disclosed any potential conflicts of interest in writing to the CF Foundation. One member, having previously served on an advisory board, was recused from discussion of inhaled aztreonam. Three committee members served as principle investigators for studies reviewed by the committee. These individuals recused themselves from discussion of these studies, but they did participate in the formulation of the recommendations.

The evidence was reviewed by the committee, and the final recommendations were graded using the U.S. Preventive Services Task Force system, which assesses net benefit and certainty of net benefit (14) (Table 2). The domains considered by the committee to determine the certainty of benefit included the number of trials identified by the search, the number of participants in each trial, the consistency of findings between the trials, and the likelihood that future studies would alter the recommendation of the committee. In addition, the committee members were provided with a report that included risk of bias assessments based on the Cochrane risk of bias tool.

A draft manuscript with recommendations was posted on the CF Foundation intranet for review and comment by members of the CF professional community and patient and parent representatives. These comments were considered in the final preparation of these guidelines.

The search identified 3,547 unique citations, of which 18 citations describing 13 studies were eligible for inclusion (Figure 1). We identified seven treatment trials of initial or newly acquired *P. aeruginosa* infection that ranged in size from 21 to 304 individuals with CF (15–21). Only three of the seven trials concealed allocation of study subjects to the intervention and used blinded or masked outcome assessment (19, 21, 22). Two trials compared inhaled tobramycin with placebo (15, 21). One trial compared inhaled colistin and oral ciprofloxacin with no therapy (20). Four studies compared a variety of combinations of oral ciprofloxacin, inhaled colistin, and inhaled tobramycin for treatment of *P. aeruginosa* infection (16–19). Two studies evaluated antibiotic or vaccine prophylaxis to prevent infection (22, 23). Four studies evaluated the accuracy of oropharyngeal (OP) cultures compared with bronchoalveolar

Table 2. United States Preventive Services Task Force evidence grading*

Certainty of Net Benefit†	Magnitude of Net Benefit (Benefit minus Harms)			
	Substantial	Moderate	Small	Zero/Negative
High	A‡	B	C	D
Moderate	B	B	C	D
Low	I (insufficient evidence)			

*The overall strength of the evidence is based on the certainty of the magnitude of benefit defined as benefit minus harm. Adapted from Reference 46.
†Certainty of net benefit: High = The available evidence includes consistent results from well-designed, well-conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies. Moderate = The available evidence is sufficient to determine the effects of the therapy on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings; or a lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. Low = The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of a limited number or size of studies, important flaws in study design or methods, inconsistency of findings across individual studies, gaps in the chain of evidence; findings not generalizable, or lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
‡Strength of recommendation: A = The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial. B = The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. C = The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms, there is likely to be only a small benefit from this therapy. D = The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this therapy. I = The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the therapy. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

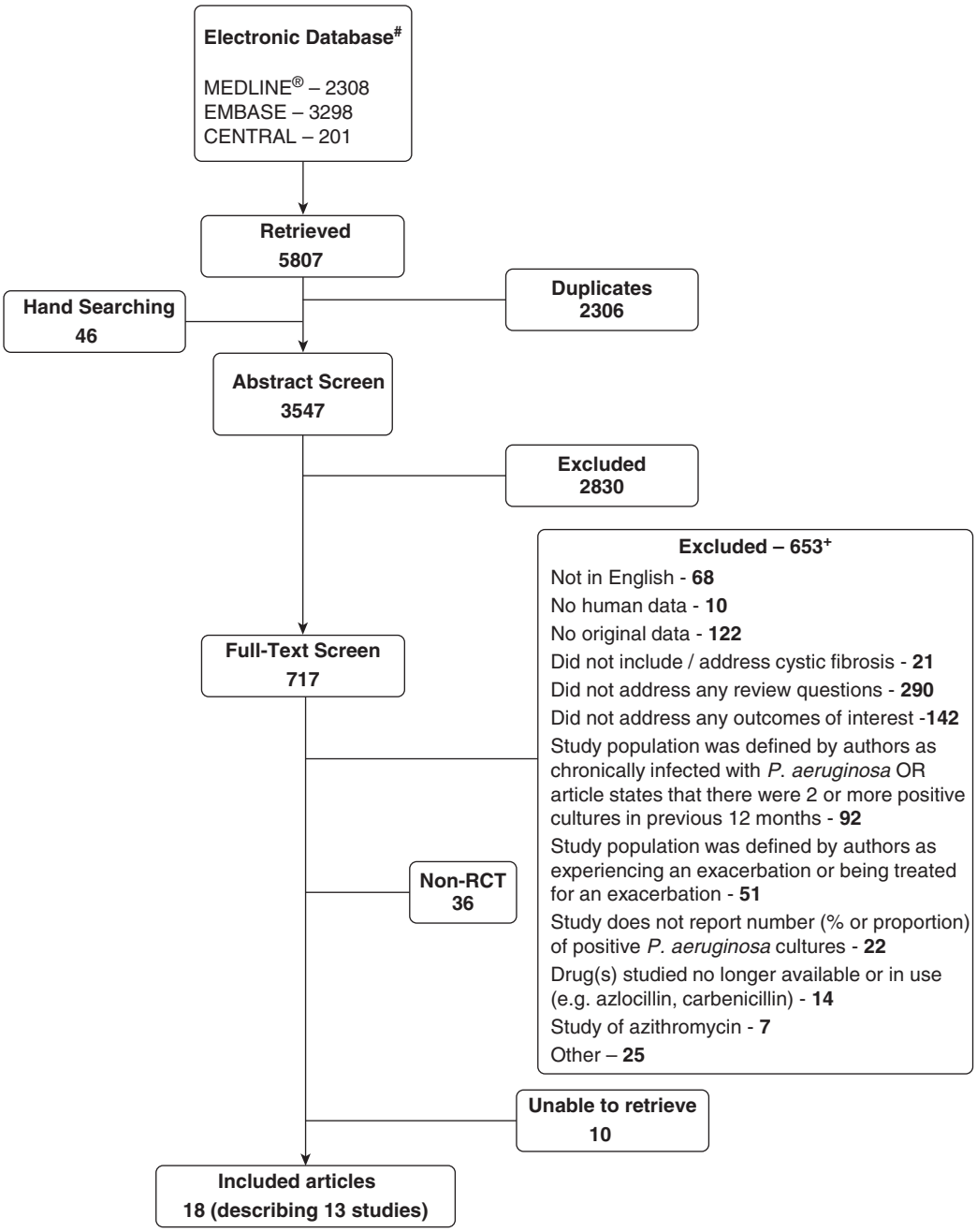

Figure 1. Summary of the search and review process. RCT = randomized controlled trial. #MEDLINE was accessed via PubMed. +Papers could be excluded for multiple reasons.

lavage fluid (BALF) cultures for the identifying *P. aeruginosa* infection (24–27).

Scientific Rationale

Eradication Therapy for Newly Acquired *P. aeruginosa* Infection

We identified seven studies that investigated approaches to *P. aeruginosa* eradication therapy (Table 3). Some studies defined population as early or new *P. aeruginosa* infection, whereas others enrolled participants up to 6 months after first *P. aeruginosa* isolation. Three studies compared inhaled and oral therapy to placebo or no therapy (15, 20, 21). The remaining studies compared various treatments to identify an optimal eradication strategy (16–19). The primary outcome of interest in these studies was *P. aeruginosa* growth in airway cultures. The committee's certainty of the net benefit was not diminished by the use of a surrogate for clinical outcomes because eradication of *P. aeruginosa* growth has been associated with both mitigation of lung function decline and delay of chronic infection (10, 12, 28). Additionally, the failure to eradicate initial *P. aeruginosa*

Table 3. Studies of *Pseudomonas aeruginosa* eradication

Study (sample size)	Mean Age ± SD (years)	Entry Criteria	Study Type	Detection Method	Interventions	Initial Eradication	Freedom from Pa Infection at Study End
Valerius *et al.*, 1991 (20); n = 26	Median, 8.6 (treatment)	First Pa and no previous antipseudomonal treatment	RCT/ OL	Sputum	Inhaled colistin (1 million IU bid) and oral ciprofloxacin (250–750 mg) for 3 wk (repeated with each positive culture) vs. no therapy		Treatment, 86% (12/14)
	Median, 10.8 (placebo)						No treatment, 42% (5/12) at 27 mo ($\chi^2 = 3.41$; $P < 0.05$)
Wiesemann *et al.*, 1998 (21); n = 22	11.4 ± 10.1 (treatment)	First Pa and no serum antibodies	RCT	OP/sputum	Inhaled tobramycin (80 mg bid) vs. placebo for 12 mo		Tobramycin, 90% (9/10)
	9.8 ± 9.8 (placebo)						Placebo, 20% (1/5) at 12 mo; $P < 0.05$
Gibson *et al.*, 2003 (15); n = 21	3.7 ± 1.6 (treatment)	Pa obtained from BAL	RCT	BAL/OP	Inhaled tobramycin (300 mg bid) vs. placebo for 28 d	Tobramycin, 100% (8/8)	Tobramycin, 75% (6/8)
	4.0 ± 1.5 (placebo)					Placebo, 8% (1/13) at 28 d; $P < 0.0001$	Placebo, 23% (3/13) at 56 d
Ratjen *et al.* (ELITE), 2010 (17); n = 88	8.7 ± 7.2 (treatment)	No Pa in the past year and no serum antibodies	RCT/ OL	OP/sputum	Inhaled tobramycin (300 mg bid) for 28 d vs. 56 d	28 d, 93% (n = 45)	28 d, 66% (n = 41)
	8.7 ± 10.5 (placebo)					56 d, 92% (n = 43) 1 m after treatment end (NS)	56 d, 69% (n = 36) at 27 mo (NS)
Treggiari *et al.* (EPIC), 2011 (19); n = 304	5.5 ± 3.5 (ciprofloxacin)	First Pa or second Pa in past 2 yr and ⩽1 courses of previous inhaled or intravenous antipseudomonal treatment	RCT	OP/sputum	Inhaled tobramycin (300 mg bid) for 28 d and oral ciprofloxacin or placebo for 14 d		Cycled ciprofloxacin cycled, 90% (60/67)
	5.9 ± 3.6 (placebo)				Treatments were given for positive cultures or cycled routinely every 3 mo		Cycled placebo, 91% (59/65)
							Culture-based ciprofloxacin, 85% (56/66)
							Culture-based placebo 91% (63/69) at 70 wk (NS)

(Continued)

Table 3. (*Continued*)

Study (sample size)	Mean Age ± SD (years)	Entry Criteria	Study Type	Detection Method	Interventions	Initial Eradication	Freedom from Pa Infection at Study End
Taccetti *et al.*, 2011 (18); n = 223	Median, 7.5 (colistin)	First Pa or no Pa in previous 6 mo (⩾3 cultures)	RCT/ OL/ parallel group	OP/sputum	Inhaled tobramycin (30 mg bid) vs. Inhaled colistin (2 million IU bid) for 28 d. Both groups received oral ciprofloxacin.	Colistin, 80% (84/105)	Colistin, 63% (66/105)
	Median, 7.6 (tobramycin)					Tobramycin, 78% (92/118) at 2 mo (NS)	Tobramycin, 65% (77/118) at 6 mo (NS)
Proesmans *et al.*, 2012 (16); n = 58	Median, 10.8 (colistin)	First Pa or no Pa in previous 6 mo (⩾ 3 cultures)	RCT/ OL	OP/ sputum/ BAL	Inhaled tobramycin (300 mg bid) for 28 d vs. Inhaled colistin (2 million IU bid) and oral ciprofloxacin for 3 mo	Colistin, 90% (26/29)	Colistin, 61% (14/23)
	Median, 8.8 (tobramycin)					Tobramycin, 79% (23/29) (NS)	Tobramycin, 54% (13/24) at 24 mo (NS)

Definition of abbreviations: BAL = bronchoalveolar lavage; NS = nonsignificant; OL = open label trial; OP = oropharyngeal; Pa = *Pseudomonas aeruginosa*; RCT = randomized control trial.

infection is associated with subsequent pulmonary exacerbations (13), and chronic infection is associated with and may contribute to loss of lung function and increased mortality (2–7).

Valerius and colleagues evaluated the efficacy of 3 weeks of inhaled colistin (1 million IU twice daily) and oral ciprofloxacin (250–750 mg, based on weight, twice daily) compared with no antipseudomonal treatment in 26 children 2 to 9 years of age whenever routine, monthly cultures grew *P. aeruginosa* (20). At the end of 27 months, only 14% (2/12) of the treated individuals were infected with *P. aeruginosa*, compared with 58% (7/12) of the untreated individuals ($P < 0.05$). Infection was defined as growth of *P. aeruginosa* in six consecutive airway cultures and/or the presence of precipitating serum antibodies to *P. aeruginosa.* Wiesemann and colleagues compared inhalation of tobramycin (80 mg twice daily) for 12 months with placebo (21). Twenty-two individuals 4 to 18 years of age who grew *P. aeruginosa* for the first time and had no serum antibodies to *P. aeruginosa* were randomized to each treatment arm. Two individuals in the tobramycin group and six individuals in the placebo group did not complete the trial. All but one individual treated with tobramycin cleared the *P. aeruginosa* infection, which was statistically significantly better than the placebo-treated group using a time to event analysis ($P < 0.05$). The median time to conversion to a *P. aeruginosa* negative culture was 1.89 months in those receiving inhaled tobramycin.

Gibson and colleagues compared the effect of 28 days of inhaled tobramycin (300 mg twice daily) with placebo in 21 children under 6 years of age who grew *P. aeruginosa* from an OP culture 2 weeks to 12 months before screening and from BALF obtained before randomization (15). They found a significant microbiologic effect in BALF from children treated with tobramycin compared with placebo. *P. aeruginosa* cultures at Day 28 were negative in 100% (8/8) of the treatment group, compared with only 7.4% (1/13) in the placebo group. This therapeutic effect was so pronounced that the study was stopped early. Interpretation of this

result is somewhat complicated by the presence of therapeutic concentrations of tobramycin in the BALF at 28 days. However, 75% of those children treated with tobramycin remained free of *P. aeruginosa* in OP cultures obtained at 56 days, compared with 23% of the children who received placebo, demonstrating that treatment of early *P. aeruginosa* infection with tobramycin can lead to clearance of the organism. Taken together, these three studies demonstrate that treatment of *P. aeruginosa* infection with inhaled antibiotics with or without oral antibiotics frequently results in clearance of the organism and may reduce the incidence of chronic airway infection compared with placebo or no treatment.

The EarLy Inhaled Tobramycin for Eradication (ELITE) trial was designed to determine the optimal length of inhaled tobramycin treatment for *P. aeruginosa* eradication (17). The effect of 28 versus 56 days of treatment with inhaled tobramycin (300 mg twice daily) was compared in 88 individuals greater than 6 months of age with a first or early *P. aeruginosa* culture and no serum antipseudomonal antibodies. Both open-label regimens were effective in clearing the organism. One month after treatment ended, 93 and 92% of individuals treated for 28 or 56 days, respectively, did not grow *P. aeruginosa* from airway cultures. The median time to recurrence was similar in the two groups (26.12 and 25.82 mo, respectively; $P = 0.593$), and 66 and 69% of individuals, respectively, remained free of *P. aeruginosa* infection at 27 months. This study suggests that treatment with 56 days of inhaled tobramycin does not convey additional benefit over 28 days of therapy.

Proesmans and colleagues compared 28 days of inhaled tobramycin (300 mg twice daily) with 3 months of inhaled colistin (2 million IU twice daily) and oral ciprofloxacin (30 mg/kg/d) in 58 children who grew *P. aeruginosa* for the first time or who had not grown the organism in the past 6 months (≥3 cultures) (16). This randomized, open-label trial was conducted at a single center in Belgium. The rate of eradication was similar in the two groups at the end of treatment (79.3 vs. 89.6%; $P = 0.47$). The median time to recurrence of *P. aeruginosa* was 5 months (95% confidence interval [CI], 1.7–8.3 mo) for the tobramycin group and 9 months (95% CI, 0.0–19.0 mo) for the colistin and ciprofloxacin group (log rank $P = 0.61$). Clinical outcomes and the presence of *P. aeruginosa* infection were similar between the two groups 2 years after treatment.

Taccetti and colleagues (18) compared the effect of 28 days of inhaled colistin (2 million IU, twice daily) and oral ciprofloxacin (30 mg/kg/d) with 28 days of inhaled tobramycin (300 mg twice daily) and oral ciprofloxacin in 223 children and adults with CF at 13 centers in Italy. Entry criteria included *P. aeruginosa* growth for the first time or after successful treatment and an infection-free period of 6 months (≥3 cultures). After treatment, *P. aeruginosa* was cleared from 62.8% (66/105) of individuals treated with colistin and ciprofloxacin and from 65.2% (77/118) of individuals treated with tobramycin and ciprofloxacin after 6 months, a difference that was not statistically different (odds ratio [OR], 0.9; 95% CI, 0.52–1.55; $P = 0.81$). The rate of eradication was similar in individuals with a first *P. aeruginosa* infection (66.1%; n = 80/121) and in those who had been successfully treated in the past (61.7%; n = 63/102). After 6 months, the rate of *P. aeruginosa* isolation from bimonthly respiratory cultures was similar between the two treatment groups. Over the course of the study, there was a significant increase in *Stenotrophomonas maltophilia* isolation in both treatment arms (OR, 3.97; 95% CI, 2.27–6.94; $P = 0.001$). *S. maltophilia* was isolated in 18.6% (18/97) of those treated with colistin and ciprofloxacin and in 20.4% (22/108) of those treated with tobramycin.

The Early *Pseudomonas* Infection Control (EPIC) trial compared four treatment groups using inhaled tobramycin (300 mg twice daily) with or without oral ciprofloxacin (30 mg/kg/d) (19). Three hundred four children 1 to 12 years of age were randomized to receive antibiotic therapy every 3 months (cycled therapy) or only when *P. aeruginosa* was cultured (culture-based therapy) for 18 months. The proportion of children who remained *P. aeruginosa* free was similar in the cycled and culture-based treatment groups (OR, 0.78; 95% CI, 0.49–1.23; $P = 0.28$). In addition, the combination of tobramycin and ciprofloxacin was no more effective than tobramycin alone in preventing *P. aeruginosa* infection at 70 months (OR, 1.10; 95% CI, 0.71–1.71; $P = 0.67$). There was no difference in the incidence of pulmonary exacerbations, the primary endpoint of the study, among any of the four treatment groups. This study suggests that the addition of ciprofloxacin does not provide additional benefit to inhaled tobramycin therapy for newly acquired *P. aeruginosa*. As in the previous study, *S. maltophilia* was isolated in 18 to 21% of the various treatment groups.

The committee also considered data from the Aztreonam Lysine for *Pseudomonas* Infection Eradication (ALPINE) study, which was presented in abstract form after our systematic review search was completed (29). Although this open-label study did not meet our inclusion criteria, it was considered because of the study size and the fact that it used an inhaled antibiotic approved in the United States for treatment of individuals with CF with chronic *P. aeruginosa* infection. The effectiveness of inhaled aztreonam (75 mg three times daily) for 28 days in clearing new *P. aeruginosa* infections in 105 children with a mean age of 6.26 ± 4.74 years (±SD) was evaluated. At the end of therapy, cultures from 89.1% of the children did not grow *P. aeruginosa*, and 58.2% (95% CI, 47.4–69.1%) remained free of the organism at 6 months (30). Although this study is not a RCT, it does suggest that inhaled aztreonam may be an effective eradication therapy for newly acquired *P. aeruginosa*.

Taken together, these studies demonstrate that inhaled antibiotics are effective in clearing newly acquired *P. aeruginosa* in the majority of individuals, which may prevent chronic infection. The committee determined that there is a high level of evidence that inhaled antibiotics are effective in treating newly acquired *P. aeruginosa* infection. A Cochrane review (31) evaluated four trials with a total of 95 participants, which were included in our review (15, 16, 20, 21), and similarly concluded that eradication therapy was effective.

The committee recommends inhaled antibiotic therapy to treat initial or new growth of *P. aeruginosa* from an airway culture. The committee's preferred regimen is tobramycin (300 mg twice daily for 28 d) based upon the following factors: (*1*) tobramycin is approved for inhalational use in the United States for chronic management of CF lung disease, (*2*) the use of a single drug for a relatively short

duration was considered the simplest approach to limit treatment burden and potential medication side effects, and (3) there is no clear evidence that a longer course of therapy or the addition of oral ciprofloxacin provides additional benefit. An expert panel recently convened by the European CF Society has also recommended the use of 28 days of inhaled tobramycin for the treatment of newly acquired *P. aeruginosa* infection (32). At this time, it is unknown if other formulations of tobramycin, such as dry powder, are equally effective.

We acknowledge that several other antibiotic strategies have been shown to be effective, but there is insufficient evidence to demonstrate that one therapy is superior over another. For example, the CF Trust in the United Kingdom recommends the use of inhaled colistin and oral ciprofloxacin for the treatment of newly acquired *P. aeruginosa* (33). Although the majority of individuals studied were children, the committee believes that there is sufficient evidence to recommend this approach for adults as well. A recent retrospective cohort study supports the use of eradication therapy in adults (34).

Prophylactic Antibiotic Therapy to Prevent *P. aeruginosa* Infection

Because acquisition of *P. aeruginosa* has significant consequences, it would make sense to prevent infection rather than treating with antibiotics after infection occurs. We found one study that addressed antibiotic prophylaxis for *P. aeruginosa* infection (22). Tramper-Stranders and colleagues sought to determine if prophylaxis could prevent acquisition of *P. aeruginosa* (22). They enrolled 65 children who did not grow *P. aeruginosa* for at least 2 years into a RCT comparing treatment with inhaled colistin (1 million IU twice daily) and oral ciprofloxacin (20 mg/kg/d) with placebo for 3 weeks every 3 months for 3 years. Treatment with colistin and ciprofloxacin did not reduce the risk of initial or chronic infection with *P. aeruginosa*. Thirty-two percent (10/31) of the placebo group and 26% (9/34) of the treated children became infected with *P. aeruginosa*. The hazard ratio for the treatment group to acquire *P. aeruginosa* was 0.736 (95% CI, 0.299–1.822; $P = 0.510$). Additionally, airway cultures from children treated with antibiotics were more likely to grow additional nonfermenting, gram-negative bacterial pathogens ($P = 0.0094$).

The committee also considered the cycled treatment arms of the EPIC trial as a form of prophylaxis after initial eradication therapy. In this context, the EPIC trial did not demonstrate a benefit to routinely treating children with inhaled tobramycin, with or without oral ciprofloxacin, compared with treating only when *P. aeruginosa* was cultured (19).

The committee did not find any benefit of routine use of antibiotics in preventing the acquisition of *P. aeruginosa*. Additionally, the prolonged use of antipseudomonal antibiotics may increase the risk of acquiring other potential pathogens.

The Role of Bronchoscopy in Obtaining Routine Airway Cultures

Obtaining routine airway cultures in individuals with CF who are well provides an opportunity to identify early infection with organisms such as *P. aeruginosa*. For this reason, the CF Foundation recommends obtaining airway cultures at least every 3 months (35). The identification of *P. aeruginosa* infection in individuals with CF who do not expectorate sputum can be problematic. In these individuals, OP swabs are routinely used to culture airway organisms. However, the value of OP cultures as a predictor of the lower airway microbiology has been disputed. Therefore, we sought to determine the test characteristics of OP cultures relative to BALF cultures obtained via bronchoscopy in individuals who are not ill. It was the committee's judgment that avoiding false-positive results (1-specificity) is more important than avoiding false-negative results (1-sensitivity) because the former may result in unnecessary therapy, with its associated risk of adverse effects, burdens, and costs, whereas the latter merely delays therapy because samples are obtained every 3 months. The committee further decided that OP cultures are a reasonable alternative to BALF cultures if they yield false-positive results fewer than 10% of the time. The threshold of 10% may seem high, but it accounts for the fact that the consequences of a false-positive result are relatively minor, whereas the alternative diagnostic test requires an invasive procedure to obtain specimens.

Our search identified four studies that evaluated the accuracy of OP cultures in predicting lower airway microbiology (Table 4) (24–27). The presence of *P. aeruginosa* in BALF cultures was considered the standard by which OP cultures were compared in all the studies. Ramsey and colleagues (26) found that OP cultures were more specific than sensitive for detecting *P. aeruginosa* in 43 individuals who were well at the time of the bronchoscopy, with a mean ± SE of 8.2 ± 6.9 years (range, 4 mo to 25 yr). Oropharyngeal cultures detected *P. aeruginosa* with a specificity of 80 and 93% among those who did and did not expectorate sputum, respectively, and with a sensitivity of 75 and 46% among those who did and did not expectorate sputum, respectively. Armstrong and colleagues (24) and Rosenfeld and colleagues (27) similarly found that OP cultures were more specific (93–95%) than sensitive (44–71%).

Taken together, these three studies found that false-positive results occurred in only 5 to 7% of patients who do not expectorate sputum, which is well below our threshold to suggest OP cultures as a preferable alternative to BALF cultures. This recommendation is further supported by a recent multicenter RCT of 170 infants diagnosed by newborn screening, which demonstrated that the use of bronchoscopy to direct therapy did not reduce the prevalence of *P. aeruginosa* at age 5 years compared with standard therapy (36), as well as a recent Cochrane review that found no evidence to support the routine use of bronchoalveolar lavage in preference to the combination of OP cultures and clinical symptoms in treating pre-school children (37).

Taken together, the studies we reviewed suggest that, for the purpose of routine surveillance of individuals without chronic *P. aeruginosa* infection, OP cultures have a high negative predictive value for the presence of *P. aeruginosa* in populations with a low prevalence of *P. aeruginosa* infection (Table 4) (24, 25, 27). It is clear that OP cultures are not a perfect representation of lower airway microbiology. However, OP cultures are informative, especially with respect to the absence of *P. aeruginosa* infection when an individual from a population with a low risk for infection is well and OP cultures are relatively easily obtained and can be repeated frequently.

Table 4. Studies comparing cultures obtained from oropharyngeal swabs and bronchoalveolar lavage fluid

Study	Individuals/ Cultures (*n*)	Groups (individuals)	*Pseudomonas aeruginosa* Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ramsey *et al.*, 1991 (26)	43/43	nonexpectorators (n = 26)	74 (12/17)	46 (17–77)*	93 (68–100)	83 (36–100)	70 (48–86)
		expectorators (n = 17)	42 (11/26)	75 (43–95)	80 (28–100)	90 (56–100)	57 (18–90)
Armstrong *et al.*, 1996 (24)	75/150		11 (17/150)	71 (44–90)	93 (89–97)	57 (34–78)	96 (91–99)
Rosenfeld *et al.*, 1999 (27)	141/286	⩽18 mo (n = 119)	8 (9/119)	44 (14–79)	95 (90–99)	44 (14–79)	95 (90–99)
		19–44 mo (n = 82)	23 (19/82)	68 (43–87)	94 (85–98)	76 (50–93)	91 (81–97)
Burns *et al.*, 2001 (25)	40/108	one OP culture	28 (30/108)			69 (48–86)	85 (76–92)
		two OP cultures†				83 (52–98)	97 (86–100)

Definition of abbreviations: NPV = negative predictive value; OP = oropharyngeal; PPV = positive predictive value.
*The 95% confidence interval is shown in parentheses.
†Analysis used two OP cultures obtained 3 mo apart.

Unanswered Questions

Can *P. aeruginosa* Infection Be Prevented?

An effective strategy to prevent *P. aeruginosa* infection would undoubtedly be of great benefit to individuals with CF. There has been longstanding interest in developing a vaccine to prevent *P. aeruginosa* infection (for review, *see* References 38 and 39). A Cochrane review has also recently summarized the progress to date (40). Our search found one large trial of a bivalent vaccine to *P. aeruginosa* flagella in 483 children; this vaccine demonstrated immunologic response, but protection against infection was less clear (23). There has also been interest in developing vaccines against other components of the *P. aeruginosa* bacterium (38). More recently, novel antipseudomonal PcrV protein antibodies have been developed as a novel approach to prevent infection (41). Currently, hand hygiene and avoidance of high-risk environments for infection are the best approaches to mitigate the risk of *P. aeruginosa* infection (42). However, development of effective methods of infection prevention remains a significant unmet need.

Can *P. aeruginosa* Infection Be Detected Earlier?

Earlier detection of *P. aeruginosa* infection provides a better opportunity to eradicate the infection. Culture-based detection is the standard for identifying *P. aeruginosa*. However, other approaches for detection of infection, such as the presence of antipseudomonal antibodies (43) and molecular techniques (44, 45), have the potential to identify infected individuals earlier. Further development of these and other techniques may help guide therapy for eradication of early and chronic *P. aeruginosa* infection.

How Can the Best Therapy for the Treatment of Newly Acquired *P. aeruginosa* Infection be Determined?

Our review of the scientific literature suggests that there may be several effective strategies to treat newly acquired *P. aeruginosa.* The committee has recommended a specific eradication strategy; however, this recommendation must be tailored to the individual clinical situation. To date, the direct comparison of one regimen to another has not identified an approach that is clearly superior. It is possible that a more aggressive approach to eradication therapy, such as the one that is currently being tested in the Trial of Optimal Therapy for *Pseudomonas* Eradication in Cystic Fibrosis (TORPEDO-CF, Current Controlled Trials # ISRCTN02734162; www.torpedo-cf.org.uk), would be more effective than inhaled and oral therapies. This study compares the benefit 3 months of inhaled colistin combined with either 2 weeks of intravenous ceftazidime and tobramycin or 3 months of oral ciprofloxacin. In addition, the OPTIMIZE study (OPTIMIZing Treatment for Early *Pseudomonas aeruginosa* Infection in Cystic Fibrosis, NCT02054156) will be an 18-month, randomized, double-blind, placebo-controlled trial assessing the clinical and microbiologic efficacy of adding chronic thrice-weekly oral azithromycin versus placebo to standardized inhaled tobramycin therapy for children with early *P. aeruginosa* infection. Additional studies of comparative effectiveness will be important to determine the optimal therapy for *P. aeruginosa* eradication.

What Is the Appropriate Therapy When Treatment of Newly Acquired *P. aeruginosa* Infection Fails to Clear the Organism?

Although inhaled tobramycin therapy is very effective in clearing newly acquired *P. aeruginosa*, it is not always successful. Most clinicians would advocate additional therapy in an attempt to eradicate the organism before committing individuals to chronic, suppressive antibiotic therapy. The use of additional or other inhaled, oral, or intravenous antibiotics could be a reasonable next step. An equally important consideration is when to move from episodic eradication therapy to chronic use of inhaled antibiotics. Unfortunately, there are no studies that directly address the question of optimal subsequent therapy. However, a recent European expert panel has proposed a potential framework for additional therapy when an initial eradication attempt fails (32). Determining the best approach

for a patient who has failed initial eradication therapy is an extremely important clinical problem that remains to be solved.

Summary

Preventing chronic infection with *P. aeruginosa* has the potential to improve the lives of individuals with CF. Unfortunately, we were not able to identify an effective strategy to prevent initial *P. aeruginosa* infection. However, our recommendation of 28 days of inhaled tobramycin for the treatment of newly acquired *P. aeruginosa* is likely to be effective in infected individuals. Future research is needed to identify strategies to best treat individuals with CF who fail to clear the infection with this approach. ■

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Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Oluwaseun Akinyede, D.V.M., M.P.H., Veronica Ivey Sawin, Sc.M., and Brittany Burton, M.H.S., from The Johns Hopkins University; Robert J. Beall, Ph.D., and Preston W. Campbell, III, M.D., from the Cystic Fibrosis Foundation; and Kevin Wilson, M.D., from the American Thoracic Society.

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