Published in final edited form as:

Adv Drug Deliv Rev. 2015 May ; 85: 1–6. doi:10.1016/j.addr.2014.10.009.

Clinical applications of pulmonary delivery of antibiotics

Patrick A. Flume, MD and

Departments of Medicine and Pediatrics, Medical University of South Carolina, Charleston, SC

Donald R. VanDevanter, PhD

Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland Ohio

Abstract

The treatment of infection typically involves administration of antibiotics by a systemic route, such as intravenous or oral. However, pulmonary infections can also be approached by inhalation of antibiotics as the infection is more directly accessible via the airways, making inhalation delivery essentially topical administration. This approach offers deposition of high antimicrobial concentrations directly at the site of infection but with a potentially reduced systemic exposure. This review covers the evidence for aerosolized antibiotics for the treatment of a number of conditions such as cystic fibrosis (CF), where it has become the standard of care for chronic infection, as well as non-CF bronchiectasis, non-tuberculous mycobacteria, and ventilator-associated infection where such therapy does not have an approved indication but has been used with increasing frequency.

Keywords

inhaled antibiotics; aerosol; cystic fibrosis; bronchiectasis; mycobacteria; *Pneumocystis*

1. Introduction

Inhaled antibiotics have long been used to treat patients with cystic fibrosis (CF); their chronic infection of the airways is associated with considerable morbidity and an early mortality, and clinicians have used inhaled antibiotics to suppress the infection in order to improve health and long-term survival. The success of aerosol antibiotics in CF has led to consideration of similar therapy in other patients with chronic airways infection. Here we will review the use of inhaled antibiotics in CF patients as well as other conditions where such therapy might be considered.

© 2014 Elsevier B.V. All rights reserved.

Corresponding author: Patrick A. Flume, MD, 96 Jonathan Lucas St. Room 812-CSB, MSC 630, Charleston, SC 29325, Office: 843-792-3167, flumepa@musc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

2. Why deliver antimicrobials by inhalation?

Microbial infections targeted by inhalation have the common attribute of a nidus of infection that is more directly accessible via the respiratory tract than the circulatory system, making inhalation delivery essentially topical administration. Direct access via the airway allows for deposition of high antimicrobial concentrations directly at the site of infection but without the systemic exposures that would be necessary to achieve similar airway levels by oral or intravenous (IV) delivery [1]. Advantages include reduced potential for the dose-limiting systemic toxicities associated with many antimicrobials and an ability to overwhelm acquired microbial resistance mechanisms by elevated local drug exposure [2].

There are, of course, shortcomings with inhalation delivery that warrant attention. Perhaps most importantly, inhalation can only deliver drug to ventilated areas of the airway, and so cannot deliver drugs past airway obstruction [3]. Further, ventilation inhomogeneity can result in variable deposition within different ventilated regions [4]. These effects can result in localized airway regions with suboptimal antibiotic exposure which may contribute to selection for less antibiotic-susceptible bacteria. Effective doses of antimicrobials may be tens to hundreds of milligrams of drug per dose, requiring extended administration times and relatively elaborate administration devices. As aerosol delivery devices become more efficient (e.g. dry powder inhalers) the burden associated with treatment can be reduced and, potentially, patient adherence improved [5]. Inhalation can be accompanied by local adverse events, including but not limited to, cough, bronchospasm, hoarseness, dysphagia, and dysgeusia. These tend to be reversible events and there is evidence that their incidence and severity can decrease with exposure, but they can be serious barriers to patient adherence. Finally, inhaled antimicrobials reach the systemic circulation to varying degrees as a function of deposited dose in the lung and the extent of drug absorption across the lung epithelia [6] Gibson, 2006 #1818;Geller, 2011 #639}, and thus treated patients are at some risk for systemic toxicity, particularly with extended exposure. Importantly, there are no preclinical animal models to predict risks associated with *very* long term (e.g., decades), low level chronic systemic exposure to these agents.

3. Airways infection in cystic fibrosis

Chronic bacterial infection of the airways is one of the key complications of patients with CF and we have our greatest knowledge about inhaled antibiotic therapy for *Pseudomonas aeruginosa*. Epidemiological data (Figure 1)[7] demonstrate that *P. aeruginosa* can be isolated by selective culture from patient airway secretions early in life, and is the most common bacterial opportunist in adult patients. In this setting *P. aeruginosa* is associated with worse symptoms, more pulmonary exacerbations, and earlier death [8–19]. This is why there has been great interest in treating *P. aeruginosa*; however, more recently there is growing interest in the other pathogens, such as methicillin resistant *Staphylococcus aureus* (MRSA) [20].

Our current understanding of the development of chronic *P. aeruginosa* infection in the CF airways is as follows. It is thought that *P. aeruginosa* is not present in the CF airways at birth, but the CF defect in mucociliary clearance is associated with eventual isolation of *P.*

aeruginosa from the airways. It is now common practice at CF centers to perform periodic surveillance cultures of respiratory secretions, whether by oropharyngeal swab, sputum, or lower airway samples obtained by bronchoscopy. The first observation of a culture positive for *P. aeruginosa* is defined as first infection, although it is more accurately named first positive culture. Repeated subsequent cultures may be intermittently positive for *P. aeruginosa* [21]; although it is conceivable that patients are able to clear an initial infection spontaneously, it is equally likely that the infection persists but is intermittently below the level of detection using standard culture techniques. Ultimately, repeated airway cultures will become mostly, or always, positive for *P. aeruginosa*; when >50% of airway cultures are positive for *P. aeruginosa* over the course of a year, a patient is considered to be chronically infected [22]. Experience has demonstrated that chronic infection is impossible to eradicate; recent approaches to treatment have tested this observation by treating first infection with the hopes of delaying the time to chronic infection.

4. Aerosol antibiotic treatment options for *Pseudomonas aeruginosa* in cystic fibrosis

4.1 Suppression

As stated earlier, chronic infection by *P. aeruginosa* is associated with excessive inflammation, progression of injury to the airways, and considerable morbidity and early mortality [9–14, 17, 18]. The use of inhaled antibiotics to suppress the infection has become standard of care [23, 24]. The history of inhaled antibiotics dates back to the 1940s, when there was *ad hoc* use of penicillins and polymyxins [25]. A crossover study design compared IV preparations of carbenicillin and gentamicin to placebo resulting in improved lung function and fewer IV antibiotics courses when on inhaled antibiotics [26]. Empiric use of aerosolization of IV formulations became increasingly common at CF care centers [27]. The first aerosol antibiotic specifically developed and approved for use in CF patients with *P. aeruginosa* airway infection was tobramycin inhalation solution (TIS) (<http://www.pharma.us.novartis.com/product/pi/pdf/tobi.pdf>). The decision to study an aminoglycoside was based on their chemical stability, data to suggest a prolonged post-antibiotic effect and an acceptable taste; tobramycin was selected based on its low systemic toxicity as well as other pragmatic factors [28]. The approved regimen of TIS 300 mg nebulized twice daily for 28 days increased lung function and subsequent cycles of therapy (i.e. month on/month off) reduced the risk of pulmonary exacerbations when compared to placebo [29]. This chronic-intermittent regimen was devised as a compromise between retained treatment efficacy and concerns for selection of tobramycin-resistant organisms with continuous treatment [28]. There are now several inhaled antibiotic formulations available for suppression of chronic *P. aeruginosa* infection. Approved inhalational antimicrobials for use in people with CF and chronic *P. aeruginosa* infection in the EU are tobramycin (TOBI[®], TOBI Podhaler[™], Bramitob[®]), colistimethate (ColoBreathe[®], Promixin[®]), and aztreonam (Cayston[®]) and in the US are tobramycin (TOBI, TOBI Podhaler, Bethkis[®]) and aztreonam (Cayston).

Published guidelines have recommended inhaled antibiotics for the chronic suppression of *P. aeruginosa* based upon study results that have shown improved lung function and a

reduction in pulmonary exacerbations [23, 24]. However, despite the use of inhaled antibiotics, patients still experience progressive loss of lung function over time [30] and suffer pulmonary exacerbations with some frequency [29, 31]. In addition, repeated treatment with the same antibiotic increases the probability of selection for *P. aeruginosa* populations in the airways with reduced antibiotic sensitivity. Such changes have been characterized for extended inhaled tobramycin treatment [32] but less well-characterized for extended treatment with other inhaled antibiotic classes. Interestingly, although there clearly are inhaled antibiotic treatment-associated shifts in bacterial antibiotic susceptibility, there has yet to be an association demonstrated between reduced *in vitro* antibiotic susceptibility and reduced clinical efficacy for inhaled or systemic antibiotic treatment in persons with CF [2, 33, 34].

The inhaled antibiotic treatment regimen used in studies is an intermittent (i.e. month on/month off) strategy; in part because it was observed that *in vitro* *P. aeruginosa* tobramycin susceptibilities decrease significantly with continuous exposure to tobramycin but recover after a rest period, and also because initial lung function improvements seen with inhaled tobramycin treatment appear to be limited after a few weeks [28]. The month on-month off treatment approach has come under question as to whether it is optimal as it allows bacterial regrowth during off-treatment periods that may further injure the airways [35]. An alternative approach, continuous treatment (i.e. daily therapy with no time off) has been used with colistimethate [36, 37]; others have used a rotational strategy (i.e. two different antibiotics) to provide continuous treatment [24]. This strategy is currently being tested in a randomized, placebo-controlled study comparing intermittent treatment of TIS with a continuous approach alternating TIS with aztreonam inhalation solution (clinicaltrials.gov NCT01641822).

Also of concern is the observed attenuation of the pulmonary function response to inhaled antibiotics with repeated administrations that is not entirely attributable to selection for antibiotic-resistant pathogens [29, 30]. This observation is often cited as demonstrating the need for more inhaled antibiotic choices. In many cases, CF clinicians who feel that management with available inhaled antibiotic formulations has become inadequate for a patient will extemporaneously formulate IV antibiotics in an off-label manner. Although such empiric treatment of individuals may be unavoidable in extreme cases, it is preferable to employ treatments for which safety and efficacy data have been collected from controlled trials.

4.2 Eradication

Since chronic airway *P. aeruginosa* infection is associated with considerable morbidity and mortality in CF, it has been suggested that we should try to prevent chronic infection either by prophylaxis or by attempting to ‘eradicate’ new *P. aeruginosa* acquisition when it may be more vulnerable to antibiotic therapy. There is evidence that early *P. aeruginosa* infection is largely limited to the upper airways and not widespread throughout the airways [38]; it is hypothesized that there is a lower burden of bacterial pathogens that are not well-established immediately after acquisition [39]. The evidence to support eradication is an inability to isolate *P. aeruginosa* from sputum or oropharyngeal swabs after antibiotic treatment.

However, a negative culture for *P. aeruginosa* could mean either that the pathogen has been eradicated or that organisms remain present but at (reduced) numbers below the level of detection. A longitudinal study that compared the bacterial genotypes of *P. aeruginosa* strains isolated before successful eradication and then at subsequent *P. aeruginosa* ‘re-acquisition’ in the same patients showed that a majority of subsequent infections were from different bacterial strains than initial infections [40]. In any case, the perceived clinical benefit of eradication therapy is extension of the time to chronic *P. aeruginosa* infection [41], with concomitant delay in damage to the lower airways.

Eradication therapy has become a standard of care for treatment of first CF *P. aeruginosa* infection [24], yet there is no specific recommendation with respect to treatment regimen. A variety of eradication treatment protocols have demonstrated microbiologic efficacy [40, 42–46], with 3 months of combined inhaled colistimethate plus oral ciprofloxacin and 28 days inhaled tobramycin being the most commonly employed regimens utilizing inhaled antibiotics [20]. Inhaled colistimethate plus oral ciprofloxacin was originally described as a 3 week regimen, but experience showed that extension to 3 months treatment increased response rates [34], which are comparable to those of 28 days inhaled tobramycin [20]. The ELITE [44] and EPIC [45] studies both demonstrated that one month of an aerosolized antibiotic (in both cases, TIS) was sufficient to convert 90% of CF patients with new *P. aeruginosa* acquisition to culture negativity. No better results were achieved by addition of oral ciprofloxacin [45] or extending the duration of inhaled antibiotic treatment to 56 days [44]. The next positive culture (for *P. aeruginosa*) occurred on average at approximately 2 years [44]. Subsequently scheduled periodic therapy (irrespective of culture results) did not improve on the strategy of intervention based on positive culture only [45].

4.3 Prophylaxis

Studies of prophylactic inhaled antibiotics to prevent infection by *P. aeruginosa* have yielded conflicting results and the practice is generally not recommended [24]. Two years of inhaled low-dose (20 mg) gentamicin in 29 children and adolescents with CF found no difference in the incidence of new sputum *P. aeruginosa* isolates. [47]. A 3-year prospective study comparing prophylactic oral ciprofloxacin and inhaled colistin treatment with placebo in children with CF [48] found no difference in the rate of acquisition of *P. aeruginosa* observed between the groups. In contrast, an open label study of inhaled gentamicin over 3 years showed that patients at high risk for infection who remained on treatment did not have *P. aeruginosa* present in their airway cultures, while nearly 50% of those patients who stopped treatment were found to have positive cultures [49], suggesting long-term-prophylaxis with inhaled gentamicin could effectively delay acquisition of *P. aeruginosa* in children with CF.

4.4 Treatment of CF Pulmonary Exacerbations

Patients with CF are subject to periodic increases in signs and symptoms of airway disease, termed pulmonary exacerbations [50]. Exacerbations are associated with decreased quality of life [51–53], accelerated disease progression [54–57], and increased risk of mortality [11, 58–60]; standard of care is treatment with antibiotics chosen based on respiratory culture results [61]. However, in this context antibiotic treatment is essentially palliative, with the

goal to reduce signs and symptoms of exacerbation, with no expectation of conversion to culture negativity. Although there have been no controlled trials demonstrating benefit, exacerbating patients with *P. aeruginosa* infections are often treated with inhaled antipseudomonal antibiotics, presumably because of the simplicity of outpatient delivery of drugs that would normally require IV delivery. A survey of 45,374 exacerbations among 13,194 patients followed in the Epidemiologic Study of CF Registry between 2003 and 2005 showed that 24.4% of treated events included treatment with inhaled antibiotics, with or without concomitant IV or oral antibiotics [62]. Treatment guidelines for pulmonary exacerbations made no recommendation on whether to use inhaled antibiotics in addition to IV antibiotics [63]. However, a recent study of TIS in inpatients demonstrated that the timing of inhaled therapy may have an influence on the interpretation of serum drug levels (i.e. tobramycin) for concomitant IV treatments. [64].

5. What about other bacterial opportunists in CF?

As seen in Figure 1, there are other bacterial species commonly isolated from CF airway respiratory secretions by selective culture [65]. There are increasing data that suggest some of these species also contribute to poor outcomes, including *B. cepacia* complex [66], methicillin-resistant *Staphylococcus aureus* (MRSA) [20], and nontuberculous mycobacteria (NTM)[67]. Given such observations, it is reasonable to ask whether similar treatment strategies (i.e. prophylaxis, eradication, suppression) have the potential to improve patient outcomes.

Unfortunately, there is a paucity of data from studies of inhaled antibiotics targeting other pathogens for suppression, eradication, or prophylaxis. There is an ongoing study of a dry powder form of vancomycin assessing the efficacy and safety of suppressive therapy for MRSA (clinicaltrials.gov NCT01746095). A study of aztreonam for inhalation solution in CF patients with chronic *Burkholderia* infection did not demonstrate a clinical benefit [68]. There are no data regarding eradication therapies for any other pathogens other than *P. aeruginosa* beyond anecdotal observations in individual patients. There are two studies of MRSA eradication in process (clinicaltrials.gov NCT01349192 and NCT01594827). Chronic prophylaxis to prevent the acquisition of *S. aureus* is used primarily in the UK [43, 69, 70], largely based on a study in infants treated with oral flucloxacillin [70]. However, a large and long US study of the broader spectrum anti-*Staphylococcal* antibiotic cephalexin did not demonstrate any clinical benefit and suggested greater subsequent *P. aeruginosa* infection [71], leading to guidelines recommending against routine use of such prophylactic therapy [23]. There are currently no other recommended prophylactic strategies for any other pathogens in CF patients [24].

6. Treatment with inhaled antibiotics for conditions other than CF

6.1 Non-CF bronchiectasis

Chronic obstruction and inflammation in the CF lung result in irreversible widening and scarring of the airways known as bronchiectasis. Bronchiectasis further impedes mucus clearance, creating an even greater probability of the establishment of chronic airway infection [72]. Individuals without CF can also develop bronchiectasis from a variety of

airway insults including inhalation injury, chronic gastro-esophageal reflux, and poor resolution of acute viral infection. These individuals with non-CF bronchiectasis have an increased risk of the establishment of chronic airway infection, including with *P. aeruginosa*, that are associated with increased risk of exacerbation and decreased quality of life [72]. Given the success that has been realized with treatment of chronic CF airway infections with inhaled antibiotics, it is not surprising that investigators have considered how inhaled antibiotics might be used in the management of individuals with non-CF bronchiectasis and chronic airway infection. It is important to note, however, that the general management of non-CF bronchiectasis differs from that of CF bronchiectasis except for those patients with the most severe disease. Perhaps most importantly, loss of lung function is not a primary cause of death among the population with non-CF bronchiectasis, and so preservation of lung function with the help of chronic respiratory therapies is not as common as a management strategy as in CF, although there has been interest in chronic inhaled antibiotic use for severely affected patients [73–78]. In contrast, both patient groups are encouraged to consistently engage in some form of chest physiotherapy/airway clearance to mobilize secretions and treatment with antibiotics to reduce the signs and symptoms of pulmonary exacerbation are routine in both populations [72]. Interestingly, the chronic mucolytic therapy dornase alfa, which has been shown to be safe and effective for the management of CF lung disease, does not appear to provide benefit for patients with non-CF bronchiectasis [79].

Chronic administration of inhaled antibiotics, including ceftazidime, tobramycin, gentamicin, colistimethate, aztreonam, and ciprofloxacin, have been studied in stable patients with *P. aeruginosa* and non-CF bronchiectasis [73–78, 80]. In general, these studies have demonstrated significant reductions in *P. aeruginosa* sputum densities, and some have shown evidence of reduced risk of pulmonary exacerbations [74], while others have shown an increased frequency of adverse events likely linked to local irritation from treatments [73, 75, 80]. Randomized controlled clinical trials continue, with the goal of demonstrating safety and clinical efficacy of a regimen sufficient to support registration. In the interim, empiric off-label use of inhaled antibiotics in non-CF bronchiectasis patients with poor quality of life and few treatment options continues, as there is the potential for patients to benefit from prolonged antibiotic treatment [81].

6.2 Non-tuberculous mycobacteria

There is growing awareness of chronic airways infection by non-tuberculous mycobacteria (NTM), most notably *Mycobacterium avium* complex (MAC) and *M. abscessus*. Published guidelines, developed conjointly between the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA), have offered recommendations on treatment of such infections [82]. The treatment generally requires multiple medications for an extended period of time. The use of inhaled amikacin is recommended for patients with rapidly growing mycobacteria (e.g. *M. abscessus*), extensive cavitary disease due to MAC, or those who have failed conventional treatments [82]. The support for the use of aerosolized amikacin is seen in demonstrated microbiological and symptomatic improvement in patients with refractory infection [83]. The intravenous formulation of amikacin has been used for aerosolization but there is an ongoing study of a formulation of

amikacin intended for aerosol use for the treatment of NTM airways infections (clinicaltrials.gov identifier NCT01315236).

6.3 Pneumocystic jiroveci

There is considerable experience with inhaled pentamidine as a prophylactic therapy for patients at risk for *Pneumocystic jiroveci* (PJP). In the early days of AIDS there was a marked increase in the cases of PJP, prompting interest in prevention of infection. Aerosolized pentamidine was demonstrated to be effective as secondary (i.e. for patients with a previous diagnosis of PJP) [84] and primary prophylaxis [85]. As there are other oral alternatives (e.g. trimethoprim-sulfamethoxazole) and the incidence of PJP has dropped considerably since the discovery of more effective anti-retroviral therapies, the use of inhaled pentamidine has diminished. It remains an option for those immunocompromised patients that are unable to tolerate oral therapies.

6.4 Ventilator-associated pneumonia

Patients who require prolonged ventilatory support are at risk for airways infection and pneumonia, often with either *P. aeruginosa* or MRSA [86]. Treatment of VAP with systemic antibiotics is generally successful but there remains a high rate of recurrence of infection, particularly when *P. aeruginosa* is present [87]. Some have suggested that these patients have chronic tracheobronchitis with persistence of bacterial infection, rendering them even more vulnerable to recurrent pneumonia [88]. Inhaled antibiotics have been used to suppress this infection in the hopes of preventing VAP [88]. A meta-analysis of 8 comparative trials of prophylactic aerosolized antibiotics (n=1877) suggested a reduction in VAP (OR = 0.49) but without a difference in mortality or adverse effects; an analysis of selection for resistant pathogens could not be performed.[89] The challenge with aerosolization of antibiotics for patients with VAP is that there is a reduced efficiency of drug delivery through the ventilator circuit[90]. Newer methods of nebulization may improve the drug delivery where this could become an important method of drug delivery. There is an ongoing study of an inhaled antibiotic in such patients (nebulized amikacin, clinicaltrials.gov NCT01799993).

7. Conclusion

Aerosolized antibiotic therapy is a recommended part of CF patient management when there is identified airways *P aeruginosa* infection and is likely an important contributor to the improved predicted survival attained over time [7]. There is active interest in learning whether a similar approach to treatment of other pathogens would be beneficial. Prophylactic antibiotic treatment remains extremely uncommon for any of the CF pathogens and is not recommended for CF bacterial opportunists. Aerosolized antibiotics are recommended for treatment of new *P. aeruginosa* acquisition with the intent of conversion to culture negativity (i.e., eradication); it has proven safe and largely successful and has become standard of care for CF patients. Inhaled antibiotics to suppress chronic infection by *P aeruginosa* also are a recommended approach to treatment. There are approved antibiotics for inhalation in CF patients; yet we still need additional antibiotic choices and to determine the best approach to treatment (e.g. intermittent vs. continuous treatment). Also for CF, there

is a need to know whether chronic antibiotic suppression targeted at other lung pathogens would also improve outcomes.

Given the success of aerosolized antibiotics in patients with CF, this approach to therapy has been used in other patients with chronic airways infection, most notably non-CF bronchiectasis, NTM, and ventilator associated infections, and with varying results. There are sufficient compelling results in some patients suggesting refinement of inclusion criteria in studies may be necessary.

References

1. Geller DE, Pitlick WH, Nardella PA, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. *Chest*. 2002; 122:219–226. [PubMed: 12114362]
2. LiPuma JJ. Microbiological and immunologic considerations with aerosolized drug delivery. *Chest*. 2001; 120:118S–123S. [PubMed: 11555566]
3. Mukhopadhyay S, Staddon GE, Eastman C, Palmer M, Davies ER, Carswell F. The quantitative distribution of nebulized antibiotic in the lung in cystic fibrosis. *Respiratory medicine*. 1994; 88:203–211. [PubMed: 8209069]
4. Laube BL, Links JM, LaFrance ND, Wagner HN Jr, Rosenstein BJ. Homogeneity of bronchopulmonary distribution of 99mTc aerosol in normal subjects and in cystic fibrosis patients. *Chest*. 1989; 95:822–830. [PubMed: 2924610]
5. Konstan MW, Flume PA, Kappler M, Chiron R, Higgins M, Brockhaus F, Zhang J, Angyalosi G, He E, Geller DE. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2011; 10:54–61. [PubMed: 21075062]
6. Gibson RL, Retsch-Bogart GZ, Oermann C, Milla C, Pilewski J, Daines C, Ahrens R, Leon K, Cohen M, McNamara S, Callahan TL, Markus R, Burns JL. Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol*. 2006; 41:656–665. [PubMed: 16703579]
7. Cystic Fibrosis Foundation Patient Registry. 2012 Annual Data Report. Bethesda, Maryland: 2013.
8. Amin R, Lam M, Dupuis A, Ratjen F. The effect of early *Pseudomonas aeruginosa* treatment on lung function in pediatric cystic fibrosis. *Pediatric pulmonology*. 2011; 46:554–558. [PubMed: 21337727]
9. Ballmann M, Rabsch P, von der Hardt H. Long-term follow up of changes in FEV1 and treatment intensity during *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. *Thorax*. 1998; 53:732–737. [PubMed: 10319054]
10. Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: *Pseudomonas aeruginosa* infection. *Journal of clinical epidemiology*. 1995; 48:1041–1049. [PubMed: 7775991]
11. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatric pulmonology*. 2002; 34:91–100. [PubMed: 12112774]
12. Henry RL, Mellis CM, Petrovic L. Mucoid *Pseudomonas aeruginosa* is a marker of poor survival in cystic fibrosis. *Pediatric pulmonology*. 1992; 12:158–161. [PubMed: 1641272]
13. Hoiby N, Flensburg EW, Beck B, Friis B, Jacobsen SV, Jacobsen L. *Pseudomonas aeruginosa* infection in cystic fibrosis. Diagnostic and prognostic significance of *Pseudomonas aeruginosa* precipitins determined by means of crossed immunoelectrophoresis. *Scand J Respir Dis*. 1977; 58:65–79. [PubMed: 404701]
14. Kosorok MR, Zeng L, West SE, Rock MJ, Splaingard ML, Laxova A, Green CG, Collins J, Farrell PM. Acceleration of lung disease in children with cystic fibrosis after *Pseudomonas aeruginosa* acquisition. *Pediatric pulmonology*. 2001; 32:277–287. [PubMed: 11568988]
15. Kozłowska WJ, Bush A, Wade A, Aurora P, Carr SB, Castle RA, Hoo AF, Lum S, Price J, Ranganathan S, Saunders C, Stanojevic S, Stroobant J, Wallis C, Stocks J. Lung function from

- infancy to the preschool years after clinical diagnosis of cystic fibrosis. *American journal of respiratory and critical care medicine*. 2008; 178:42–49. [PubMed: 18403721]
16. Mayer-Hamblett N, Kronmal RA, Gibson RL, Rosenfeld M, Retsch-Bogart G, Treggiari MM, Burns JL, Khan U, Ramsey BW. Initial *Pseudomonas aeruginosa* treatment failure is associated with exacerbations in cystic fibrosis. *Pediatric pulmonology*. 2012; 47:125–134. [PubMed: 21830317]
 17. Pamukcu A, Bush A, Buchdahl R. Effects of *pseudomonas aeruginosa* colonization on lung function and anthropometric variables in children with cystic fibrosis. *Pediatric pulmonology*. 1995; 19:10–15. [PubMed: 7675552]
 18. Parad RB, Gerard CJ, Zurakowski D, Nichols DP, Pier GB. Pulmonary outcome in cystic fibrosis is influenced primarily by mucoid *Pseudomonas aeruginosa* infection and immune status and only modestly by genotype. *Infection and immunity*. 1999; 67:4744–4750. [PubMed: 10456926]
 19. Taccetti G, Campana S, Festini F, Mascherini M, Doring G. Early eradication therapy against *Pseudomonas aeruginosa* in cystic fibrosis patients. *The European respiratory journal*. 2005; 26:458–461. [PubMed: 16135728]
 20. Dasenbrook EC, Checkley W, Merlo CA, Konstan MW, Lechtzin N, Boyle MP. Association between respiratory tract methicillin-resistant *Staphylococcus aureus* and survival in cystic fibrosis. *JAMA : the journal of the American Medical Association*. 2010; 303:2386–2392.
 21. Burns JL, Gibson RL, McNamara S, Yim D, Emerson J, Rosenfeld M, Hiatt P, McCoy K, Castile R, Smith AL, Ramsey BW. Longitudinal assessment of *Pseudomonas aeruginosa* in young children with cystic fibrosis. *The Journal of infectious diseases*. 2001; 183:444–452. [PubMed: 11133376]
 22. Lee TW, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic *Pseudomonas aeruginosa* infection in cystic fibrosis patients. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2003; 2:29–34. [PubMed: 15463843]
 23. Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sadosky K, Marshall B. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *American journal of respiratory and critical care medicine*. 2013; 187:680–689. [PubMed: 23540878]
 24. Doring G, Flume P, Heijerman H, Elborn JS. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2012; 11:461–479. [PubMed: 23137712]
 25. Geddes DM. Nebulised therapy and cystic fibrosis. *Eur Respir Rev*. 1997; 7:173–176.
 26. Hodson ME, Penketh AR, Batten JC. Aerosol carbenicillin and gentamicin treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. *Lancet*. 1981; 2:1137–1139. [PubMed: 6118579]
 27. Touw DJ, Brimicombe RW, Hodson ME, Heijerman HG, Bakker W. Inhalation of antibiotics in cystic fibrosis. *The European respiratory journal*. 1995; 8:1594–1604. [PubMed: 8575589]
 28. Smith AL. Inhaled antibiotic therapy: What drug? What dose? What regimen? What formulation? *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2002; 1:189–193. [PubMed: 15463833]
 29. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, Vasiljev KM, Borowitz D, Bowman CM, Marshall BC, Marshall S, Smith AL. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *Cystic Fibrosis Inhaled Tobramycin Study Group. The New England journal of medicine*. 1999; 340:23–30. [PubMed: 9878641]
 30. Moss RB. Administration of aerosolized antibiotics in cystic fibrosis patients. *Chest*. 2001; 120:107S–113S. [PubMed: 11555564]
 31. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *American journal of respiratory and critical care medicine*. 2008; 178:921–928. [PubMed: 18658109]
 32. Burns JL, Van Dalfsen JM, Shawar RM, Otto KL, Garber RL, Quan JM, Montgomery AB, Albers GM, Ramsey BW, Smith AL. Effect of chronic intermittent administration of inhaled tobramycin on respiratory microbial flora in patients with cystic fibrosis. *The Journal of infectious diseases*. 1999; 179:1190–1196. [PubMed: 10191222]

33. Hurley MN, Ariff AH, Bertenshaw C, Bhatt J, Smyth AR. Results of antibiotic susceptibility testing do not influence clinical outcome in children with cystic fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2012; 11:288–292. [PubMed: 22436723]
34. Smith AL, Fiel SB, Mayer-Hamblett N, Ramsey B, Burns JL. Susceptibility testing of *Pseudomonas aeruginosa* isolates and clinical response to parenteral antibiotic administration: lack of association in cystic fibrosis. *Chest*. 2003; 123:1495–1502. [PubMed: 12740266]
35. Lo D, VanDevanter DR, Flume P, Smyth A. Aerosolized antibiotic therapy for chronic cystic fibrosis airway infections: continuous or intermittent? *Respiratory medicine*. 2011; 105(Suppl 2):S9–17. [PubMed: 22208548]
36. Hodson ME, Gallagher CG, Govan JR. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. *The European respiratory journal*. 2002; 20:658–664. [PubMed: 12358344]
37. Schuster A, Haliburn C, Doring G, Goldman MH. Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study. *Thorax*. 2013; 68:344–350. [PubMed: 23135343]
38. Rosenfeld M, Emerson J, Accurso F, Armstrong D, Castile R, Grimwood K, Hiatt P, McCoy K, McNamara S, Ramsey B, Wagener J. Diagnostic accuracy of oropharyngeal cultures in infants and young children with cystic fibrosis. *Pediatric pulmonology*. 1999; 28:321–328. [PubMed: 10536062]
39. Rosenfeld M, Ramsey BW, Gibson RL. *Pseudomonas* acquisition in young patients with cystic fibrosis: pathophysiology, diagnosis, and management. *Current opinion in pulmonary medicine*. 2003; 9:492–497. [PubMed: 14534401]
40. Munck A, Bonacorsi S, Mariani-Kurkdjian P, Lebourgeois M, Gerardin M, Brahimi N, Navarro J, Bingen E. Genotypic characterization of *Pseudomonas aeruginosa* strains recovered from patients with cystic fibrosis after initial and subsequent colonization. *Pediatric pulmonology*. 2001; 32:288–292. [PubMed: 11568989]
41. Frederiksen B, Koch C, Hoiby N. Changing epidemiology of *Pseudomonas aeruginosa* infection in Danish cystic fibrosis patients (1974–1995). *Pediatric pulmonology*. 1999; 28:159–166. [PubMed: 10495331]
42. Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonization with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. *Pediatric pulmonology*. 1997; 23:330–335. [PubMed: 9168506]
43. Ratjen F, Comes G, Paul K, Posselt HG, Wagner TO, Harms K. Effect of continuous antistaphylococcal therapy on the rate of *P. aeruginosa* acquisition in patients with cystic fibrosis. *Pediatric pulmonology*. 2001; 31:13–16. [PubMed: 11180669]
44. Ratjen F, Munck A, Kho P, Angyalosi G. Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial. *Thorax*. 2010; 65:286–291. [PubMed: 19996339]
45. Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, Khan U, Kulich M, Kronmal R, Williams J, Hiatt P, Gibson RL, Spencer T, Orenstein D, Chatfield BA, Froh DK, Burns JL, Rosenfeld M, Ramsey BW. Comparative efficacy and safety of 4 randomized regimens to treat early *Pseudomonas aeruginosa* infection in children with cystic fibrosis. *Archives of pediatrics & adolescent medicine*. 2011; 165:847–856. [PubMed: 21893650]
46. Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. *Lancet*. 1991; 338:725–726. [PubMed: 1679870]
47. Kun P, Landau LI, Phelan PD. Nebulized gentamicin in children and adolescents with cystic fibrosis. *Aust Paediatr J*. 1984; 20:43–45. [PubMed: 6466215]
48. Tramper-Stranders GA, van der Ent CK, Molin S, Yang L, Hansen SK, Rau MH, Ciofu O, Johansen HK, Wolfs TF. Initial *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: characteristics of eradicated and persistent isolates. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2012; 18:567–574.
49. Heinzl B, Eber E, Oberwaldner B, Haas G, Zach MS. Effects of inhaled gentamicin prophylaxis on acquisition of *Pseudomonas aeruginosa* in children with cystic fibrosis: a pilot study. *Pediatric pulmonology*. 2002; 33:32–37. [PubMed: 11747258]

50. Ferkol T, Rosenfeld M, Milla CE. Cystic fibrosis pulmonary exacerbations. *The Journal of pediatrics*. 2006; 148:259–264. [PubMed: 16492439]
51. Orenstein DM, Pattishall EN, Nixon PA, Ross EA, Kaplan RM. Quality of well-being before and after antibiotic treatment of pulmonary exacerbation in patients with cystic fibrosis. *Chest*. 1990; 98:1081–1084. [PubMed: 2225948]
52. Bradley J, McAlister O, Elborn S. Pulmonary function, inflammation, exercise capacity and quality of life in cystic fibrosis. *The European respiratory journal*. 2001; 17:712–715. [PubMed: 11401068]
53. Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. *Chest*. 2002; 121:64–72. [PubMed: 11796433]
54. Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, Stokes DC, Wohl ME, Wagener JS, Regelman WE, Johnson CA. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *The Journal of pediatrics*. 2007; 151:134–139. 139 e131. [PubMed: 17643762]
55. VanDevanter DR, Wagener JS, Pasta DJ, Elkin E, Jacobs JR, Morgan WJ, Konstan MW. Pulmonary outcome prediction (POP) tools for cystic fibrosis patients. *Pediatric pulmonology*. 2010; 45:1156–1166. [PubMed: 20717915]
56. Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *American journal of respiratory and critical care medicine*. 2010; 182:627–632. [PubMed: 20463179]
57. Sanders DB, Bittner RC, Rosenfeld M, Redding GJ, Goss CH. Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis. *Pediatric pulmonology*. 2011; 46:393–400. [PubMed: 20967845]
58. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol*. 2001; 153:345–352. [PubMed: 11207152]
59. Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *American journal of respiratory and critical care medicine*. 2002; 166:1550–1555. [PubMed: 12406843]
60. Ellaffi M, Vinsonneau C, Coste J, Hubert D, Burgel PR, Dhainaut JF, Dusser D. One-year outcome after severe pulmonary exacerbation in adults with cystic fibrosis. *American journal of respiratory and critical care medicine*. 2005; 171:158–164. [PubMed: 15502116]
61. Cystic Fibrosis Foundation. Clinical Practice Guidelines for Cystic Fibrosis. 1997. Treatment of pulmonary exacerbation of cystic fibrosis.
62. Wagener JS, Rasouliyan L, VanDevanter DR, Pasta DJ, Regelman WE, Morgan WJ, Konstan MW. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic fibrosis. *Pediatric pulmonology*. 2013; 48:666–673. [PubMed: 22888106]
63. Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, Marshall BC. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *American journal of respiratory and critical care medicine*. 2009; 180:802–808. [PubMed: 19729669]
64. Stenbit AE, Bullington WM, Heh JL, Flume PA. Timing of inhaled tobramycin affects assessment of intravenous tobramycin pharmacokinetic monitoring. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2013; 12:403–406. [PubMed: 23266092]
65. LiPuma J. The new microbiology of cystic fibrosis: it takes a community. *Thorax*. 2012; 67:851–852. [PubMed: 22752196]
66. Ledson MJ, Gallagher MJ, Jackson M, Hart CA, Walshaw MJ. Outcome of *Burkholderia cepacia* colonisation in an adult cystic fibrosis centre. *Thorax*. 2002; 57:142–145. [PubMed: 11828044]
67. Esther CR Jr, Esserman DA, Gilligan P, Kerr A, Noone PG. Chronic *Mycobacterium abscessus* infection and lung function decline in cystic fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2010; 9:117–123. [PubMed: 20071249]
68. Tullis DE, Burns JL, Retsch-Bogart GZ, Bresnik M, Henig NR, Lewis SA, Lipuma JJ. Inhaled aztreonam for chronic *Burkholderia* infection in cystic fibrosis: A placebo-controlled trial. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. 2014; 13:296–305. [PubMed: 24176390]

69. Smyth A, Walters S. Prophylactic antibiotics for cystic fibrosis. The Cochrane database of systematic reviews. 2003;CD001912. [PubMed: 12917916]
70. Weaver LT, Green MR, Nicholson K, Mills J, Heeley ME, Kuzemko JA, Austin S, Gregory GA, Dux AE, Davis JA. Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period. *Archives of disease in childhood*. 1994; 70:84–89. [PubMed: 8129449]
71. Stutman HR, Lieberman JM, Nussbaum E, Marks MI. Antibiotic prophylaxis in infants and young children with cystic fibrosis: a randomized controlled trial. *The Journal of pediatrics*. 2002; 140:299–305. [PubMed: 11953726]
72. McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. *American journal of respiratory and critical care medicine*. 2013; 188:647–656. [PubMed: 23898922]
73. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, O'Donnell A, Sahn SA, Smith LJ, Stewart JO, Abuan T, Tully H, Van Dalen J, Wells CD, Quan J. Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *American journal of respiratory and critical care medicine*. 2000; 162:481–485. [PubMed: 10934074]
74. Orriols R, Roig J, Ferrer J, Sampol G, Rosell A, Ferrer A, Vallano A. Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*. *Respiratory medicine*. 1999; 93:476–480. [PubMed: 10464834]
75. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest*. 2005; 127:1420–1426. [PubMed: 15821224]
76. Dhar R, Anwar GA, Bourke SC, Doherty L, Middleton P, Ward C, Rutherford RM. Efficacy of nebulised colomycin in patients with non-cystic fibrosis bronchiectasis colonised with *Pseudomonas aeruginosa*. *Thorax*. 2010; 65:553. [PubMed: 20522858]
77. Murray MP, Govan JR, Doherty CJ, Simpson AJ, Wilkinson TS, Chalmers JD, Greening AP, Haslett C, Hill AT. A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. *American journal of respiratory and critical care medicine*. 2011; 183:491–499. [PubMed: 20870753]
78. Wilson R, Welte T, Polverino E, De Soyza A, Greville H, O'Donnell A, Alder J, Reimnitz P, Hampel B. Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study. *The European respiratory journal*. 2013; 41:1107–1115. [PubMed: 23018904]
79. Crockett AJ, Cranston JM, Latimer KM, Alpers JH. Mucolytics for bronchiectasis. The Cochrane database of systematic reviews. 2001;CD001289. [PubMed: 11279712]
80. Barker AF, O'Donnell AE, Flume P, Thompson PJ, Ruzi JD, de Gracia J, Boersma WG, De Soyza A, Shao L, Zhang J, Haas L, Lewis SA, Leitzinger S, Montgomery AB, McKevitt MT, Gossage D, Quittner AL, O'Riordan TG. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials, *The Lancet*. *Respiratory medicine*. 2014
81. Evans DJ, Bara AI, Greenstone M. Prolonged antibiotics for purulent bronchiectasis in children and adults. The Cochrane database of systematic reviews. 2007;CD001392. [PubMed: 17443506]
82. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K. A.T.S.M.D. Subcommittee, S. American Thoracic A. Infectious Disease Society of, An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *American journal of respiratory and critical care medicine*. 2007; 175:367–416. [PubMed: 17277290]
83. Olivier KN, Shaw PA, Glaser TS, Bhattacharyya D, Fleshner M, Brewer CC, Zalewski CK, Folio LR, Siegelman JR, Shallom S, Park IK, Sampaio EP, Zelazny AM, Holland SM, Prevots DR. Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease. *Annals of the American Thoracic Society*. 2014; 11:30–35. [PubMed: 24460437]
84. Leoung GS, Feigal DW Jr, Montgomery AB, Corkery K, Wardlaw L, Adams M, Busch D, Gordon S, Jacobson MA, Volberding PA, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia. The San Francisco community prophylaxis trial. *The New England journal of medicine*. 1990; 323:769–775. [PubMed: 1975426]

85. Hirschel B, Lazzarin A, Chopard P, Opravil M, Furrer HJ, Ruttimann S, Vernazza P, Chave JP, Ancarani F, Gabriel V, et al. A controlled study of inhaled pentamidine for primary prevention of *Pneumocystis carinii* pneumonia. *The New England journal of medicine*. 1991; 324:1079–1083. [PubMed: 2008181]
86. S. American Thoracic A. Infectious Diseases Society of, Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American journal of respiratory and critical care medicine*. 2005; 171:388–416. [PubMed: 15699079]
87. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S, Pneum ATG. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA : the journal of the American Medical Association*. 2003; 290:2588–2598.
88. Palmer LB. Aerosolized antibiotics in critically ill ventilated patients. *Current opinion in critical care*. 2009; 15:413–418. [PubMed: 19657273]
89. Falagas ME, Siempos IA II, Bliziotis A Michalopoulos. Administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia: a meta-analysis of comparative trials. *Critical care*. 2006; 10:R123. [PubMed: 16934148]
90. Fink JB, Dhand R. Aerosol therapy in mechanically ventilated patients: recent advances and new techniques. *Seminars in respiratory and critical care medicine*. 2000; 21:183–201. [PubMed: 16088731]

Figure 1. Pathogens identified in a CF population

Prevalence of bacterial species cultured from respiratory specimens in CF patients.[7]. These data are derived from the US CF Patient Registry and represent a cross-sectional analysis of the respiratory culture results include 27,804 unique patients in 2012. MDR-PA: multi-drug resistant *P. aeruginosa*.