Review

Treatment of lung infection in patients with cystic fibrosis: Current and future strategies☆,☆☆

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for the Consensus Study Group

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Abstract

In patients with cystic fibrosis (CF) lung damage secondary to chronic infection is the main cause of death. Treatment of lung disease to reduce the impact of infection, inflammation and subsequent lung injury is therefore of major importance. Here we discuss the present status of antibiotic therapy for the major pathogens in CF airways, including prophylaxis against infection, eradication of early infection, suppression of chronic infection, and the treatment of infective exacerbations. We outline measures to optimize maintenance treatment for infection in the light of novel antibiotic drug formulations. We discuss new developments in culture-independent microbiological diagnostic techniques and the use of tools for monitoring the success of antibiotic treatment courses. Finally, cost-effectiveness analyses for antibiotic treatment in CF patients are discussed.
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1. Introduction

Lung damage secondary to chronic infection is the main determinant of morbidity and mortality in individuals with cystic fibrosis (CF) [1,2]. CF individuals are highly susceptible to bacterial infections in the respiratory tract and repeated and intensive antibiotic therapy is required to maintain lung function and quality of life and reduce exacerbations in infected patients. Antibiotic therapy aimed at eradicating *Pseudomonas aeruginosa*, the major bacterial pathogen in CF, after early lung infection, and improved regimens to treat chronic *P. aeruginosa* infection have played a major role in the increasing median survival of CF patients during the last decades. In 1969 CF patients in industrialized countries had a mean survival of 14 years. By 2010 this had improved to more than 40 years [3]. Sadly, this positive development has not been observed in all CF centers worldwide and median age at death is still in the 2nd/3rd decade. CF genotype, different approaches to care delivery including the treatment of infection, antibiotic selection and the mode of delivery, as well as health care resources and the socio-economic status of the patient [4–6] may be responsible for the different outcomes.

The objective of this consensus document is to provide guidance for current antibiotic treatment strategies for lung infections in CF. Here we discuss treatment courses for antibiotic eradication therapy (AET), including the window of opportunity in which this treatment option can be most successfully applied. We describe treatment strategies for chronic *P. aeruginosa* infection which cannot be eradicated with current antibiotics. Measures to optimize treatment in the light of new antibiotic drug formulations are considered and novel tools to determine the success of antibiotic treatment courses will be highlighted. In addition to *P. aeruginosa*, sputum specimens from CF patients generally contain many other bacterial species. We describe developments in diagnostic methods for their detection, the relevance of these pathogens for lung disease in CF patients and the impact this may have on therapeutic strategies. Finally, cost-effectiveness analyses for antibiotic treatment in CF patients are presented and recommendations are provided for important clinical questions. This consensus document updates related previous documents supported by ECFS [7–9].

2. Current understanding of the pathophysiology of CF airways infection

It is believed that the CF airways are not infected at birth and that opportunistically pathogenic bacteria enter the lower airways from the environment. These bacteria are able to eventually establish a chronic presence in the airways due to impaired innate immunity [10] and are associated with a chronic inflammatory response. The bacteria most commonly believed to be pathogenic in CF include *P aeruginosa*, *Staphylococcus aureus*, *Hemophilus influenzae*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Burkholderia* species [3]. Recent microbiological studies have demonstrated that the infection of the CF airways is more complicated than demonstrated by standard culturing methods, and this will be discussed later. Although we believe the majority of these bacteria to be pathogenic, our understanding of how best to treat each of them remains incomplete. We know more about the pathogenesis and treatment of *P. aeruginosa*. Thus it will receive the most attention in these recommendations.

P. aeruginosa enters the lower airways presumably by inhalation and may transiently infect the airways of some CF

patients (range: ∼10–50%); that is, it appears that some CF patients are able to clear the pathogen spontaneously, or more specifically, become culture-negative in subsequent specimens [11–14]. However, the pathogen will persist or recur and eventually develop into a chronic infection, which is defined as repeatedly positive microbiological cultures and the presence of positive serum antibodies against the pathogen [8] (Table 1). The Leeds definition [15] classifies patients into 4 groups according to airway culture results obtained over the last 12 months. "Chronic infection" refers to patients in whom more than 50% of the preceding 12 months P. aeruginosa was culture positive, and "intermittent infection" refers to patients with less than 50% of cultures positive for P. aeruginosa. A patient is defined as "free of P. aeruginosa" when no P. aeruginosa was grown from samples in the previous 12 months, despite a history of prior colonization with P. aeruginosa. "Never infected" refers to patients in whom P. aeruginosa has never been cultured. This definition has been evaluated in pediatric and adult CF populations and appears to classify patients appropriately with respect to clinical scores [15,16]. This definition is useful but requires that frequent surveillance samples of sputum are taken and may not be pragmatic in clinical trials.

Chronic infection results in a prolonged inflammatory response, which is believed to cause respiratory tissue injury leading to progressive loss of lung function. There is sufficient evidence that eradication of early infection and prevention of chronic infection is associated with clinical benefit. In general young CF patients without P. aeruginosa infection and those undergoing AET have preserved lung function (by spirometry), which only marginally decreased over years in contrast to CF patients with chronic P. aeruginosa infection [17,18]. For example, the decline in "forced expiratory volume in 1 s % predicted" (FEV_1%) in CF patients who had received AET was less compared to that in chronically infected patients (ΔFEV_1/year: −1.65% vs. −4.74%) [17]. AET studies that have followed patients up to 18 months did not observe a lung function decline [19,20]. In a retrospective analysis of the Toronto data base, patients who cleared P. aeruginosa after first infection had a similar lung function decline over the subsequent years as those who had never been infected [21]. In studies of antibiotic treatment of early airways infection, the failure to eradicate the P. aeruginosa was associated with an increased risk of pulmonary exacerbation and persistent P. aeruginosa infection was associated with even a greater risk of exacerbation [22], further raising the concern that persistent or recurrent infection has a negative impact on lung health. P. aeruginosa acquisition is associated with further deterioration in lung function in CF, even when the pathogen is eradicated [18], suggesting that airflow obstruction of uncomplicated CF needs to be treated, and rigorous strategies to prevent P. aeruginosa acquisition should be implemented.

3. Current status of antibiotic prophylaxis for P aeruginosa

As P. aeruginosa infection of the CF airways may not cause symptoms and may develop into chronic infection that cannot be eradicated, then *can prophylactic administration of antipseudomonal antibiotics be beneficial in the prevention of chronic airways infection by P. aeruginosa*? A prospective 3-year study compared the effect of prophylactic oral ciprofloxacin and inhaled colistin treatment with placebo on prevention of initial P. aeruginosa infection in children with CF [23]. No difference in the rate of acquisition of P. aeruginosa was observed between the control and treatment groups, although P. aeruginosa antibodies emerged earlier in the control group. The authors concluded that a three-monthly cycled prophylactic antibiotic therapy would not reduce the risk of initial P. aeruginosa infection in children with CF. The risks for selecting other pathogens, the time commitment, and the lack of cost efficacy for this strategy may prevent further studies with similar designs. Thus, the current data suggest that *prophylactic treatment with antipseudomonal antibiotics are not recommended to prevent P. aeruginosa infections in CF patients*. Of note, alternative strategies for primary or secondary prevention have been evaluated [24] or are under evaluation (gargling of avian anti-Pseudomonas IgY antibodies; EUDRACT-2011-000801-39).

Table 1
Definition of relevant terms.

Surveillance cultures	Periodic sampling of the upper or lower airways for the purpose of identifying the presence of a CF pathogen.
Colonization	The presence of pathogenic bacteria in the upper or lower airways in the absence of an inflammatory response.
Infection	The presence of pathogenic bacteria in the upper or lower airways associated with an inflammatory response.
Spontaneous clearance	Subsequent culture of the CF upper or lower airways that is culture-negative when the previous cultures had been positive.
Intermittent infection	<50% of cultures are positive for the pathogen of interest [15].
Chronic infection	>50% of cultures are positive for the pathogen of interest; this may also be defined by the presence of serum antibodies or the observation of mucoidy [15].
Free of P. aeruginosa	When no P. aeruginosa was grown from samples in the previous 12 months, despite a history of prior colonization with P. aeruginosa [15].
Never infected with P. aeruginosa	Patients in whom P. aeruginosa has never been cultured [15].
Eradication	Subsequent cultures are free of the pathogen following treatment with antibiotics.
Failure of eradication	Subsequent cultures are positive for the pathogen following treatment with antibiotics.
Recurrence/re-infection	Cultures of the upper or lower airways are again positive for the pathogen following a period where the patient was free of the pathogen following successful eradication.

4. Current status of antibiotic eradication therapy for *P. aeruginosa*

There is strong published evidence that rigorous antibiotic treatment of early *P. aeruginosa* colonization/infection is beneficial for CF patients because it has a significantly high eradication rate [13] and keeps the lower airways free of this pathogen for longer periods compared to patients who are not treated. AET is now routinely recommended in many countries and the success of various regimens has been documented [8,19,20,25]. Thus, *AET for P. aeruginosa is recommended in CF*. Although there is evidence that in some patients a positive culture may be transient, in most patients *P. aeruginosa* will persist. Considering that a risk/benefit ratio favors AET, it seems reasonable to initiate AET as soon as possible after a positive *P. aeruginosa* respiratory culture. However, there is currently no specific treatment strategy for the eradication of *P. aeruginosa* that has been recommended. Thus, *what is the best strategy of antibiotic therapy for eradication of P. aeruginosa*?

The success rates to eradicate *P. aeruginosa* in different AET studies [12,13,17,19,20,26–29] ranges between 63% and 100% (mean: 81.2%). In the open-label, randomized ELITE trial [19], which compared the efficacy and safety of 2 regimens (28 and 56 days) of 300 mg twice daily tobramycin inhalation solution (TIS), >90% of patients in both groups had negative cultures for *P. aeruginosa* 1 month after the end of treatment and the majority of these patients remained free from infection for up to 27 months. The median time to recurrence of *P. aeruginosa* in patients' sputum/cough swab was similar in the 2 cohorts. In the EPIC study [20], 304 children, aged 1–12 years, were randomized to 1 of 4 eradication treatment regimens for 18 months. The participants, randomized to cycled therapy, received TIS (300 mg twice a day) for 28 days, with either oral ciprofloxacin (15–20 mg/kg twice a day) or oral placebo for 14 days every quarter, while the participants randomized to the culture-based therapy received the same treatment only during quarters with a positive *P. aeruginosa* culture. There was no statistically significant difference between all groups in the proportion of *P. aeruginosa* positive cultures throughout the study period. Thus, adding ciprofloxacin produced no further benefits nor did routine periodic treatment even in the absence of positive cultures [20].

The combination of inhaled colistin for 3 weeks–3 months of treatment plus oral ciprofloxacin has been used successfully [30]. The efficacy of the combination of ciprofloxacin and inhaled colistin for 3 months compared to TIS for 1 month to eradicate early *P. aeruginosa* infection was compared in a real-life setting and was similar in outcomes [31]. Furthermore, when CF patients were assigned to inhaled colistin/oral ciprofloxacin or to inhaled tobramycin/oral ciprofloxacin no differences in outcome between the two arms were observed [29]. Intravenously administered antibiotics have also been used in AET protocols [32]. In a trial comparing oral/inhaled versus intravenous therapy, decreased lung inflammation was observed in the latter group [33].

Although various AET protocols have demonstrated success, none have shown clear superiority. Thus the clinician may choose the treatment strategy that has been shown to be the most convenient with the same degree of success. Safety issues must also be taken into account. AET with TIS appears to be safe in young patients and not to cause the adverse effects seen with recurrent parenteral administration of aminoglycosides [8,34]. Recent European Guidelines recommend the inclusion of data from very young children in clinical studies [CHMP Guideline on the clinical development of medicinal products for the treatment of CF, 2011]. In patients aged 6 months to 6 years with normal renal function, systemic exposure following inhalation of 300 mg/5 mL of TIS was safe [35]. The use of the same doses of TIS from infancy to adulthood is supported by the ELITE trial [19] and in the EPIC trial [20]. A double-blind randomized multi-national study is currently ongoing, which includes patients aged 3 months to 7 years with the aim to provide regulatory-grade evidence of the efficacy and safety of TIS (EUDRACT-2011-002000-32). Thus, the current data suggest that *28 days of TIS when there is a positive culture is a recommended treatment strategy for the purpose of eradication of P. aeruginosa. However, because a number of treatment protocols have been shown to be of similar effectiveness including oral, inhalation and intravenous therapy, and there are only few comparative studies available, the optimal antibiotic regimen is not known.*

4.1. Why is AET not always successful?

Although AET has shown mean eradication rates of 81.2%, there are some patients for whom this strategy fails (definition Table 1). There are potential patient and pathogen factors that may limit the ability of AET to eradicate *P. aeruginosa* from CF airways. First, the patient must be adherent to the treatment regimen in order for it to be successful. Timing may be critical as there may be a window of opportunity after which AET will not be successful. Although several studies suggest that eradication of *P. aeruginosa* from CF airways by AET is most successful up to 12 weeks from initial detection [36,37], this period is not well defined and further studies are needed to better define early, intermittent and chronic *P. aeruginosa* infection (Table 1). Many factors impair the efficacy of antimicrobial drugs and preclude the eradication of *P. aeruginosa* in CF, once the infection is chronically established in the patients' airways [38–40]. These include bacterial [39,41–47] and host factors [8,10,48–50].

It is not known whether CF patients who fail to eradicate *P. aeruginosa* after AET have more lung inflammation and/or lung tissue injury due to the underlying CF defect or as a consequence of bacterial infections with pathogens other than *P. aeruginosa*. Maintenance of the CF patient's lung function over extended periods of time in the presence of the persistent pathogen in the airways is therefore a key in the antibiotic management of chronic *P. aeruginosa* lung infection. Peripheral distribution of aerosolized medications is reduced in the presence of airway obstruction, so drug may not get to the site of infection.

It is also possible that there is successful eradication of infection from the lower airways, but there is rapid re-infection. The source of the original infection may be the sinonasal cavities, which may not be reached by inhaled antibiotics. A

cross-sectional study showed frequently different microorganisms cultured from oral swab, sinus and BAL fluid [51] which makes it unlikely that the sinonasal cavities initiate lower bacterial lung infections in CF. However, other studies contradict this hypothesis [52–54].

Finally, it is recognized that culture negativity following AET does not necessarily mean that the pathogen was eradicated. It may be possible that the pathogen persists, though undetectable, after AET in the CF airways [55]. It is not known if there is a means of detecting the difference between true eradication and suppression of the numbers of the viable pathogen. A serological analysis of the EPIC AET study suggests that positive serology in CF patients identified the participants at higher risk for re-infection with *P. aeruginosa* after AET and identified CF individuals who failed to clear *P. aeruginosa* infection [56]. Given the fact that AET is considered to be the standard of care in CF, observational studies are the only way to assess the long-term effect of this intervention. It is important to determine whether patients who have successfully eradicated *P. aeruginosa* after AET courses, differ with regard to lung function from those patients who never had episodes of *P. aeruginosa* infections and such studies should be designed. Thus, the current data suggest that *a number of different reasons are responsible for the observation that eradication therapy is not successful.*

4.2. What is the best next strategy for the patient who has failed AET?

The potential failure of AET argues for optimal surveillance of *P. aeruginosa* in respiratory cultures (see Section 7) in order to know when alternative treatment options are needed. In the EPIC trial, the subjects who did not clear *P. aeruginosa* after 3 weeks of treatment of the first cycle were further treated for 28 days with the study drug. The rate of treatment failure was low (unpublished data) suggesting that repeating the initial AET is reasonable. For those who have failed a second attempt at eradication using inhaled and/or oral antibiotics, systemic treatment with intravenous antibiotics may be tried. *The scheme depicted in* Fig. 1 *is proposed as a potential care scheme for patients undergoing AET.*

5. Optimizing antibiotic therapy for treatment of chronic *P. aeruginosa* infections

Although AET has considerably decreased the prevalence of *P. aeruginosa* in younger CF patients, the pathogen is still present in the majority of older CF patients [3,5,57,58]. Chronic suppressive antibiotics have proven successful as a treatment of chronic airways infection in the maintenance of lung health [59]. Tobramycin inhalation solution (TIS, Novartis) was the first approved inhaled antibiotic, but since then there are a number of new formulations developed for the treatment of *P. aeruginosa* infections in CF patients.

5.1. Approved aerosol antibiotics

5.1.1. Tobramycin
Tobramycin is an aminoglycoside antibiotic that has long been used as an aerosol therapy for CF. TIS was the first aerosol antibiotic approved for CF and has been a workhorse chronic
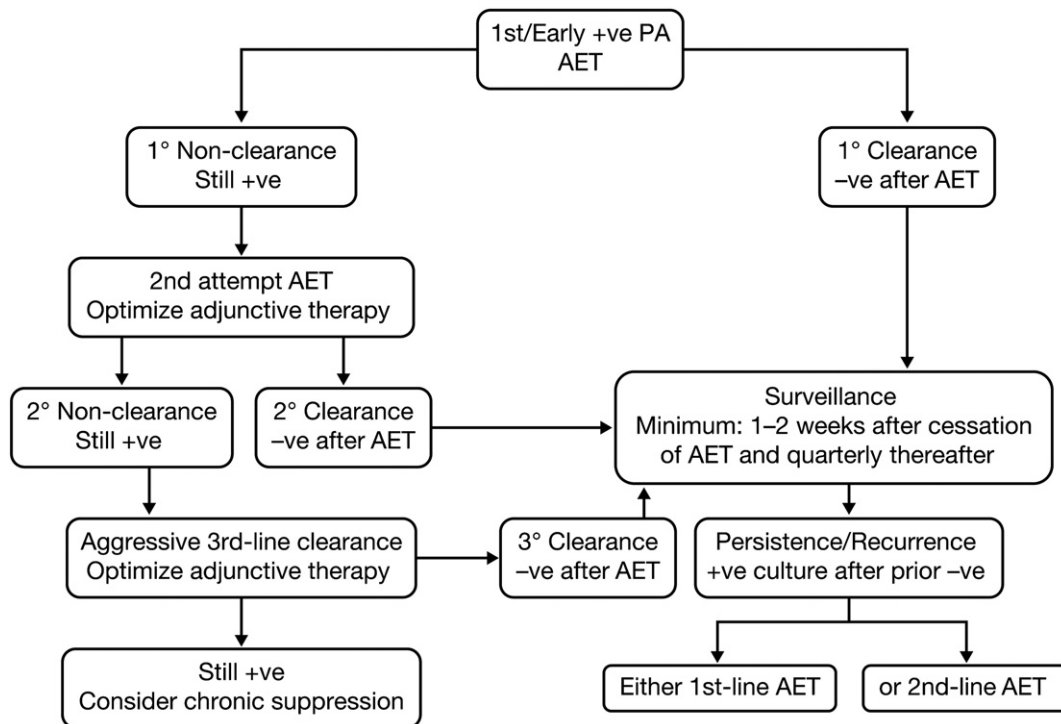

Fig. 1. The Artimino Algorithm for antibiotic eradication therapy (AET). Scheme for treatment of persistent *P. aeruginosa* following an initial AET intervention (+ve: positive; −ve: negative).

medication and is included in the CF treatment guidelines [59–61] for the suppression of *P. aeruginosa* infection, resulting in improved lung function and prevention of pulmonary exacerbations. The approved dose is 300 mg nebulized twice daily every other month. TIS is available in most countries.

Tobramycin is also available in another nebulized formulation (Bramitob®, Chiesi) [62]. The total dose is the same as for TIS, but it is more concentrated (75 mg/mL versus 60 mg/mL) to decrease nebulization time. In a double-blind randomized study, 247 CF patients with chronic *P. aeruginosa* infection were randomized to receive nebulized 300 mg/4 mL tobramycin or placebo over a 24-week study period in 4-week on and off cycles. At week 20, FEV_1 was significantly increased in the intention-to-treat population versus placebo. Treatment induced a trend toward decreased hospitalizations, increased nutritional status, and was well tolerated. The approved dose is 300 mg nebulized twice daily every other month. Bramitob is currently available only in European countries.

Tobramycin has also been developed as a dry powder formulation (TOBI® Podhaler®, TIP™, Novartis) for the management of chronic *P. aeruginosa* infection in CF patients. Tobramycin inhalation powder (TIP) capsules are formed of low density porous particles (PulmoSphere™), which exhibit improved flow and dispersion by inhalation via the passive T-326 dry powder inhaler (Podhaler). The dose was developed to replicate the pharmacokinetics of TIS [63]. Two controlled studies investigated the efficacy and safety of TOBI Podhaler. The EAGER trial enrolled 553 CF patients comparing TIP to TIS over 3 cycles of treatment [64]. The EVOLVE trial, including 102 CF patients [65], was placebo-controlled for 1 cycle followed by open label treatment with the TOBI Podhaler for 2 additional cycles of treatment. The Podhaler formulation displayed similar tolerability and efficacy to TIS and significantly improved FEV_1 compared with placebo. Cough was the most frequently reported adverse reaction related to the dry powder in both clinical studies. The recommended dose is 112 mg (four 28 mg capsules) inhaled twice daily in alternating cycles of 28 days on treatment followed by 28 days off treatment. TIP is currently available in some European countries, South America, and Canada.

5.2. Aztreonam lysine for inhalation

The nebulized monobactam aztreonam lysine inhalation solution (AZLI, Cayston®, Gilead) was approved in 2010 for improvement of respiratory symptoms in CF patients 6 years old and over with chronic *P. aeruginosa* infection. Cayston® is delivered via the PARI eFlow platform through a portable Altera handset which controls particle size for optimal airway deposition, minimizes delivery time, and increases particle delivery efficiency. Inhalation time in clinical trials averaged 2 min for each 75 mg dose [66,67]. The recommended dose is 75 mg inhaled thrice daily, with a minimum of four hours between doses, in alternating cycles of 28 days on treatment followed by 28 days off treatment.

In several clinical studies Cayston® has been shown to be safe and efficacious in suppressing chronic *P. aeruginosa* lung infection in CF patients [66–69]. In a randomized, placebo-controlled study of 164 CF patients [67], Cayston significantly improved CFQ-R Respiratory Symptoms Score (RSS) and FEV_1 after one cycle of use at 28 days, with a treatment difference compared to placebo of 9.7 points and 10.3%, respectively. In a second pivotal trial of 211 patients with CF [66], Cayston increased the median time to need for additional antipseudomonal antibiotics for symptoms of pulmonary exacerbation by 21 days, versus placebo. In the open-label follow-on study of these two trials, Cayston safety and efficacy was examined in 274 patients over 18 [68]. FEV_1 values, CFQ-R RSS, and body weight increased with each 28 day course of Cayston, and this effect was maintained over 18 months. No significant safety concerns were observed in studies over 12 months [70] and 18 months [68]; including no evidence of development of antibiotic resistance.

In a 6 month active comparator trial of 273 CF patients receiving either Cayston® or TIS, Cayston® was superior to TIS with regard to lung function improvements, with a treatment difference of 7.8% at 28 days and 2.7% at 24 weeks. Significant reductions in pulmonary exacerbations and mean change in CFQ-R RSS after 28 days of Cayston treatment were also seen, compared to TIS. In the follow-on 6 month open-label extension of this active comparator trial, the FEV_1 response of previous TIS subjects who were switched to Cayston® improved and was sustained over time. Patients receiving Cayston® also gained weight throughout the 12 month trial, compared to those who received TIS who initially lost weight and then improved upon switch to Cayston® [70]. Cayston® is available in the EU, Switzerland, USA and Canada. Cayston® is licensed for use in patients 6 years and older.

5.2.1. Colistin

The polymyxin derivative colistimethate sodium increases Gram-negative bacterial membrane permeability causing cell death. It has been used by inhalation for many years in CF patients for the treatment of chronic *P. aeruginosa* lung infection [8]. Colobreathe® (Forest Laboratories) contains 1,662,500 IU of colistimethate sodium inhalation powder, for the management of chronic *P. aeruginosa* pulmonary infections in CF patients, aged 6 years and older [71]. In a phase III open-label trial, Colobreathe® (125 mg twice daily) was not inferior to TIS, based on change in FEV_1 % predicted after 24 weeks [71]. Colobreathe® was safe and well tolerated in adult and pediatric subjects with CF [71]. Colobreathe® may be available in some EU countries in 2012.

5.3. Medications in development

5.3.1. Liposomal amikacin

Liposomes are biodegradable vesicles composed of single or multiple phospholipid layers, which may protect entrapped polycationic antibiotics, such as aminoglycosides, from inactivation by polyanionic components present in sputum, such as mucins or DNA. In airways, liposomes can also be taken up by macrophages. Based on this notion, liposomal amikacin for inhalation (Arikace®, INSMED) comprised of neutral charge liposomes has been developed to improve the penetration of the aminoglycoside antibiotic into mucus plugs and *P. aeruginosa* biofilms [72]. Clinical studies with Arikace, delivered via the

eFlow® nebulizer system, revealed a sustained release of amikacin in CF lungs [73]. The clinical pharmacokinetics and pharmacodynamics of Arikace have been evaluated in Phase Ib studies in 24 CF patients with chronic *P. aeruginosa* infection who received 500 mg of Arikace once daily for 14 days [73]. Randomized, placebo-controlled dose escalating phase II trials in CF patients with chronic *P. aeruginosa* infection showed a dose response and indicated that Arikace, delivered at a dose of 560 mg once daily for 28 consecutive days, followed by 28 days off drug, demonstrated superior clinical benefit compared to placebo as measured by significant and sustained improvement in lung function and reduction in *P. aeruginosa* density [74]. Also, patients receiving Arikace showed superior improvement in their respiratory symptoms as compared to those on placebo [74]. In addition, Arikace® was well-tolerated [74].

5.3.2. Ciproinhale

Ciprofloxacin dry powder inhaler (DPI) has been developed for the management of chronic *P. aeruginosa* infection in CF patients. Ciprofloxacin DPI uses the PulmoSphere® technology. Phase I studies with ciprofloxacin DPI in pediatric and adult CF patients showed that high concentrations in the lung were achieved with very low systemic exposure following single and multiple dose administration. A Phase II study of ciprofloxacin DPI, given at 2 dose levels (32.5 and 48.75 mg) twice a day for 28 days, showed significant decrease in *P. aeruginosa* density compared to placebo, but did not significantly improve the primary endpoint FEV_1. There was also no significant change in other endpoints such as respiratory symptoms or exacerbations [75].

5.3.3. Levofloxacin

A novel formulation of levofloxacin, levofloxacin inhalation solution (MP-376, Aeroquin) is being developed for the management of chronic *P. aeruginosa* infection in CF patients. As with inhaled ciprofloxacin, pharmacokinetic studies show high levels in sputum with low systemic exposure [76]. In a phase II study [76], 151 patients with CF were randomized to one of three doses of MP-376 (120 mg every day, 240 mg every day, and 240 mg twice a day) or placebo for 28 days. The primary efficacy endpoint was the change in sputum *P. aeruginosa* density. All doses of MP-376 reduced *P. aeruginosa* sputum density at day 28. A dose-dependent increase in FEV_1 was observed between the 240 mg MP-376 twice-daily group and placebo. A significantly reduced need for other anti-*P. aeruginosa* antibiotics was observed in all MP-376 treatment groups compared with placebo. MP-376 was generally well tolerated relative to placebo.

5.3.4. Fosfomycin/tobramycin

A broad spectrum combination antibiotic, consisting of fosfomycin and tobramycin, is currently developed for the management of chronic bacterial infection in CF patients. A phase II study has been completed (NCT00794586) in which the safety and efficacy of 2 dose combinations of fosfomycin/tobramycin for inhalation (FTI), following a 28-day course of AZLI in CF patients and *P. aeruginosa* lung infection has been evaluated [77].

5.3.5. What is the best strategy of chronic suppressive antibiotics for P. aeruginosa?

It is reasonable when initiating therapy for chronic airways infection to implement a strategy as was used during drug development; that is, an approved inhaled antibiotic should be used in repeated cycles of 4 weeks of treatment, followed by 4 weeks off treatment. However, the original strategy of four-week on–off cycle of TIS [78], chosen for decreasing the development of resistance during antibiotic therapy, has been challenged as to whether it is the optimum treatment strategy noting the observation of a decrease in lung function during the off cycle [78]. The development of new antibiotic formulations has now given clinicians and patients greater opportunity to determine the best treatment approach. Potential strategies could employ continuous antibiotic rather than an intermittent approach, or to use a rotation of antibiotics rather than a single antibiotic. Thus, *it is recommended that therapeutic options for inhaled antibiotic therapy in patients with chronic P. aeruginosa infection include an intermittent one month-on one month-off regime for inhaled aminoglycosides or continuous administration for inhaled colistin. In parallel with re-evaluation of all other aspects of care, a change of the inhalation antibiotic regimen should be considered in patients who frequently suffer from acute exacerbations or whose lung function deteriorates rapidly. Patients may remain on an intermittent one month-on one month-off regime but administering another inhaled antibiotic in the off month cycle or administering continuously inhaled antibiotic is also rationale and may benefit those patients with unstable disease. Current evidence from short-term studies suggests that inhaled antibiotics are safe and that the benefit outweighs the possible risk.*

Combining different antibiotics in a given CF patient for treating chronic *P. aeruginosa* lung infection may prove useful, based on *in vitro* observations [79,80] and animal experiments [80].

6. Optimizing antibiotic therapy for treatment of acute exacerbations of chronic *P. aeruginosa* infections

During chronic bacterial lung infection, CF patients suffer from acute worsening of signs and symptoms, often called an acute pulmonary exacerbation [81], a phenomenon for which the pathophysiology has not been completely elucidated. Antibiotics are typically a component of the treatment of a pulmonary exacerbation. Besides maintaining lung function, a further important goal of antibiotic therapy for chronic *P. aeruginosa* infection is to prolong the time period to the next acute respiratory exacerbation [82]. Some have recommended systemic antibiotics for the treatment of acute exacerbations [8], based upon the rationale that an increased production of mucus plugs that obstruct the airways during acute exacerbations, may allow inhaled antibiotics only to reach the bacterial pathogens in the larger bronchi, but not in deeper areas of the respiratory tract. There is no evidence that using inhaled antibiotics during a course of intravenous antibiotics adds additional benefit. Even so, inhaled antibiotics were reportedly used in one fourth

of pulmonary exacerbations in North America between the years 2003 and 2005 [83].

A significant decrease of *P. aeruginosa* cell numbers and an increase in lung function after a course of antibiotics should in theory be linked to a considerably large bacterial population in the patients' airways which is susceptible to the given antibiotic. Thus, reliable *in vitro* antibiotic susceptibility testing should establish this link [84]. However, substantial differences in antibiotic susceptibilities between *P. aeruginosa* isolates with the same colony morphology, and inconsistent results from different laboratories question this approach [42,85,86]. A poor correlation between *in vitro* susceptibility data and clinical outcome in chronically infected CF patients after antibiotic therapy courses has been demonstrated [87–89]. Thus, not surprisingly, a critical assessment of the success rate of a given antibiotic treatment course using microbiological data is often missing and rather indirect clinical data are used to evaluate a given treatment option in this context [90].

One quarter of CF patients treated with antibiotics for acute exacerbations did not recover to baseline lung function [91,92]. In one study, 57% of exacerbations were successfully treated even though the *P. aeruginosa* was resistant to the antibiotics used for treatment [92]. This leads to the question, whether antibiotic therapy for patients with CF should be selected and rationalized on the basis of *in vitro* antibiotic susceptibility testing or whether routine susceptibility testing in *P. aeruginosa* should be abandoned as there is no relation between the outcome of treatment for exacerbations and the *in vitro* susceptibility for the systemic antibiotics used.

What is the optimal antibiotic treatment of acute exacerbations of chronic *P. aeruginosa* infection? *There is no evidence to support the use of inhaled antibiotics in addition to intravenously administered antibiotics. If an antibiotic is administered by two different routes of administration, potential additional toxicity should be considered. For instance in cases of significant renal impairment, inhaled aminoglycosides are frequently used for treatment of exacerbations limiting further systemic toxicity. There is no evidence to treat pulmonary exacerbations with inhaled antibiotics only.*

6.1. What is the optimal duration of antibiotic therapy for treatment of acute exacerbations of chronic P. aeruginosa infection?

The length of antibiotic therapy for acute exacerbations in CF patients, typically 10–14 days [8,81], is defined by clinical [93] rather than by quantitative microbial data. The latter may shed some light on the question whether the established time frame for the treatment is justified or needs to be changed. Thus, *it is recommended that exacerbations should be treated until symptoms resolve and lung function recovers, however therapy should not be extended more than 3 weeks, except under very special circumstances. Patients with multi-drug resistant P. aeruginosa infection may require longer therapy. Careful evaluation of the patients' clinical status is required throughout the course of therapy.*

7. Current role of microbiological testing in the clinical care of patients as well as in clinical trials

The understanding of the pathophysiology of CF airways disease has depended on the ability to identify pathogens through standard and novel microbiology methods. Optimal clinical care of the CF patient requires access to a sophisticated microbiology laboratory that is able to perform diagnostic testing relevant to CF disease. What is evolving is our understanding of how best to use the information derived from the microbiology lab to provide optimal care.

As *P. aeruginosa* is known to be associated with worse lung disease and current treatment strategies have shown benefit to AET, it appears necessary to treat early infection with the hopes of eradicating the infection (Table 1). Early acquisition of *P. aeruginosa* may not cause symptoms, suggesting that routine surveillance cultures of respiratory specimens should be performed. Thus, *what is the best method of routine surveillance for infection of the CF airways*?

Early diagnosis of *P. aeruginosa* lung infections may be difficult in patients not producing sputum [1,11]. Thus, nasopharyngeal aspirate, throat or cough swabs, sputum induction, bronchoalveolar lavage (BAL) and serological tests have been used for detecting infection with *P. aeruginosa* [8]. Antibody testing against the *P. aeruginosa* enzymes AP, ELA and ExoA offers high sensitivity and specificity for the presence of *P. aeruginosa* in respiratory cultures of CF patients [94]. Also other assays have been developed [95]. Early identification of *P. aeruginosa* by BAL did not improve the outcome of early eradication compared to conventional techniques [69]. *P. aeruginosa* serology has been demonstrated to be a useful marker for successful eradication of the pathogen [17,27,94] and elevated levels of specific anti-*P. aeruginosa* antibodies have been shown to be a risk factor for developing chronic *P. aeruginosa* infection [95]. Thus, *periodic monitoring of the patient who has never been infected or who has had successful eradication should be performed and a period of no more than 3 months is acceptable. For those patients who have a new infection that is treated with AET, a subsequent culture should be obtained 2–4 weeks after completion of the antibiotics to assess eradication. Routine serological testing is not recommended.*

For those patients with chronic infection, there is benefit to routine monitoring, especially for those who are on suppressive antibiotic therapy or who have had acute pulmonary exacerbations. Patients with chronic infection do aquire new infections so regular culture is potentially of benefit. The emergence of bacterial species in antibiotic treated patients has been investigated using culture-based methods in several clinical studies. For instance, in the ELITE trial [19], regular monthly monitoring of respiratory cultures in the first year did not reveal obvious trends in the emergence of non-*P. aeruginosa* pathogens. However, clearly only a very small number of microbial species have been investigated on a qualitative basis.

7.1. What is the role for antibiotic susceptibility testing?

Susceptibility testing may not be helpful for selecting antibiotics for those patients with chronic infection as they have

not proven to be predictive of outcomes. Antibiotic susceptibility may not apply to chronic inhalation therapy because a resistant organism according to conventional breakpoints may be still susceptible due to the high level of antibiotic applied. Susceptibility testing may not be helpful for selecting antibiotics for treatment of acute exacerbations as patients may respond clinically in spite of *in vitro* resistance. Furthermore, it remains unclear whether specific clinical information can be used to identify individuals at increased risk of initial management failure [91,92]. *P. aeruginosa susceptibility testing should be considered for (a) surveillance of resistant or multi-resistant P. aeruginosa strains in combination with strain typing; (b) when a new isolate of P. aeruginosa is identified in an individual patient; and (c) when a change of therapy (intravenous, nebulized or oral) is proposed because of a lack of response to treatment. The finding of in vitro antibiotic resistance does not necessarily indicate that treatment should be changed if the patient is responding to the current therapy.*

7.2. What is the role for quantification of bacteria?

The correct determination of bacterial cell numbers including those for *P. aeruginosa* before and after a course of antibiotics is labor intensive, particularly when culture-based strategies are used. During chronic infection *P. aeruginosa* cell numbers may reach 10^7 to 10^8 colony forming units (cfu) per gram of sputum [96,97] and a reduction of two log orders of magnitude after antibiotic therapy can be regarded as a major effect [96,98].

Quantitation of bacteria has been used to measure the microbiological effect of inhaled antibiotics and a reduction in bacterial numbers was seen in early studies of inhaled therapy [77]. There are conflicting reports of the impact of treatment for acute exacerbation on the bacterial load in the airways. Some studies show an average reduction in cfu following antibiotics for acute exacerbation [96] but others have shown a range of post treatment bacterial load indicating that bacterial numbers do not decrease in all patients [50,99]. Sputum specimens may differ in viscosity and contain various bacterial phenotypes including small colony variants, which may be difficult to culture. This can make reliable bacterial quantitation difficult using conventional culture based methods. *At this time, quantification of bacteria does not offer clinical utility but may still prove useful in clinical trials.*

7.3. What is the role for culture-independent microbiology?

Culture-independent diagnostic methods such as quantitative polymerase chain reaction (qPCR) can determine total bacteria or bacteria belonging to a particular species in clinical samples and may avoid problems associated with culture-based strategies [97,100–102]. The inherent problem of qPCR relates to the inability of this approach to distinguish between living or dead bacterial cells. Such differentiation is needed to evaluate the impact of antibiotic therapy. This may be successfully circumvented by tagging bacterial DNA in viable cells with propidium monoazide photo-crosslinking before analysis or the use of RNA-based techniques [100]. This method could also shed light on the

question whether a *P. aeruginosa*-specific antibiotic therapy would also affect cell numbers of other CF-related pathogens such as *H. influenzae* [103] and *S. aureus* [46]. However, molecular methods have shown a large heterogeneity of bacterial species and their concentrations within a given sputum sample [100] and it is not known what role these other microorganisms play in the pathogenicity of lung infection in CF. Furthermore, the results of culture-independent diagnostic methods may vary with regard to the DNA isolation method used [100,104]. Finally, culture-independent techniques have not been validated and reproducibility is an important issue, it remains uncertain whether these quantitative culture-independent microbial diagnostic techniques should be used instead of culture-based methods to assess the efficacy of antibiotic therapies in CF patients or whether antibiotic therapy should be guided by clinical and lung function parameters alone.

Culture-independent diagnostic methods for the detection of microbial species have also demonstrated that CF sputum specimens generally contain a larger number of different bacterial species in high concentrations than we thought previously [38]. For instance, several strict anaerobic species may be present in CF sputum in numbers comparable to those of *P. aeruginosa* [99]. This novel insight immediately raises the question whether specific antibiotic therapy against *P. aeruginosa* would not only affect *P. aeruginosa* alone but would also change the composition of the larger microbiota in the CF airways. Theoretically, a decrease of *P. aeruginosa* during effective antibiotic therapy may provoke the growth of other species already present in the microbiota which would dampen the beneficial effect of the antibiotic on inflammation, tissue destruction and lung function. On the other hand, it may cause a significant reduction of other antibiotic susceptible bacterial species leading to less inflammation and tissue destruction and increased lung function. *At this time, culture-independent diagnostic methods do not offer clinical utility but may prove useful in clinical trials.*

8. Current status of antibiotic treatment of other bacterial pathogens

As noted earlier, traditional and novel methods of microbiology have demonstrated that the airways infection in CF is rather complex, and include multiple bacterial species. The most common species include *S. aureus*, both methicillin-susceptible (MSSA) and methicillin-resistant (MRSA), *H. influenzae*, *S. maltophilia*, *A. xylosoxidans*, members of the *Burkholderia cepacia* complex, and non-tuberculous mycobacteria (NTM) species [105]. It is likely that these microorganisms also contribute to lung inflammation and lung tissue destruction/remodeling. As evidence is growing that these are indeed pathogens in the CF airways, it would seem appropriate to consider using similar treatment strategies against them as are used to treat *P. aeruginosa*, including AET and chronic antibiotic suppression. Unfortunately there are no data to support the clinical benefit for either strategy for these organisms.

8.1. S. aureus

S. aureus has long been found in the airways of CF patients and has been thought to be a predecessor of later infection by P. aeruginosa and appears to be associated with increased lower airway inflammation [106,107]. As such, some have advocated for prophylactic therapy against S. aureus [108], a strategy that is being recommended in the UK and other countries [105] but has not been adopted by clinical practice guidelines in the US [59]. This is based upon data from a long-term placebo controlled trial in which there was no clinical benefit for those on prophylactic antibiotic therapy after 7 years of treatment [109].

MRSA strains have been increasingly recognized among CF patients in the last decade [3,110]. In a recent epidemiological study in Italy Penton Valentine Leukocidin (PVL)-negative MRSA strains with a high resistance rate to clindamycin and moderate resistance to trimethoprim/sulpha-methoxazole were detected in 31.4% of Italian CF patients. Recent data suggest that MRSA strains are markers of more severe disease in CF patients but are not more virulent than MSSA strains [11–116]. Acquisition of MRSA has been associated with hospitalization, the F508del genotype and the presence of bronchiectasis [116]. For treatment of S. aureus, recommended drugs, doses and regimens are given in Table 2.

Other methods of infection control would also seem prudent. In countries with a policy of segregation and eradication of first infection of MRSA, chronic infection with MRSA is rare [117]. It seems that the rates of MRSA in CF patients parallel those in the overall community, suggesting that differing rates in different countries do not reflect different treatment modalities in the CF patient population.

8.2. S. maltophilia and A. xylosoxidans

S. maltophilia prevalence rates still vary considerably between CF centers with a mean prevalence rate of up to 25% in single centers [118] with rapidly increasing prevalence in others [119]. Studies have presented conflicting data regarding the clinical significance of S. maltophilia [120,121]. Chronic infection associated with the development of an immune response against the organism, predicts more exacerbations [122], but not more progression in decline of lung function [122]. Relatively little is known about the clinical significance of A xylosoxidans in CF and more studies are needed to determine when treatment should be given and which antibiotics should be used. Recommended antibiotics for therapy against S. maltophilia and A. xylosoxidans infections in patients with CF are given in Table 3.

8.3. Burkholderia cepacia complex strains

Other antibiotic resistant bacterial pathogens, associated with CF patients, include the Burkholderia cepacia complex (Bcc), a group of at least 17 closely related bacterial species [123], from which B. cenocepacia, B. multivorans and B. dolosa are the most prevalent in CF. Due to its high virulence, effective antibiotics to treat Bcc-infected CF patients are urgently needed [124]. Few trials have systematically examined the antibiotic treatment of Bcc infection in CF patients.

Recently, a large randomized, controlled trial enrolled 101 CF patients to evaluate the safety and efficacy of Cayston® versus placebo in BCC-infected CF patients. Subjects received Cayston® or placebo continuously every month in addition to standard therapy for the first 6 months of the study. No difference in FEV_1 was demonstrated between the two groups. No benefit was realized in the 6 month cross over phase [125]. Recommended

Table 2
Recommended antibiotics for therapy against Staphylococcus aureus in patients with CF.

Antibiotic	Route of administration	Dose (mg/kg/day)	Administrations per day	Maximum daily dose (g)	
				Oral	IV
Flucloxacillin	Oral	100	3–4	4.5	12.0
Dicloxacillin	Oral, i.v.	50	3–4	4.0	12.0
Fusidic acid	Oral, i.v.	25–50	2–3	2.0	2.0
Clindamycin	Oral, i.v.	20–40	2–4	1.8	1.8
Rifampicin	Oral, i.v.	15–20	2	0.6	0.6
Vancomycin	I.v.	40	2	–	2.0
Teicoplanin	I.v.	10	1	–	0.8
Linezolid	Oral, i.v. (<5 years)	30	3	1.2	1.2
Linezolid	Oral, i.v. (>5 years)	20	2	1.2	1.2
Cotrimoxazole (trimetoprim compound)	Oral	8–10	2	0.32	–
Amoxicillin/clavulanic acid	Oral	50–100	3	4.0	
Cefuroxime/axetil	Oral	20–30	2	1.0	

If rifampicin or fusidic acid or clindamycin or macrolides such as azithromycin are used, a high risk to develop resistance is present. Therefore these drugs should be considered in combination with e.g., dicloxacillin or flucloxacillin. For pathogens difficult to treat such as MRSA, rifampicin+fusidic acid or rifampicin+clindamycin can be used. Linezolid is an expensive drug and clinical experience is limited. Linezolid has a high barrier to the development of resistance. Long-term therapy with linezolid is associated with neuropathy. Other drugs listed should be used for combination therapy of MRSA. Augmentin (amoxicillin+clavulanic acid) is a broad-spectrum antibiotic and therefore influences the normal flora. It can be used when both H. influenzae and S. aureus are cultured [172]. Drug doses may need to be adapted according to comorbidities. Always check for drug–drug interactions, especially with fusidic acid and rifampicin.

Table 3
Recommended antibiotics for therapy against *S. maltophilia* and *A. xyloxidans* in patients with CF *.

Antibiotic	Route of administration	Dose (mg/kg/day)	Administrations per day	Maximum daily dose (g)	
				Oral	IV
Minocyclin	Oral	2–3	1–2	0.2	–
Doxycyclin	Oral	2–3	1	0.2	–
Sulfamethoxazol/trimetoprim	Oral, i.v.	50–100 + 10–20	2–4	0.48	0.48
Ceftazidime	I.v.	150–200	3	–	12.0
Meropenem	I.v.	100–150	3	–	6
Colistin **	I.v.	2–5	2–4	–	0.48
Tobramycin	I.v.	5–10	1–3	–	0.48
Ciprofloxacin	Oral, i.v.	20–30	2–3	1.5	1.2
Aztreonam	I.v.	150–250	3	–	8.0
Ticarcillin/clavulanic acid	I.v.	200–300/6–10	4–6	–	16.0 (ticar comp)
Piperacillin/tazobactam	I.v.	200–240/25–30	3–4	–	16.0 (piperacillin comp)

* These species are resistant to many antibiotics and easily become resistant to antibiotics during treatment. Susceptibility testing must therefore guide the choice of antibiotics and combination therapy is usually recommended: Aztreonam/ticarcillin/clavulanic acid combination therapy because of synergism against *S. maltophilia*. Tetracyclines should not be used in children. Tobramycin drug levels need to be measured. Drug doses may need to be adapted according to comorbidities. Always check for drug–drug interactions.

antibiotics for therapy against Bcc infections in patients with CF are given in Table 4.

8.4. NTM species

Increasingly NTM species, in particular *M. avium-intracellulare* complex, *M. chelonae* and *M. abscessus* complex are diagnosed in airway specimens of mainly older CF patients [126]. Because infection is associated with an accelerated clinical decline [126], and clinical improvements have been observed after anti-mycobacterial therapy, these pathogens should be treated when associated with a clinical deterioration or when the patient does not respond to the antibiotic treatment against other microorganisms detected in parallel in respiratory cultures [127]. However, there is no treatment regimen that has been demonstrated to be routinely successful in deriving a clinical benefit or eradicating the infection.

8.5. What is the optimal treatment strategy of NTM infections in CF patients?

Diagnosis and treatment guidelines have been published [ATS guidelines] for NTM infections in general, and for CF in particular. Treatment of NTM infection is a serious commitment, requiring multiple antibiotics and for an extended treatment period [128] (Tables 5, and 6). Novel therapies are being considered. For example, the possibility that liposomes can be taken up by macrophages may provide Arikace® with enhanced activity against intracellular NTM species such as *M. avium-intracellulare* complex, *M. chelonae* and *M. abscessus* which are found in airway specimens of CF patients [126,129].

Of note, the long-term use of the macrolide azithromycin has become an accepted therapy for patients with CF [59]. Azithromycin has multiple beneficial effects on inflammation and lung physiology [38,130–132] and reduces *P. aeruginosa* biofilm formation and quorum sensing regulated extracellular

virulence factors [133,134]. It is recommended that chronic macrolides are withheld in patients with NTM infection in order to prevent selection of resistant pathogens [59]. Recent concern that macrolides may increase the risk of acquiring NTM infections is based upon *in vitro* studies of human macrophages where azithromycin prevented lysosomal acidification, thereby impairing autophagic and phagosomal degradation and as a consequence inhibited intracellular killing of mycobacteria within macrophages, resulting in chronic infection with NTM in mice [135]. However, this phenomenon has not been observed in clinical CF trials with azithromycin [136].

8.6. Anaerobic species

The potential role for anaerobic species in the pathogenesis of CF airways disease has become of greater interest as culture-independent analysis of CF respiratory specimens has revealed the presence of strict anaerobic species [97,99,137–140]. Many strict anaerobic bacteria are antibiotic resistant [99,141]. Studies show that a higher diversity of strict anaerobes is associated with a younger age [142], and better lung function [143]. The major reason why clinicians have not specifically treated anaerobes is because the clinical significance of these species remains unclear. For *Prevotella intermedia*, however, *in vitro* data suggest that the pathogen may contribute to lung disease in CF patients [144]. The demonstration that *P. intermedia* produces cytotoxins and provokes inflammation *in vitro* suggests that it causes airway damage, which if demonstrated *in vivo* would facilitate the decision for antibiotic treatment.

8.7. Other microbial pathogens

Other commonly identified microbial pathogens present in airways of CF patients include *Aspergillus fumigatus*, for which increasing prevalence is clearly associated with the use of inhaled antibiotics [145]. *A. fumigatus* may cause severe

Table 4
Recommended antibiotics for therapy against *B. cepacia* complex in patients with CF *.

Antibiotic	Route of administration	Dose (mg/kg/day)	Administrations per day	Maximum daily dose (g)	
				Oral	IV
Doxycyclin	Oral	2–3	1	0.20	–
Sulfamethoxal/trimetoprim	Oral, i.v.	50–100 + 10–20	2–4	0.48 **	0.48 **
Ceftazidime	I.v.	150–200	3	–	12.0
Meropenem	I.v.	120	3	–	6.0
Tobramycin	I.v.	5–10	1–3	–	0.48
Aztreonam	I.v.	150–250	3	–	8.0
Ticarcillin/clavulanic acid	I.v.	200–300/6–10	4–6	–	16.0 ***
Piperacillin/tazobactam	I.v.	200–240/25–30	3–4	–	16.0 ***

  * These species are resistant to many antibiotics and easily become resistant to antibiotics during treatment. Susceptibility testing must therefore guide the choice of antibiotics and combination therapy is usually recommended. For *B. cepacia complex* three i.v. drugs are recommended.

  ** Trimethoprim compound.

*** Ticarcillin and piperacillin compound. Drug doses may need to be adapted according to comorbidities. Always check for drug–drug interactions.

endobronchial infections and allergic bronchopulmonary aspergillosis (ABPA) in 2–7.8% of CF patients [146,147].

In summary, the presence of many other bacterial species besides *P. aeruginosa* in CF airways may represent a target for therapy, because they are either directly pathogenic or they may increase the virulence of other pathogens [148] or inhibit antibiotics thereby diluting their effects on *P. aeruginosa* [100]. The path from identification of the organism to management decisions requires epidemiological studies that demonstrate the role the organism plays in the pathogenesis of disease and the observation of clinical benefit from treatment interventions designated specifically at the pathogen. Early epidemiological studies of these pathogens have begun to inform us that these are indeed pathogens, but we lack clinical studies of intervention and such studies are clearly needed.

9. Comparative efficacy of inhaled antibiotics in CF and endpoints in clinical trials

There is a perceived need for additional antibiotic choices for the management of CF airways disease. As there are no new antibiotic classes being developed, new options for inhaled antibiotics are the most likely new development and some have been discussed earlier (Section 5). The clinical need is due to the fact that some patients cannot tolerate current available options, they have become refractory to the current therapy or the treatment burden results in poor adherence and thus, reduced efficacy [149–151]. Technological advances, such as

Table 5
Recommended antibiotics for therapy against *Mycobacterium avium* complex infections in patients with CF.

Antibiotic	Route of administration	Dose	
Clarithromycin	Oral	500–1000	mg/d
Azithromycin	Oral	250–300	mg/d
Ethambutol	Oral	15	mg/kg/d
Rifabutin	Oral	150–300	mg/d
Rifampicin	Oral	450–600	mg/d
Amikacin	I.v.	15	mg/kg/day

Aim for eradication: 12 months of negative sputum cultures while on therapy.

faster and smarter nebulizers and dry powder formulations, offer great opportunity, but there is also a need for additional drug classes, as current approved formulations include only an aminoglycoside, a monobactam, and a polymyxin.

The challenge to further development of new aerosol antibiotic options is how best to study them. In general, the clinical trials for developing new inhaled antibiotics are designed either as superiority studies versus placebo. However, when such studies require extended periods of no antibiotic, they are no longer considered ethical for patients. Although non-inferiority studies can be performed, given the relatively small treatment benefits it is difficult to agree on an optimal non-inferiority margins. Non-inferiority trials typically require large numbers of patients making such studies more difficult to conduct.

In the light of novel antibiotic formulations for CF patients, which bring important patient benefits for the same clinical efficacy, as reported in clinical trials, it is important to further discuss how these benefits can be valued and included in a comparative effectiveness research reflecting real-life benefits. In the context of a clinical trial setting, the patients' adherence is generally high, whereas in the real-world, rates of adherence and persistence rates are much lower and the efficacy of a drug can be therefore decreased [149,152]. In addition, it is important to explore how patient satisfaction due to new delivery systems can be translated in real-life increased compliance, reduced treatment burden and better clinical outcomes.

9.1. How do we assess the response to antibiotic treatment in CF patients?

Regulators such as the EMA [153] and the FDA rely particularly on phase III trials with clinical endpoints such as improvement in FEV_1 [154]. However, short-term increases in lung function observed in antibiotic trials a decade ago [77] are currently rarely observed as patients are better treated and rates of lung function decline are drastically reduced [68,155]. These developments make FEV_1 difficult to use as an endpoint in CF trials with antibiotics. Therefore, other techniques and clinical endpoints have been suggested which are currently under investigation including several lung imaging techniques and

Table 6
Recommended antibiotics for therapy against *Mycobacterium abscessus* infections in patients with CF.

Antibiotic	Route of administration	Dose	
Clarithromycin	Oral	500–1000	mg/d
Azithromycin	Oral	250–300	mg/d
Cefoxitin: i.v.	200		mg/kg/d *
Amikacin	I.v.	15	mg/kg/d **
	Inhaled	250–500	mg twice daily
Meropenem:	I.v.	40	mg/kg ***
Tigecycline:	I.v.	50	mg twice daily ****
Linezolid	Oral	600	mg twice daily
Interferon gamma	s.c.	25–50	µg/m2, 2 or 3 times weekly

   * Divided every 8 h, max 12 g.
  ** Inhaled 250–500 mg twice daily.
 *** Divided every 8 h, max 6 g.
**** $t1/2 = 40$ h. In case of hepatotoxicity 100 mg every other day. Comment: aim for stable disease although reported cases show a decline in lung function despite maintenance therapy.

several sputum biomarkers. Novel bacteriological tools may provide valuable information in phase II studies which may have an impact for the design and conduct of phase III trials.

Other benefits, such as improvement in health-related quality of life (HRQoL), which includes improvement in respiratory symptoms, satisfaction, convenience, reduced administration time of the different antibiotics and their delivery device, should be considered in making treatment choices. CF patients have a high treatment burden due to an increased number of drugs and they need to execute lengthy procedures every day for the administration of their medications. A drug, with a novel technology which provides a decrease in the administration time and that eases the burden for the same efficacy and safety, is therefore highly beneficial. Assessment of the patient's perspective of symptom improvement, adherence, convenience and persistence, and their reported increase in HRQoL and satisfaction should be part of the treatment decision making [156]. Patient reported outcomes (PROs) have been used for regulatory approval and are considered increasingly important as secondary outcome parameters [156–158].

10. Economic evaluation of antibiotics in CF

In an increasing number of countries decisions to reimburse medicines, medical devices and medical procedures are based on health economic assessments (e.g. cost effectiveness analyses, CEA, or cost-utility analyses, CUA) and budget impact estimation [159,160]. The results of such evaluations, whereby different treatment alternatives are compared are typically summarized in an incremental cost-effectiveness ratio (ICER). The denominator of ICER reflects the incremental health gain which is the combined increase in life expectancy and in HRQoL, expressed as quality adjusted life-years (QALY) gained from the better intervention. The numerator in ICER reflects the incremental cost of obtaining that health gain. Note that the incremental cost already accounts for the

potential savings of the intervention and thus represents a net cost of the intervention [161].

Guidelines have been developed which provide recommendations for the conduct of economic evaluations in order to improve their validity and reliability [162,163]. In addition, comparative effectiveness research is gaining importance in evaluating real-world benefits of different strategies. This concept is defined as "the comparison of effective interventions among patients in typical patients care settings, with decisions tailored to individual patient's needs" [164].

There have been relatively few economic evaluations of antibiotic treatments in CF, with three different areas of interest: (a) the economic value of home- versus hospital-based intravenous therapy, (b) assessment of cost-effectiveness of inhaled antibiotics, specifically TIS and AZLI and (c) the relationship between costs, including patient co-payments and out of pocket expenses, and adherence and (d) the economic value of antibiotic eradication therapy.

10.1. Intravenous antibiotics

A CEA of using home-based and hospital-based treatment with intravenous antibiotics for respiratory exacerbations in adults with CF has been carried out in UK [165]. During one year, 454 courses of intravenous antibiotics in 116 CF patients were retrospectively analyzed (213 courses were hospital-based and 214 courses were home-based). Lung function as measured by FEV_1 increased in hospital-treated patients and decreased in home-treated patients after one year, suggesting that hospital-based treatment was more effective and most costly in hospital than home-based treatment. The mean ICER of hospital versus home-based treatment was £46,098 over 1-year of treatment. However, in Sweden home intravenous antibiotic treatment is successfully practiced since 1985 [166,167]. Decisions to treat patients at home or in the hospital are driven by various medical and social aspects.

10.2. Inhaled antibiotics

At the time of this document development the only published economic evaluations available were for TIS. Economic evaluations of TIS have been conducted in the UK from the perspective of the National Health Service (NHS) [168] and in Canada from the perspective of the Canadian Health Service in Ontario and Quebec [169]. In Canada, the acquisition cost of TIS was estimated to be CA$8602 over a 24-week period. Mean offsets in direct medical costs for all patients treated with TIS versus placebo were CA$4916 in Quebec and CA$4055 in Ontario.

In the UK, in all patients the cost of TIS was partially offset by savings of £3719 per year compared with placebo in 2001 [168]. This was primarily because of a reduction in the mean number of days spent in the hospital (7.8 days), resulting in savings of £2345 and a reduction in the mean number of days' treatment with intravenous antibiotics (6.4 days), resulting in savings of £1344. The net direct cost was £6292 per year, based on a TIS acquisition cost to the NHS of £10,010 in 2001. In

patients aged ≤18 years, the direct cost offset was £6180, resulting in a net cost versus placebo of £3830.

Recently, a cost-effectiveness analysis of the AZLI–TIS active comparator study was performed using a Markov model with health states defined principally by FEV_1 % predicted levels [170]. Over 3 years, AZLI use was associated with increased life-years, reduced number of hospitalizations, increased QALYs, and a subsequent cost savings of over $6000 over TIS.

10.3. Antibiotic eradication therapy

A CEA was done to compare costs for AET and for treatment of chronic *P. aeruginosa* lung infection in CF [17,171]. The 47 AET-treated patients received a total of 104 antibiotic therapy courses over 7 years, costing in total €34,681 (€105.4/patient/year). The 47 age-matched, chronically *P. aeruginosa*-infected CF patients received 683 courses in 7 years costing in total €1,767,025 (€5371/patient/year). Thus, treating CF patients with AET is recommended, because costs for AET are significantly lower compared with those needed to treat chronically infected CF patients. Various AET study designs revealed similar success rates and cost-effectiveness analyses for this strategy are recommended to harmonize current regimens and to implement a standard operating procedure for AET in different CF centers. Questions concerning the window of opportunity to eradicate the pathogen in a given CF patient, the choice and doses of the antibiotic(s), the length of the treatment course, and the prophylactic use of antibiotics for AET, could be answered in such analyses.

Although few economic analyses were performed to compare different treatment strategies (AET, inhaled antibiotics), future discussions are needed. The limited number of comparative studies and the non-inferiority designs allow for cost-minimization analysis and it is difficult to conduct proper CEAs or CUAs for inhaled antibiotic treatments in CF patients. Even more challenging is the model framework and the model inputs. Generally the model uses data from clinical trials. However, almost all trials are of short duration (not longer than 3 cycles of treatment) and do not use hard outcomes such as survival. It is difficult to design models with lifetime horizon based on short-term trials. In the case of CF, economic model work needs to be done to link FEV_1% predicted outcomes to survival. This link could be helpful to design a model over a lifetime horizon and provide a better understanding of the economic value of treating a *P. aeruginosa* infected CF patient with a given inhaled antibiotic versus alternative drugs.

Discussion among experts involving clinicians and health economists with regard to the design of economic evaluations will help to find optimal solutions. Furthermore, comparative effectiveness research should be developed also to compare the real-life benefits of different CF therapies. In particular, research should address multiple stakeholders' demands, should demonstrate real-world value of the CF drug and should apply transparent and harmonized protocols.

11. Members of the Consensus Study Group

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