Challenges in managing *Pseudomonas aeruginosa* in non-cystic fibrosis bronchiectasis

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A B S T R A C T

**Background:** An Expert Forum was held at the 2014 European Respiratory Society International Congress to address issues involved in the management of *Pseudomonas aeruginosa* infection in patients with non-cystic fibrosis bronchiectasis (NCFB). Multiple studies have found that chronic *P. aeruginosa* infection is associated with more severe disease and higher morbidity and mortality.

**Overview:** Participants discussed appropriate management of *P. aeruginosa* infection at three stages: 1) first isolation, including eradication protocols; 2) during exacerbations; and 3) during chronic infection, including long-term antibiotic therapy to reduce the severity of symptoms and frequency of exacerbations. Topics covered included frequency of sputum cultures, antibiotic treatment at first isolation and for exacerbations, optimal use of inhaled antibiotics, indications for long-term therapy, and treatment regimens that may reduce the frequency or severity of symptoms. Electronic polling and roundtable discussions followed by expert insights were used to address these topics. Significant diversity in management practices was reported among different countries and centres, and in many cases clinical management was at variance with published guidelines.

**Conclusions:** This Expert Forum identified standardised terminology, clinician training, additional research into management strategies, and the development of new drugs as areas requiring improvement for the optimal management of *P. aeruginosa* in NCFB.

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1. Introduction

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic respiratory disease characterised by chronic cough, sputum production, recurrent infection, and sometimes fatigue and haemoptysis. Patients with NCFB may have functional limitations due to reduced lung function, bronchial inflammation, and airway obstruction [1,2]. As the disease progresses, NCFB patients frequently experience significant morbidity, reduced quality of life, and high treatment burdens [2–4]. NCFB is associated with high mortality rates. In a recent study in Belgium, overall mortality was 20% during a 5-year period [5], and the mortality rate in England and Wales is reported to be increasing by 3% per year [6]. The prevalence of NCFB is higher in women and in older individuals and appears to be increasing over the last decade in Europe and the United States [4,7–9]. Estimates based on data from the CPRD-GOLD database in the UK indicate that more than 1% of individuals 70 years of age and older have NCFB [7]. NCFB has diverse aetiology and this variability may affect management [3,10].

Although the pathophysiology of NCFB is not well defined, the vicious cycle model originally proposed by Cole [11], in which bacterial infection drives airway inflammation and disease progression, has been supported by numerous studies (reviewed by Mandal and Hill [12], including a study by Chalmers et al. demonstrating that high bacterial loads in the airways of patients with NCFB are associated with markers of local and systemic inflammation [13]. Although a number of bacteria are associated with NCFB, Pseudomonas aeruginosa is one of the most common and significant pathogens in patients with this disease [14–16]. The presence of P. aeruginosa is associated with greater impairment in lung function [17–22], increased airway inflammation [13], more frequent exacerbations [16], worse quality of life [22], greater risk of hospitalisation [22,23], and increased mortality [5,23,24]. The impact of Pseudomonas on the natural course of the disease has been confirmed by its identification as a key determinant of bronchiectasis severity in two recently developed severity scoring systems, the Bronchiectasis Severity Index and the FACED score [23,25]. Accordingly, appropriate management of P. aeruginosa is an important concern throughout the course of NCFB.

In clinical practice, there are three distinct points that present opportunities for managing P. aeruginosa infection in patients with NCFB: (1) at first isolation; (2) during exacerbations; and (3) during chronic P. aeruginosa infection (Fig. 1).

There are limited data available to inform clinicians on optimal management at each point, and both national audit and anecdotal reports suggest that there is significant variation among practices [26].

To better understand current clinical practices for the management of P. aeruginosa in patients with NCFB, an Evening Expert Forum was held during the 2014 European Respiratory Society International Congress in Munich, Germany. This interactive seminar included an international group of practicing clinicians with a common interest in NCFB. Most (64%) of the 55 participants were from Europe, but other areas of the world, including Africa (5%), Asia (7%), Australia (7%), the Middle East (7%), South America (7%), and the United States (5%), were also represented. Of the 47 participants who responded to additional questions, 64% saw patients as part of a general respiratory clinic, 32% saw patients at a dedicated bronchiectasis clinic, and 4% saw patients as part of a cystic fibrosis (CF) clinic. These participants reported a wide variation in the estimated number of NCFB patients seen per year, ranging from <10 for 9% of participants to >50 for 32% of participants.

Following a case presentation of a common scenario seen in an NCFB patient with recurring P. aeruginosa infection, a number of questions were posed and electronic “live” polling was used to capture responses. The clinicians divided into three groups, each focusing on one of the three points described above, for roundtable discussions. Moderators presented the conclusions from each group, followed by expert feedback.

The ensuing discussion provided an overview of the diversity in clinical opinion among different centres and countries and offered an opportunity for expert feedback on current clinical practices (Table 1).

In addition, the Expert Forum identified an unmet need in the medical community for more comprehensive clinical guidelines on this topic, such as those that are being developed by the European Respiratory Society Bronchiectasis Guidelines Task Force [29]. Finally, areas requiring future research were discussed, with an emphasis on the need for standardised definitions — which remain an area of debate [30] — and practices in NCFB clinical research and an international registry to allow advancement of the knowledge base and accurate translation to clinical practice.

2. Management of P. aeruginosa infection at first isolation

Much of the clinical practice involved in managing P. aeruginosa
in patients with NCFB is derived from studies conducted in CF, as there are limited data to guide NCFB practitioners [231]. In CF, it is clearly established that early infection with *P. aeruginosa* is associated with worse outcomes (reviewed by Stuart et al.) [32], and eradication is associated with clinical benefits, including improved pulmonary function and reduced hospitalisation [33–36]. Accordingly, sputum cultures for CF patients are screened for *P. aeruginosa* on a regular basis; European guidelines recommend that airway cultures be obtained at every visit [37]. For NCFB, the benefits and feasibility of early *P. aeruginosa* eradication attempts are still debated, as this patient population may have been colonised with this pathogen for extended periods of time before initial detection, and the frequent presence of comorbid conditions may complicate management decisions. In addition, although spontaneous clearing of *Pseudomonas* infection in CF is considered an unusual event, intermittent isolation of *P. aeruginosa* with spontaneous clearing of the infection (as judged by sputum culture) is not considered uncommon in NCFB. In a recent study of *Pseudomonas* persistence in patients with NCFB, 16 of 47 patients (34.0%) who were colonised with *P. aeruginosa* (defined as isolation on 2 or more occasions, at least 3 months apart, within a 1-year period) subsequently became culture negative during follow-up without any specific eradication treatment [20].

2.1. Sputum cultures

Significant diversity in clinical practice patterns for monitoring sputum cultures in patients with NCFB was revealed during this meeting (Fig. 2). In electronic polling responses to the question “How often do you send sputum for culture?” 42% of clinical practitioners reported that they send a sample to the lab at every outpatient visit, in keeping with the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) recommendations that sputum cultures be obtained at each check-up [27]. The second most common answer (32%) was “only during an exacerbation.” The experts noted that obtaining sputum cultures only during an exacerbation may impair the effective use of past microbiology to guide empiric treatment. Eight percent of participants chose once yearly, but the experts emphasised that the need for a high-quality sputum sample, obtained during physiotherapy if possible. The potential need for more sensitive methods for *P. aeruginosa* identification, such as molecular tests, was also discussed. Participants felt that if first isolation did prove to offer the best chance of eradication, as is the case for CF, then more sensitive methods of *P. aeruginosa* identification would be important in facilitating early detection. Discussion focused on a recent study which found that standard culture methods only detect about one-third of samples identified as positive for *P. aeruginosa* by molecular methods [16]. The expert panel noted, however, that the presumed benefits of more sensitive detection methods are based on the assumption that molecular methods and culture results represent different positions on the same clinical continuum, and this hypothesis is yet to be proven.

The key information derived from the sputum sample was qualitative in nature, namely pathogen identification. The round-table participants did not consider quantitative information (e.g., colony counts) to be relevant to treatment choices. Antibiotic susceptibility tests were generally performed for the first isolation of *P. aeruginosa*, but not necessarily for routine chronic infections.

2.2. Concept of *P. aeruginosa* eradication

Although European CF guidelines support eradication protocols for first isolation of *P. aeruginosa* [37,38], the evidence base for NCFB is less clear. As a result, there were differing opinions at this Expert Forum concerning whether *P. aeruginosa* eradication attempts at first isolation are achievable or useful. One expert noted that the concept of “first isolation” was a difficult one in this older population, and heavily dependent on the frequency of testing and accuracy of the lab results. This observation highlights the importance of the significant variance in the frequency of obtaining cultures revealed in earlier discussion. Although data in NCFB are limited, a recent study suggests that eradication of *P. aeruginosa* in NCFB patients may be associated with improvements in health in some patients. This single-centre retrospective study involved 30 NCFB patients and found that eradication protocols were initially successful in 80%. However, approximately half of these patients had subsequent positive *P. aeruginosa* cultures at a median of 6.2 months after eradication. Patients treated with eradication protocols had a reduced frequency of exacerbations in the year following eradication, but there...
Table 1: Management of *P. aeruginosa* in patients with non-cystic fibrosis bronchiectasis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Question</th>
<th>Guidelines [1,27]</th>
<th>Current clinical practice*</th>
<th>Expert panel comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First isolation</td>
<td>How often do you send sputum samples to culture?</td>
<td>BTS: Respiratory tract specimens should be obtained in all patients; frequency not specified; SEPAR: Cultures should be performed at every check-up</td>
<td>At every visit (42%); During an exacerbation (32%); When the sample is purulent (18%); Once a year (8%)</td>
<td>Awaiting culture results during exacerbations may delay commencement of empiric antibiotic directed by prior surveillance microbiology; Once yearly cultures should be reserved for patients with very stable disease</td>
</tr>
<tr>
<td></td>
<td>Should <em>P. aeruginosa</em> eradication be attempted?</td>
<td>BTS: There are no studies to guide practice, but “an attempt to eradicate seems pragmatic”; SEPAR: An eradication attempt is desirable to delay chronic colonisation</td>
<td>Most clinicians attempt eradication at first isolation, but the approach to therapy varies; Some clinicians did not consider eradication to be a viable option and so were more focused on reducing symptoms than on eradicating <em>P. aeruginosa</em></td>
<td>“First isolation” may be misleading, as initial sputum culture may not represent the first appearance of <em>P. aeruginosa</em> in a patient; A clinical trial is required to determine whether eradication is achievable and associated with clinical improvements</td>
</tr>
<tr>
<td>What treatment do you use for <em>P. aeruginosa</em> eradication?</td>
<td>BTS: Oral ciprofloxacin for 2 weeks; if further treatment required, 2 weeks of IV anti-pseudomonal antibiotics, nebulised colistin for 3 months, or nebulised colistin for 3 months with an additional 4 weeks of oral ciprofloxacin; SEPAR: 3 weeks of oral ciprofloxacin plus an inhaled antibiotic, which is continued for up to 12 months</td>
<td>Oral ciprofloxacin (most common choice); IV antibiotics; Oral or IV antibiotic + inhaled antibiotic; Other combination therapy</td>
<td>Expert experience with guideline-recommended regimens varied with no evidence for clear superiority of a specific regimen in clinical practice; Clinical trials are needed to address the best regimens for <em>P. aeruginosa</em> eradication in NCFB [28]</td>
<td></td>
</tr>
<tr>
<td>During an exacerbation</td>
<td>How do you define an exacerbation?</td>
<td>BTS*: Acute deterioration with increased sputum volume or change in viscosity, increased sputum purulence, and worsening local symptoms (increased cough, wheeze, breathlessness) or systemic upset; SEPAR: Acute development and persistence of changes in sputum characteristics and/or increased breathlessness unrelated to other causes</td>
<td>No overall consensus; Symptoms were the most frequent criteria for defining an exacerbation; some required 2 or more; Other definitions were based on pulmonary function tests or culture results</td>
<td>Expert practice is generally consistent with guidelines; Pulmonary function tests and culture results may not accurately reflect exacerbations, as some patients have only minimal change in FEV1 during an NCFB exacerbation and well patients may have chronic bacterial colonisation</td>
</tr>
<tr>
<td></td>
<td>How often do you perform sputum cultures/susceptibility tests during an exacerbation?</td>
<td>BTS and SEPAR: Sputum cultures with susceptibility tests should be performed for each exacerbation prior to administration of antibiotics</td>
<td>Consistent with guidelines; Cultures usually repeated 4–8 weeks after treatment</td>
<td>Expert practice is consistent with guidelines</td>
</tr>
<tr>
<td></td>
<td>What antibiotics do you use to treat a patient with <em>P. aeruginosa</em> and exacerbations?</td>
<td>BTS: Oral ciprofloxacin (14-day course of 500 mg or 750 mg twice daily depending on severity of infection) for ciprofloxacin-susceptible <em>P. aeruginosa</em>; ciprofloxacin-resistant isolates should be treated with combination therapy with anti-pseudomonal antibiotics; SEPAR: Oral ciprofloxacin (14- to 21-day course of 750 mg twice daily) for mild exacerbations; combination therapy with anti-pseudomonal antibiotics should be used for moderate to severe exacerbations or patients who do not respond to oral therapy</td>
<td>For ciprofloxacin-resistant strains: generally oral ciprofloxacin; For ciprofloxacin-resistant strains: no consensus. Options included azithromycin, ciprofloxacin, nebulised colistin, and outpatient IV antibiotics; Patients with severe exacerbations are generally hospitalised and treated with 2 anti-pseudomonal drugs (beta-lactam or 3rd-generation cephalosporin + aminoglycoside); therapy is modified on the basis of clinical response on day 3</td>
<td>Ciprofloxacin-resistant isolates pose a dilemma: it can be difficult to ascertain if culture-determined resistance is clinically relevant, or if <em>P. aeruginosa</em> is the only pathogen involved. Accordingly, oral ciprofloxacin is a viable option for initial therapy, followed by IV antibiotics if the patient does not respond clinically; It is speculated that even antibiotics without direct activity against <em>P. aeruginosa</em> may result in clinical improvement by affecting the “microbiome” or reducing inflammation</td>
</tr>
<tr>
<td>Stage</td>
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</table>
| Chronic infection, including long-term antibiotic therapy | How do you use inhaled antibiotics during exacerbations in patients with *P. aeruginosa* infections? | • BTS: Inhaled antibiotics are a possible component of second-line combination therapy  
• SEPAR: Inhaled antibiotics are not listed as an option for treatment of exacerbations | • In the experience of the expert panel, patients tend to tolerate inhaled antibiotics better than the literature suggests; nevertheless, inhaled antibiotics are probably best used as continuation therapy following oral or IV antibiotics rather than as acute therapy | |
| | | | | |
| | How do you evaluate treatment success? | • BTS and SEPAR: Not addressed | • Reliable, validated markers of treatment outcome are required to evaluate treatment success and develop new therapies | |
| | What is the definition of chronic infection? | • BTS: No definition specified  
• SEPAR: 3 or more positive cultures of the same microorganism within 6 months in samples collected at least 1 month apart | • Definitions varied; most common were:  
○ 50% of sputum samples positive for *P. aeruginosa*  
○ 2 to 3 consecutive positive sputum cultures following an attempt at eradication | • Clinical trials vary with respect to definition of chronic infection; this term should be standardised |
| | Which patients are candidates for long-term antibiotic therapy? | • BTS: Should be considered in patients having ≥3 exacerbations/year requiring antibiotic treatment or patients with fewer exacerbations that are causing significant morbidity  
• SEPAR: Should be considered in patients with recurrent exacerbations, early relapse, hospitalisation, declining lung function, or chronic *Pseudomonas* infection | • Varying criteria, including:  
○ Patients on optimal therapy with a high burden of symptoms  
○ Patients who had been hospitalised, were older, or reported feeling more unwell  
○ Generally >3 exacerbations/year (30% of participants would consider long-term therapy after 2 exacerbations/year) | • Expert practice is generally consistent with guidelines  
• Some considered >2 exacerbations per year as an indication for long-term antibiotics |
| | What are the best options for long-term antibiotic therapy in patients with chronic *P. aeruginosa* infection? | • BTS and SEPAR: An inhaled antibiotic should be first-line therapy for patients with chronic *Pseudomonas* infections in patients who meet criteria for long-term therapy  
• BTS: Long-term oral ciprofloxacin is not recommended due to concerns with resistance and potential side effects  
• SEPAR: Ciprofloxacin-resistant *P. aeruginosa* treatment should be considered in continuous therapy rather than alternating drugs or month on/month off regimens  
• SEPAR: Inhaled antibiotics are not an option for treatment of exacerbations | • Macrolide (76%)  
• Inhaled aminoglycoside (24%)  
• Others:  
○ Nebulised colistin  
○ Oral ciprofloxacin  
○ Combination therapy for ciprofloxacin-resistant *P. aeruginosa*  
• Treatment was usually administered as continuous therapy rather than alternating drugs or month on/month off regimens | • Anti-pseudomonal inhaled antibiotic preferred, consistent with guidelines  
• The expert panel acknowledged that macrolides worked well as chronic therapy, but expressed concerns about resistance development (especially in NTM) and side effects  
• There is currently no evidence to support alternating or month on/month off regimens in NCFB |
| | Which outcome measures do you use to evaluate the success of long-term antibiotic therapy? | • BTS and SEPAR: Not addressed | • Symptomatic improvement, including reduction in the number of exacerbations  
• Improvement in lung function  
• Culture-based results do not factor into the assessment of outcome | • Reliable, validated markers of treatment outcome are required to evaluate treatment success and develop new therapies |
| | What is the optimal duration of long-term antibiotic therapy? | • BTS: Not addressed  
• SEPAR: Depends on how well the infection is controlled | • 3 months for eradication protocol or following IV antibiotics  
• 1 year or longer for patients with more severe disease  
• Some clinicians take patients off therapy during the spring or summer, or cycle therapy during the year | • Not yet addressed in clinical trials  
• No hard and fast rules; decisions are often driven by patient symptoms and preferences |

BTS, British Thoracic Society; FEV1, forced expiratory volume in 1 s; IV, intravenous; NCFB, non-cystic fibrosis bronchiectasis; NTM, non-tuberculous mycobacteria; SEPAR, Spanish Society of Pulmonology and Thoracic Surgery.

* Percentages are based on polling results; qualitative summaries are based on presentations of roundtable summaries.

b The BTS definition is specifically for an exacerbation requiring antibiotics.
was no difference in hospitalisation [39]. Although these data suggest some benefit from eradication protocols, randomised clinical trials with larger patient populations will be required to determine the outcomes associated with *P. aeruginosa* eradication following first isolation in NCFB patients. Although the participants generally believed that such trials would be justifiable and valuable, they agreed there would be significant practical difficulties in conducting these studies.

### 2.3. Treatment options including eradication protocols

Treatment of *P. aeruginosa* following first isolation varied significantly among clinicians at this Expert Forum. This diversity reflected differing local guidelines and opinions on the feasibility of eradication as well as the lack of a clearly preferred eradication protocol for CF. In a recent Cochrane review of CF therapies used for *P. aeruginosa* eradication, various treatment regimens with inhaled antibiotics (colistin or tobramycin), with or without oral ciprofloxacin, appeared to have comparable efficacy, although some of the studies were underpowered to show a difference between therapies [40].

Many of the roundtable participants use oral ciprofloxacin for *P. aeruginosa* eradication therapy in NCFB patients. However, more aggressive strategies, such as combination therapy with oral or intravenous (IV) antibiotics, sometimes with the addition of inhaled antibiotics, were also employed by the participants. The SEPAR guidelines recommend eradication of *P. aeruginosa* with 3 weeks of oral ciprofloxacin plus an inhaled antibiotic that is continued for 3–12 months [27]. The British Thoracic Society (BTS) NCFB guidelines note that although there is no evidence to support the benefits of eradication, an eradication attempt is a reasonable intervention; 2 weeks of oral ciprofloxacin is the recommended treatment. If this therapy fails to eradicate *Pseudomonas*, further treatment can be considered, such as 2 weeks of IV anti-pseudomonal antibiotics, nebulised colistin for 3 months, or nebulised colistin for 3 months with an additional 4 weeks of oral ciprofloxacin [1].

Participants reported that they judge the success of treatment by both sputum cultures and clinical improvement. Sputum cultures are typically performed by participants before and approximately 4–6 weeks after treatment. Most participants require 2 or 3 negative sputum samples over the next year before they consider *P. aeruginosa* to be eradicated. The expert panel agreed with this definition but noted that reliable, validated definitions of eradication and treatment outcome are required to evaluate treatment success and allow the development of new therapies for NCFB [41].

### 3. Management of *P. aeruginosa* during an exacerbation

Exacerbations are a significant complication in patients with NCFB and are associated with reductions in lung function and quality of life [19,42]. NCFB patients with *P. aeruginosa* infections have more frequent exacerbations and more severe disease [16,20,23,25]. Accordingly, optimal management of exacerbations is a critical topic for clinical practitioners with NCFB patients. As with *P. aeruginosa* eradication protocols, exacerbation treatment choices for NCFB often rely on research conducted in CF patients. However, CF practices have a rather disappointing record of success in NCFB, and in some cases unexpected adverse events have occurred [43]. For instance, inhaled tobramycin, an established CF therapy, was found to result in unexpected pulmonary adverse events in NCFB patients, including increased cough and wheezing [44]. Although it is becoming increasingly clear that management practices for other diseases cannot always be directly transferred to NCFB, there are few clinical studies available in patients with NCFB to fill the current knowledge gap.

#### 3.1. Defining an exacerbation

There was no consensus on how to define an exacerbation in the groups assigned to this topic. Most roundtable participants rely primarily on symptoms, such as increasing sputum volume, increasing sputum purulence, breathlessness, fatigue, and fever, and some specified that they require two or more significant symptoms to classify the event as an exacerbation. Other participants look at changes in pulmonary function tests or base their assessment on culture results or radiographs. However, the expert panel emphasised that pulmonary function tests and culture results may not accurately reflect exacerbations, as in many patients there is either no change or only minimal change in FEV1 during an NCFB exacerbation, and well patients may still have chronic bacterial colonisation.

The BTS guidelines define an exacerbation requiring antibiotics as acute deterioration (usually over several days) with all 3 of the following features: 1) increased sputum volume or change in viscosity; 2) increased sputum purulence, breathlessness, fatigue, and fever; and/or increased local symptoms (increased cough, wheeze, breathlessness) or systemic upset [1]. The SEPAR guidelines define an exacerbation as the acute development and persistence of changes in sputum characteristics and/or increased breathlessness unrelated to other causes [27]. Clinical trials use a variety of different definitions for exacerbation, including a requirement for systemic antibiotics. The expert panel noted that standardisation of this term would allow different treatments and management practices to be compared more accurately across different studies.

#### 3.2. Sputum cultures

The roundtable participants concurred that optimal management of exacerbations includes a sputum sample with antibiogram data for each exacerbation prior to administration of antibiotics, in agreement with BTS and SEPAR guidelines [1,27]. Until this information is available, empirical antibiotic therapy is usually guided by past culture data. Post-exacerbation cultures are usually repeated approximately 4–8 weeks after treatment.
3.3. Treatment options

Roundtable participants usually treat patients with mild exacerbations and a *P. aeruginosa* infection known or presumed to be ciprofloxacin-susceptible as outpatients, typically with oral ciprofloxacin as recommended by the BTS and SEPAR guidelines [1,27]. BTS guidelines recommend a 14-day course of oral ciprofloxacin at a dose of 500 or 750 mg twice daily depending on the severity of infection [1], and SEPAR guidelines recommend oral ciprofloxacin at 750 mg twice daily for 14–21 days [27]. It should be noted, however, that these recommendations are based on limited evidence due to the paucity of data from randomised placebo-controlled trials of antibiotics in NCFB [1].

Patients with more severe exacerbations, such as those with hypoxaemia or respiratory distress, are often hospitalised, although some centres operate a home delivery IV antibiotic programme. Treatment for severe exacerbations varied among participants and included monotherapy or dual anti-pseudomonal therapy. Most participants modified regimens on the basis of clinical response on the third day of treatment; they agreed that not all patients will show signs of improvement by this time point, but patients who have worsened should be changed to an alternative therapy within 48 hours. If the clinical response is satisfactory, treatment is continued for at least 10 days. If the clinical response is suboptimal, the clinicians change antibiotics, usually by opting for a broader spectrum antibiotic or converting to combination therapy. The assessment of clinical response is typically based on improvement in symptoms and blood inflammatory markers. The roundtable participants felt that better markers of treatment response would be helpful.

Participants usually scheduled post-exacerbation follow-up visits approximately one month after the event. During this appointment, they obtain sputum samples and review self-management of the disease and adherence to treatment. Participants emphasised the need for effective and clear communication with the patient and the patient’s primary care physician concerning exacerbation and post-exacerbation management.

Although treatment of ciprofloxacin-sensitive isolates was similar among different centres, there was no consensus on the preferred option for treatment of ciprofloxacin-resistant *P. aeruginosa*. Interactive electronic polling was used to explore the choice of treatment for a patient with a ciprofloxacin-resistant isolate and a non-severe chest infection (Fig. 3).

Dosing and duration of treatment choices were as follows: ciprofloxacin 750 mg bd for 14 days; co-amoxiclavulanate (standard dose for your country) for 14 days; azithromycin 500 mg od 6 days, then 250 mg od 6 days; colistin nebulised 1 mL bd one month; outpatient IV antibiotic e.g. ceftazidime 2 g td 10 days; something else.

The most frequent choice of therapy was azithromycin (23%) followed by “something else” (21%), but ciprofloxacin, nebulised colistin, and outpatient IV antibiotics were other popular options, each receiving 15% of the vote. The BTS guidelines recommend combination antibiotics for patients with *P. aeruginosa* resistant to one or more anti-pseudomonal antibiotics [1], and the SEPAR guidelines recommend combination therapy with IV anti-pseudomonal antibiotics for patients with severe exacerbations and those who do not respond to oral therapy [27].

The expert panel noted that ciprofloxacin-resistant *P. aeruginosa* often represents a conflict between therapeutic choices based on susceptibility results and those based on pragmatic considerations. Although ciprofloxacin-resistant *P. aeruginosa* may be treated more effectively with IV antibiotics, it is likely that many patients would respond to less aggressive treatment options, as *in vitro* susceptibility findings do not always translate into clinical response in patients with more severe exacerbations, such as those with hypoxaemia or respiratory distress, are often hospitalised, although some centres operate a home delivery IV antibiotic programme. Treatment for severe exacerbations varied among participants and included monotherapy or dual anti-pseudomonal therapy. Most participants modified regimens on the basis of clinical response on the third day of treatment; they agreed that not all patients will show signs of improvement by this time point, but patients who have worsened should be changed to an alternative therapy within 48 hours. If the clinical response is satisfactory, treatment is continued for at least 10 days. If the clinical response is suboptimal, the clinicians change antibiotics, usually by opting for a broader spectrum antibiotic or converting to combination therapy. The assessment of clinical response is typically based on improvement in symptoms and blood inflammatory markers. The roundtable participants felt that better markers of treatment response would be helpful.

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The most frequent choice of therapy was azithromycin (23%) followed by “something else” (21%), but ciprofloxacin, nebulised colistin, and outpatient IV antibiotics were other popular options, each receiving 15% of the vote. The BTS guidelines recommend combination antibiotics for patients with *P. aeruginosa* resistant to one or more anti-pseudomonal antibiotics [1], and the SEPAR guidelines recommend combination therapy with IV anti-pseudomonal antibiotics for patients with severe exacerbations and those who do not respond to oral therapy [27].

The expert panel noted that ciprofloxacin-resistant *P. aeruginosa* often represents a conflict between therapeutic choices based on susceptibility results and those based on pragmatic considerations. Although ciprofloxacin-resistant *P. aeruginosa* may be treated more effectively with IV antibiotics, it is likely that many patients would respond to less aggressive treatment options, as *in vitro* susceptibility findings do not always translate into clinical response in...
P. aeruginosa [1]. The SEPAR guidelines do not list inhaled antibiotics as an option for treatment of exacerbations, although they are recommended for initial and chronic infections with Pseudomonas [27].

There was no clear consensus on the continued use or cessation of nebulised agents during an exacerbation with significant bronchospasm, and the participants expressed some concern about the ability of sicker patients to tolerate inhaled antibiotics. The meta-analysis of inhaled antibiotics in NCFB reported an overall bronchospasm rate of 10% in seven trials involving 526 patients; the use of inhaled aminoglycosides was associated with a 4.78-fold increase in the risk of bronchospasm, but ciprofloxacin and colistin were not significantly associated with this adverse event [48]. However, the expert panel concurred that some patients tended to tolerate inhaled tobramycin quite well, despite the high rates of bronchospasm reported in the literature.

3.5. Inhaled antibiotics in the prevention of exacerbations

Two formulations of inhaled ciprofloxacin are currently in development to reduce exacerbations: Ciprofloxacin dry powder for inhalation (DPI) and a liquid combination formulation consisting of a solution of liposomal ciprofloxacin mixed with a solution of un-formulated (free) ciprofloxacin. Ciprofloxacin DPI is delivered twice-daily in one to two breaths via a small, hand-held, breath-actuated inhaler while free/liposomal ciprofloxacin is delivered via nebulisation. Results of Phase III trials will help identify those patients who may benefit from inhaled forms of the drug in this scenario [49–52].

4. Management of chronic infection with P. aeruginosa

As discussed previously, chronic colonisation with P. aeruginosa is associated with more severe disease and worse patient outcomes [5,20,22,23,25]. Although to date no rigorous clinical data support the benefits of treating chronic P. aeruginosa infections, there are strong theoretical reasons for doing so as well as anecdotal evidence from clinical practice [1]. As might be expected from the lack of data on this topic, there was a wide range of management strategies for chronic P. aeruginosa infections among the clinicians at the Expert Forum. Potential therapeutic options for patients with chronic P. aeruginosa infections are in development (see clinicaltrials.gov for more information).

4.1. Defining chronic infection

The roundtable participants at this Expert Forum generally defined chronic infection as at least 50% of sputum cultures positive for P. aeruginosa over a one year period, or, alternatively, as two to three consecutive positive sputum cultures following an attempt at eradication. The SEPAR guidelines define chronic infection as three or more positive cultures for the same microorganism within 6 months in samples collected at least 1 month apart [27], while the BTS guidelines state that varying definitions exist [1]. The expert panel noted that there are various definitions for chronic P. aeruginosa infection in CF, including the Copenhagen definition and the Leeds criteria (reviewed by Pressler et al.) [53], but that these are based on more frequent sputum cultures (7–10 per year) and therefore may not be directly applicable to NCFB. Clinical trials in NCFB differ with respect to criteria for chronic infection, and a uniform definition should be established for this term to facilitate comparisons among research studies and standardise care. Although increasing levels of antibodies to Pseudomonas are risk factors and surrogate markers for chronic infection in patients with CF (reviewed by Pressler et al.) [53], the value of monitoring anti-pseudomonal antibodies has not been established for NCFB and was not commonly performed by the participants.

4.2. Indications for long-term antibiotic therapy

In recognition of the impact of exacerbations on patient wellbeing, the BTS guidelines identify reductions in exacerbations as the aim of chronic management [1]. The roundtable participants stated that they frequently instituted long-term antibiotic therapy in patients with NCFB to reduce the frequency and severity of symptoms, including exacerbations.

The decision to initiate long-term antibiotic therapy in patients with chronic P. aeruginosa typically depends on the burden of symptoms. The clinicians considered patients on optimal therapy (such as physiotherapy and therapy to promote expectoration) who continue to experience significant symptoms, including frequent exacerbations, a high volume of sputum, purulent sputum, poor lung function, and fatigue, to be good candidates for long-term therapy. Other key considerations include hospitalisations, age, inflammatory markers, and the patient’s overall feeling of ill health.

In interactive electronic polling, three exacerbations per year was the most common threshold required by participants before initiating long-term antibiotic therapy (46%), although two exacerbations was sufficient for 30% of the respondents (Fig. 4).

Together, these data indicate a general threshold of two or more exacerbations per year for the majority (76%) of respondents. The BTS guidelines recommend consideration of long-term antibiotics in patients having three or more exacerbations per year requiring antibiotic therapy or patients with fewer exacerbations that are causing significant morbidity [1], while the SEPAR guidelines recommend that prolonged antibiotics therapy should be considered in patients with recurrent exacerbations, early relapse, hospitalisation, declining lung function, or chronic Pseudomonas infection [27].

4.3. Long-term antibiotic therapy for patients with chronic P. aeruginosa infection

Electronic polling was also used to assess the participants’ choice of therapy in patients with chronic P. aeruginosa infection. When asked whether they generally preferred long-term therapy with a macrolide, which has been shown to reduce the overall number of exacerbations [54–56], or with an inhaled antibiotic...
that would target *Pseudomonas* in patients with chronic infections, macrolides were chosen by 76% of respondents vs 24% for an inhaled antibiotic. The preference for macrolides was attributed to the strong evidence base for the benefit of low-dose chronic therapy with these agents in NCFB [54–56] and the lack of high quality evidence for inhaled antibiotics. Participants also noted the simplicity and acceptability of chronic macrolide use [57]. The choice of macrolide varied among participants and countries due to availability, cost, and concerns about side effects, including cardiac toxicity and adverse effects on hearing. Some participants stated that they are reluctant to institute this therapy in patients with comorbid cardiac disease. Patients who fail or cannot tolerate macrolides are typically switched to nebulised colistin or gentamicin.

In contrast to the preference of participants for macrolides, the majority of the expert panel preferred an anti-pseudomonal inhaled antibiotic as long-term antibiotic therapy due to concerns that the widespread use of chronic macrolide therapy may promote resistance to these drugs in the airway microbiota, particularly in non-tuberculous mycobacteria (NTM) [58]. The experts agreed that it is imperative to screen patient's sputum for NTM before commencing macrolide therapy. Because there are few effective treatment options for NTM infection, widespread macrolide resistance in NTM could have dire consequences. The BTS and SEPAR guidelines both recommend an inhaled antibiotic as the first option for patients with chronic *Pseudomonas* infections who meet criteria for long-term antibiotic therapy [1,27].

A recent meta-analysis reported that NTM has an overall prevalence of 9.3% in patients with bronchiectasis [59], but some studies have reported rates as high as 37% [60]. NTM infections frequently go undetected. In a recent study, 14 of 126 (11%) individuals undergoing lung volume reduction surgery had histological evidence of mycobacterial infection despite an absence of clinical symptoms suggestive of NTM [61]. Before initiation of long-term macrolide therapy, NTM lung disease should be thoroughly screened for and excluded on the basis of clinical, radiographic, and microbiologic criteria [62].

Additional choices for long-term antibiotic therapy mentioned by the participants included oral ciprofloxacin or levofloxacin. This is counter to the BTS guidelines, which caution against the use of long-term oral ciprofloxacin due to the potential development of antibiotic resistance and adverse events [1].

Inhaled antibiotics might afford a means to overcome bacterial resistance if the optimal dosing regimen is used [63]. Pharmacokinetic data show that higher concentrations of inhaled vs systemic ciprofloxacin are found in sputum and that the terminal half-life, clearance and volume of distribution are also greater than previously reported values for an oral or IV therapeutic dose [64,65]. It is this increase in drug concentration at the site of infection that is key to the avoidance of resistance. The lower systemic exposure of inhaled vs oral formulations is also important when considering resistance. Oral ciprofloxacin is mainly absorbed through the gut and results in high systemic exposure [66]. This can negatively impact on gut flora and put selection pressure on non-Pseudomonal organisms [67]. The peak systemic concentration measured in healthy volunteers was 0.056 mg/L after Ciprofloxacin DPI 32.5 mg [64], and 0.169 mg/L after administration of one dose (210 mg ciprofloxacin) of the nebulised ciprofloxacin mixed formulation (60 mg as free and 150 mg liposomal ciprofloxacin) [68]. As inhaled antibiotics have low systemic exposure it can be expected to have a reduced impact on the gut microbiome and resistance rates. Data from recent and ongoing studies of inhaled ciprofloxacin for the reduction of exacerbations in NCFB will further aid understanding of the impact of inhaled ciprofloxacin on resistance patterns.

### 4.4. Outcome measures

Success of long-term antibiotic therapy was loosely defined as “the patient feeling better.” The round table participants agreed that symptomatic improvements, such as decreased exacerbations, reduced sputum volume, and improvements in lung function, are more important in determining the success and continuation of therapy than culture-based results. The expert panel noted that this is an area not addressed by guidelines and another term that lacks a standardised definition. Recently validated patient-reported assessments of symptoms, such as the Quality of Life Questionnaire-Bronchiectasis [69,70], may help allow more accurate evaluations of symptomatic improvements.

### 4.5. Duration of long-term antibiotic treatment

The roundtable participants typically continue long-term antibiotic treatment for approximately 3 months in patients undergoing an eradication attempt or following IV antibiotics, and for a year or more in patients with more severe disease. Some clinicians support the patient’s choice of a treatment holiday and take patients off therapy in the spring or summer months, while others give the patient 2 or 3 cycles of therapy over the course of the year. For inhaled agents, continuous therapy was more common than alternating agents or month on/month off regimens, in contrast to common practice in CF patients and NCFB clinical trials. Decisions concerning the duration of chronic treatment are made with the patient’s input and are often guided by the prevailing seasonality of respiratory viruses. BTS guidelines do not address the duration of long-term therapy, while SEPAR guidelines state that it depends on how well the infection is controlled [1,27].

### 5. Improving the management of *P. aeruginosa* in NCFB

On the basis of the roundtable discussions at this Expert Forum, the attendees concluded that there was a wide variety of approaches to the management of *P. aeruginosa* in NCFB and a need for greater international collaboration to ensure appropriate dissemination of information on this important topic. The roundtable discussions also highlighted the importance of standardised terminology, including uniform definitions for eradication, exacerbation, chronic infection, treatment response, and outcomes of long-term antibiotic therapy. Widely-accepted, common definitions are essential so that treatment practices and outcomes can be accurately and rigorously evaluated in clinical trials and compared among different centres.

The participants also identified several clinical research questions that need to be addressed, including:

- Do *P. aeruginosa* eradication protocols provide long-term benefits to NCFB patients?
- Is culture-directed antibiotic therapy more effective than empiric therapy during exacerbations?
- Is long-term suppressive antibiotic therapy associated with increased antibiotic resistance?
- What is the optimal regimen and duration for long-term antibiotic treatment regimens?

Although retrospective studies and analyses of bronchiectasis registries may be able to address some of these research questions, randomised clinical trials in NCFB will be required for definitive answers. The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC), which was created to promote research and education in the field of bronchiectasis, provides a network that will hopefully encourage and facilitate clinical trials in...
Europe (see https://www.bronchiectasis.eu/ for more information). In addition, results from studies of new therapeutic agents will hopefully broaden available treatment options and provide additional insights into the effects of therapy on the course of the disease.

6. Conclusions

This Expert Forum revealed significant diversity among different centres and countries with respect to the management of P. aeruginosa-infected NCFB patients. These differences are predominantly driven by the lack of a robust evidence base. Sharing treatment insights and expert guidance may help improve patient management. The care of NCFB would be improved by clinician training on this topic, standardisation of terminology, and clinical research designed to address key questions and provide additional information on the most beneficial therapeutic options.

Note on terminology

Dr. Elborn prefers the use of the designation of Bronchiectasis rather than non-CF bronchiectasis as discussed in Chalmers and Elborn, 2015 [30].

Authorship

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