Pseudomonas aeruginosa infection in patients with cystic fibrosis: scientific evidence regarding clinical impact, diagnosis, and treatment*

Infecção por *Pseudomonas aeruginosa* em pacientes com fibrose cística: evidências científicas sobre o impacto clínico, diagnóstico e tratamento*

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Abstract

Evidence-based techniques have been increasingly used in the creation of clinical guidelines and the development of recommendations for medical practice. The use of levels of evidence allows the reader to identify the quality of scientific information that supports the recommendations made by experts. The objective of this review was to address current concepts related to the clinical impact, diagnosis, and treatment of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. For the preparation of this review, the authors defined a group of questions that would be answered in accordance with the principles of PICO—an acronym based on questions regarding the Patients of interest, Intervention being studied, Comparison of the intervention, and Outcome of interest. For each question, a structured review of the literature was performed using the Medline database in order to identify the studies with the methodological design most appropriate to answering the question. The questions were designed so that each of the authors could write a response. A first draft was prepared and discussed by the group. Recommendations were then made on the basis of the level of scientific evidence, in accordance with the classification system devised by the Oxford Centre for Evidence-Based Medicine, as well as the level of agreement among the members of the group.

Keywords: Cystic fibrosis/diagnosis; Cystic fibrosis/drug therapy; Pseudomonas aeruginosa; Evidence-based medicine.

Resumo

As técnicas de medicina baseada em evidências são cada vez mais utilizadas para a construção de diretrizes clínicas e recomendações para a prática médica. O uso de níveis de evidências permite que o leitor identifique a qualidade da informação científica que sustenta as recomendações feitas pelos especialistas. Esta revisão teve por objetivo abordar conceitos atuais sobre o impacto clínico, diagnóstico e tratamento das infecções por *Pseudomonas aeruginosa* em pacientes com fibrose cística. Para a elaboração desta revisão, o grupo de autores definiu as perguntas que seriam respondidas, seguindo os preceitos de PICO, acrônimo baseado em perguntas referentes aos Pacientes de interesse, Intervenção a ser estudada, Comparação da intervenção e *Outcome* (desfecho) de interesse. Para cada pergunta, uma revisão estruturada da literatura foi realizada nas bases de dados do Medline, buscando identificar os estudos com desenho metodológico mais adequado para responder à questão. As perguntas foram designadas para que cada um dos autores redigisse uma resposta, e um primeiro rascunho foi elaborado e discutido pelo grupo em uma reunião presencial. Após essa discussão, recomendações foram emitidas com base na força das evidências e na concordância entre os membros do grupo segundo o sistema de classificação do *Oxford Centre for Evidence Based Medicine*.

Descritores: Fibrose cística/diagnóstico; Fibrose cística/quimioterapia; Pseudomonas aeruginosa; Medicina baseada em evidências.

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Introduction

Cystic fibrosis (CF) is a complex genetic disease with multisystem involvement and pulmonary manifestations of a suppurative nature.[1] Patients with CF are born with structurally normal lungs, but develop a progressive respiratory disease with recurrent chronic infections that result in the formation of bronchiectasis and lead to respiratory failure, which is the leading cause of death in these subjects.[2]

The basic defect in CF is related to chlorine transport through epithelial cell membranes by the cystic fibrosis transmembrane conductance regulator (CFTR) protein, the dysfunction of which was identified as being the principal mechanism of the disease in 1989.[3] There are more than 1,500 described mutations in the CFTR gene sequence, but most of them have very low prevalence, the ΔF508 mutation (deletion of phenylalanine residue at position 508) being the most prevalent worldwide.[4]

Patients with CF are peculiarly susceptible to infection and colonization of the respiratory tract with pathogens, such as *Staphylococcus aureus*, *Haemophilus influenza,* and glucose-nonfermenting gram-negative bacilli, including *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, and *Stenotrophomonas maltophilia*, among others.[5,6] The prevalence of these pathogens varies with age, with *S. aureus* infections usually occurring early (generally in the first months of life) and pathogens such as *P. aeruginosa* tending to appear a little later,[7] although this sequence of infections are greatly influenced by therapeutic and microbiological surveillance practices, as well as by hospitalizations, exposure to other patients with CF, and environmental conditions that have yet to be defined.

The etiologic diagnosis of respiratory infections in patients with CF is habitually established through culture of respiratory tract samples, such as sputum and oropharyngeal swabs, the latter method generally being used in infants and children who are unable to expectorate sputum.[8] In recent years, some attention has been given to alternative methods of diagnosis, such as serology and molecular techniques, especially for early identification of infection with *P. aeruginosa*, a pathogen that has the greatest impact on this group of patients.[9]

P. aeruginosa infections typically evolve to a pattern of persistence (chronicity), and strains undergo a phenotypic change, which is characterized by the production of a polysaccharide known as alginate.[6] This bacterial phenotype, known as the mucoid phenotype, is associated with the greater difficulty in (or near impossibility of) eradicating the pathogen, eliciting a major inflammatory response and resulting in accelerated functional loss and poorer prognosis.[6,10,11]

Since the early 1990s, various treatment centers for patients with CF have recommended eradication therapies for initial *P. aeruginosa* infection, which is when strains are more susceptible to antimicrobials, in order to prevent the chronicity of the infection.[12] In addition, strategies to suppress *P. aeruginosa* (or to reduce the bacterial load) with the use of inhaled antibiotics are one of the major therapeutic resources in the management of patients chronically infected with *P. aeruginosa*, causing improvement in pulmonary function, reducing the frequency of respiratory exacerbations, and improving the quality of life of these patients.[2]

Despite the growing knowledge in the field of respiratory infections in patients with CF, there are still many questions regarding the knowledge of the actual clinical impact, the most appropriate diagnostic methods, and the evidence on the treatment of *P. aeruginosa* infections. Evidence-based techniques have been increasingly used in the creation of clinical guidelines and the development of recommendations for medical practice. This type of approach allows the systematic use of available scientific information, with less emphasis on isolated experiences. The objective of the present review was to address current concepts related to the clinical impact, diagnosis, and treatment of *P. aeruginosa* infections in patients with CF.

Methods

For the preparation of this study, the following steps were performed:

1. Question preparation: the authors, in a preliminary meeting, defined a group of questions that would be answered in accordance with the principles of PICO—an acronym based on questions regarding the Patients of interest, Intervention being studied, Comparison of the intervention, and Outcome of interest. The questions were designed so that one of the authors could write a response.

2. Search of the literature: an initial search of the literature was conducted using

the Medline database and search terms related to each question. One of the authors, who is an expert in evidence-based medicine, made the initial selection of relevant studies, which were sent to each responsible author for preparing the responses. These authors then conducted their own search and added other references that were judged relevant.

3. First draft of responses: each author was responsible for writing responses that were subsequently discussed by the entire group at a face-to-face meeting.

4. Discussion meeting: the group had a face-to-face meeting to discuss and, if necessary, to make changes to the responses proposed by each author separately. In that meeting, new information was sought and added to the original text. In addition, there was an explicit discussion about the level of evidence (LE) of the information, in accordance with the criteria set out by the Oxford Centre for Evidence-Based Medicine in 2011,[13] which are shown in Chart 1.

5. Final draft: at the end of the meeting, each author sent the consensus response to the expert in evidence-based medicine, who was responsible for reviewing the LE, revising the text, and checking the references.

6. Revision: each author revised and approved the final draft of their responses and of the manuscript.

Questions addressed in the study

1. Does early *P. aeruginosa* colonization worsen the prognosis of patients with CF?

2. Can serologic testing for anti-*Pseudomonas* antibodies be useful for early detection of infection with this agent?

3. Does eradication of initial colonization with *P. aeruginosa* improve the prognosis in CF?

4. How does one identify and treat acute pulmonary exacerbations (APEs) in patients colonized with *P. aeruginosa*?

Chart 1 - Grades of recommendation and levels of evidence of scientific articles.[a]

Grade of recommendation		
A: More consistent experimental or observational studies		
B: Less consistent experimental or observational studies		
C: Case reports (uncontrolled studies)		
D: Opinion without critical appraisal, based on consensus, physiological studies, or animal models		
Strength of evidence		
Level of evidence	Studies on prognosis	Studies on treatment
1a	Systematic review of cohort studies (inception cohort), validated in different populations	Systematic review of two or more independent randomized studies rated as level 1b
1b	Individual cohort studies (inception cohort)	Randomized study of good methodological quality, including a sufficient number of patients
2a	Systematic review of either retrospective cohort studies or untreated control groups in randomized studies	Systematic review of level 2b cohort studies
2b	Retrospective cohort studies or follow-up of untreated control groups in randomized studies	Individual cohort studies (including poor quality randomized studies)
3a		Systematic review of level 3b case-control studies
3b		Case-control studies
4	Case series	Case series
5	Expert opinions	Expert opinions without explicit critical appraisal, or based on pathophysiology

[a]In accordance with the Oxford Centre for Evidence-Based Medicine.[13]

5. When should chronic inhaled antibiotic therapy be initiated in CF? Which inhaled antibiotics can be used in the treatment of chronic *P. aeruginosa* infection in CF?

6. Does adherence to clinical treatment affect the prognosis of patients with CF?

7. Is azithromycin efficacious in slowing the progression of lung disease in CF patients colonized with *P. aeruginosa*?

8. Is there a good correlation between antibiogram results and clinical response in chronic *P. aeruginosa* infection?

9. Does multidrug-resistant *P. aeruginosa* infection worsen prognosis?

Does early P. aeruginosa colonization worsen the prognosis of patients with CF?

Definitions

Colonization means the presence of bacteria as detected by colony culture, i.e., by isolation of the bacterium in culture. Colonization can be initial (or acute)—in the first bacterial isolations—or chronic, in accordance with the referral center criteria: three or more positive cultures for *P. aeruginosa* within a 6-month period, with an interval of at least one month between them or more than 50% of positive cultures within 12 months.[14]

Various parameters are used to characterize the prognosis in CF. The most common are pulmonary function testing and median survival: pulmonary function is in turn the best predictor of survival **(LE 2b).**[15]

Initial colonization with *P. aeruginosa* in children under 2 years of age significantly increases morbidity, and its association with *S. aureus* from the beginning significantly increases the mortality rate in the first 10 years after diagnosis **(LE 2b).**[10,16] The radiographic score deteriorates significantly and the Tiffeneau index (FEV_1/FVC ratio) falls more rapidly after *P. aeruginosa* acquisition in patients diagnosed by newborn screening **(LE 2b).**[17] Data from the U.S. Cystic Fibrosis Foundation national registry showed that, between 1990 and 1998, the presence of *P. aeruginosa* was the greatest predictor of morbidity and mortality in patients aged 1-5 years (n = 3,325)—with the risk of death being 2.6 times higher in those with than in those without *P. aeruginosa* respiratory infection **(LE 2b).**[18]

In a cohort study conducted in the USA, nonmucoid *P. aeruginosa* acquisition occurred in patients with a median age of 1 year, being observed in 29% of the patients under 6 months of age; identification of *P. aeruginosa* strains with a mucoid phenotype occurred in patients aged 4-16 years (median of 13 years). Eradication of nonmucoid *P. aeruginosa*, preventing chronicity and conversion to a mucoid phenotype, would allow a better prognosis **(LE 2b).**[7]

Early *P. aeruginosa* colonization predisposes to chronic colonization with this pathogen. A low level of chronic colonization can be achieved with intermittent use of inhaled antibiotics and less use of intravenous antibiotics. **A lower level of chronic *P. aeruginosa* colonization improves prognosis (LE 2b).**[19]

Recommendation

Early *P. aeruginosa* colonization, especially if associated with initial *S. aureus* colonization, worsens prognosis for morbidity and mortality **(LE 2b; grade of recommendation [GR] B).**

Can serologic testing for anti-Pseudomonas antibodies be useful for early detection of infection with this agent?

Early identification of *P. aeruginosa* infection is essential for the initiation of eradication therapy, the goal of which is to prevent or delay chronic infection with the bacterium.[20]

Respiratory infection with *P. aeruginosa* is routinely diagnosed by examination of sputum, oropharyngeal secretion, or laryngeal aspirates after respiratory therapy or inhalation of hypertonic sodium chloride solution (3-7%). Positive oropharyngeal secretion cultures have a high predictive value, although false-negative results can occur.[21] Other resources used for diagnosis are bronchoalveolar lavage (BAL) culture, serology for detection of specific antibodies in serum, and methods for the detection of bacterial DNA (by PCR) in respiratory secretion specimens.[9]

The difficulty in obtaining representative respiratory specimens from the airways of infants and children under 6 years of age indicates the need for the use of methods that can complement or be an alternative to culture.[22] In the 1970s,

the initial experience of a group of researchers in Denmark[23] regarding the use of serum precipitins to characterize stages of pulmonary infection with *P. aeruginosa* was the main incentive for the use of serological resources in early identification of infections with the pathogen.[24]

West et al.[25] evaluated a cohort of 68 infants diagnosed by neonatal screening and described the natural history of *P. aeruginosa* infections over a 15-year period. The detection of anti-*P. aeruginosa* antibodies allowed the identification of infection with the pathogen before it was isolated from a culture, with bacterial anti-cell lysate antibodies being detected 12 months before culture. Significant *P. aeruginosa* anti-cell lysate antibody titers were detected before or simultaneously with the first isolation of the bacterium in approximately 60% of the patients **(LE 2b).**[25]

In 2006, two studies reporting conflicting serological results were published in the same journal. Kappler et al.[26] used commercial ELISA kits in a prospective study involving 183 patients with CF and reported a sensitivity of 86%, a specificity of 96%, and a positive predictive value of 97%. Those authors propose *P. aeruginosa* eradication therapy in the event of a rise in antibody titers, even in the absence of positive cultures **(LE 2b).**[26] Tramper-Stranders et al.[27] used other ELISA kits in 220 CF patients with different *P. aeruginosa* infection status and found a sensitivity of 96% and a specificity of 79% for the combination of methods. The fact that 15 serological conversions were identified during the study period, with varying response patterns, draw attention to the possibility of failure in identifying early *P. aeruginosa* infection through the use of serological methods **(LE 2b).**[27]

Subsequently, Ratjen et al.,[28] evaluating the usefulness of serological methods in initial *P. aeruginosa* infection in approximately 1,800 serum samples from 375 patients with CF, found inter-individual variability in antibody titers, but reported an association between the serological response and the intensity of the respiratory infection, which, according to the authors, suggested potential for the use of serological methods in conjunction with microbiology **(LE 2b).**[28]

In 2007 in Brazil, da Silva Filho et al.,[22] in a study comparing single-sample PCR, culture, and serology in 87 patients with CF, reported that the combination of the three methods resulted in higher positivity, PCR being the method with the highest positivity. Because the study was cross-sectional, no further conclusions could be drawn **(LE 3).**[22] Methods for molecular identification of *P. aeruginosa* should be viewed with caution, because they do not depend on bacterial viability and they are affected by various technical aspects, such as DNA extraction methods, primers used, sample concentration, etc.[9]

Another group of authors, seeking to establish whether it would be possible to use saliva as a tool for the detection of anti-*P. aeruginosa* antibodies in patients with CF and in normal individuals,[29] described significant titers in the oral fluids from 15 of the 17 patients with CF but in none from the healthy volunteers **(LE 2b).**

Pressler et al.[30] comparatively analyzed three different serological methods (exotoxin A ELISA, CF-IgG ELISA, and counterimmunoelectrophoresis) in 791 Scandinavian patients with CF and concluded that the performance of the tests was very similar. Another relevant finding was the association between the antibody titers observed and the duration and characteristic of the infection, which means that serology could be used in characterizing the chronicity of the infection **(LE 2b).**[30]

In another study conducted in Brazil, Milagres et al.[31] studied 51 patients with CF over a 2-year period, using two types of antigen (bacterial lysate and recombinant PcrV). For 44% of the patients with previously negative cultures or intermittent isolations, serology allowed the detection of *P. aeruginosa*, on average, 21 months before its detection by culture, suggesting that the method should be part of the routine follow-up of patients with CF **(LE 2b).**[31]

More recently, two studies have generated more controversy on the subject. Hayes et al.,[32] in an approximately 6-year longitudinal study evaluating 69 children with CF diagnosed by newborn screening, reported that serology allowed the early identification of *P. aeruginosa* infection in those patients. In contrast, Douglas et al.[33] described paired BAL culture and serology results and found a low positive predictive value and a high negative predictive value using BALF culture as a reference. In view of these findings, there is questioning regarding the potential of serology for monitoring *P. aeruginosa* infection **(LE 2b)**, although recently, the role of BALF culture as a decision-making tool in the treatment of

respiratory infection in patients with CF has also been questioned.[34]

Recommendation

Positive serology results and culture-negative samples of respiratory secretion should alert health professionals to perform a more thorough search for a probable infection, by repeating the test or by using methods that are more sensitive and more specific. In contrast, increasing levels of antibodies are associated with a greater likelihood of persistent chronic infection with the bacterium. Their use in routine practice remains controversial **(LE 2b; GR B).**

Does eradication of initial colonization with P. aeruginosa improve the prognosis in CF?

P. aeruginosa is the most common pathogen in lung infections in patients with CF. The importance of its early detection is due to its correlation with a more pronounced reduction in pulmonary function, which results in impaired quality of life and poorer prognosis of patients chronically colonized with the bacterium. Early identification of *P. aeruginosa* infection is essential for the initiation of eradication therapy, the goal of which is to prevent or delay chronic infection with the bacterium at a phase in which strains are more susceptible to antibiotics.

Studies dating back to the 1980s investigated the effects of early treatment in patients infected with *P. aeruginosa*, suggesting that early eradication could lead to a decrease in the number of patients with chronic colonization. Since the initial studies by Littlewood et al.,[35] there has been growing evidence that the early initiation of antibiotic therapy is an effective strategy to delay chronic *P. aeruginosa* infection.[36-38]

A broader assessment of the effects of eradication therapy was performed by Taccetti et al.,[12] who, in a study of 47 patients, showed that the early use of oral ciprofloxacin + inhaled colomycin resulted in reduced chronicity, causing no increase in bacterial resistance or in the emergence of other pathogens. In addition, those authors found a reduction in pulmonary function decline and in treatment costs.[12]

In a recently published study,[39] the authors concluded that the implementation of an early intervention protocol led to decreased prevalence of chronic *P. aeruginosa* infection, improved pulmonary function, and decreased hospital costs **(LE 1b).** The decision on the best antimicrobial strategy for *P. aeruginosa* eradication remains controversial. In an open-label randomized multicenter study,[40] patients with CF (age ≥ 6 months) and primary infection with *P. aeruginosa* were treated for 28 days or 56 days with inhaled tobramycin administered twice daily. The study showed that more than 90% of patients had negative cultures for *P. aeruginosa* one month after the end of treatment, and that most of those patients remained free from infection for up to 27 months. There was no significant difference when the period of treatment with inhaled tobramycin was extended to 56 days **(LE 1b).**[40]

In another recent multicenter study,[41] the participants were randomized 1:1 to one of four treatment algorithms for 18 months. The treatment regimens were as follows: (a) intermittent courses (every 3 months) of inhaled tobramycin (300 mg twice daily) for 28 days + oral ciprofloxacin (15-20 mg/kg twice daily) for 14 days; (b) intermittent courses (every 3 months) of inhaled tobramycin for 28 days + oral placebo for 14 days; (c) inhaled tobramycin for 28 days + oral ciprofloxacin for 14 days in the presence of a positive culture for *P. aeruginosa*; and (d) inhaled tobramycin for 28 days + oral placebo for 14 days in the presence of a positive culture for *P. aeruginosa*. Those authors concluded that, after 18 months, there were no differences in the rates of exacerbation or prevalence of *P. aeruginosa* between prophylactic treatment and treatment based on positive cultures. There was no additional benefit from the addition of ciprofloxacin during that study **(LE 1b).**[41]

Recommendation

Evidence suggests that the early initiation of inhaled antibiotic therapy, combined or not with oral antibiotics, is an efficient strategy to delay chronic *P. aeruginosa* infection. Studies suggest that short-term eradication can be achieved **(LE 1b; GR A).**[42]

How does one identify and treat acute pulmonary exacerbations (APEs) in patients colonized with P. aeruginosa?

In patients with CF, APEs are a common complication. Although there are published

guidelines for the management of APEs in patients with CF, it is not possible to know for sure which are the best treatment strategies, given the insufficient data.[2]

Chronic *P. aeruginosa* infection becomes more common as patients grow older and is associated with increased morbidity and mortality. Chronic infection is interspersed with APEs, which require additional and more aggressive antibiotic therapy. There is evidence that APEs result in functional loss that often is not completely reversed by treatment.[43]

In APEs with no obvious precipitating factor, several questions arise:

a. How does one define an APE?

b. Should intravenous therapy for an APE be administered in the home or in the hospital?

c. Which antibiotic(s) should intravenous therapy for an APE include?

d. Can (or should) aminoglycosides be used once daily?

e. What should be the duration of intravenous therapy for an APE?

How does one define an APE?

In 1994, Fuchs et al.[44] established criteria for defining APEs in CF, criteria that were subsequently used in a number of scientific studies in the field. According to those authors, an APE could be defined as the clinical need for intravenous antibiotics as indicated by the presence of at least 4 of the 12 signs or symptoms described below:

- Change in sputum volume or color
- Hemoptysis
- Increased cough
- Increased dyspnea
- Increased malaise, fatigue, or lethargy
- Temperature over 38°C
- Anorexia or weight loss
- Maxillary sinus pain or sensitivity
- Change or increase in postnasal discharge
- Change in chest physical examination findings
- Decrease in FEV_1 of 10% or higher
- New radiographic changes

Given that APEs have a negative impact on survival, quality of life, and costs (because of the high costs of hospitalizations and medications), they are an important outcome measure in clinical trials, and although various authors have proposed alternative methods for their objective characterization in patients with CF,[45-47] this definition remains a source of controversy.[48]

In 2011, a group of European experts met in Hamburg and proposed new consensus criteria for characterizing an APE[49]: the need for antibiotic therapy resulting from a recent change in at least 2 of the following 7 items:

- Change in sputum volume or color
- Increased cough
- Increased malaise, fatigue, or lethargy
- Anorexia or weight loss
- Decrease in FEV_1 of 10% or higher
- New radiographic changes
- Increased dyspnea
- Recommendation

The criteria for defining an APE are derived from several studies, and there is a consensus among authors that most of the criteria are adopted on the basis of accumulated experience, although the scientific basis remains flimsy **(LE 2b; GR B).**[47]

Should intravenous therapy for an APE be administered in the home or in the hospital?

A cohort study conducted in the USA and involving twins and siblings with CF retrospectively analyzed APEs in 1,535 patients, comparing the FEV_1 outcomes of approximately 5,000 courses of intravenous antibiotics administered in the hospital with those of the same number of courses administered in the home, and concluded that there was no difference in functional outcome between the two approaches **(LE 2b).**[43]

A recent systematic review of the literature[50] evaluated whether or not home therapy can replace hospitalization in cases of APE. Although several databases were searched, only a small randomized study involving 17 patients was found. The authors concluded that the current evidence is too limited: the results of the only randomized study suggest that, in the short term, home therapy is efficient and cheaper, as well as resulting in reduced social costs. There are advantages and disadvantages in terms of quality of life. The decision to attempt treatment in the home should be made on a case-by-case basis. The authors concluded that further research is necessary **(LE 3a).**[50]

Recommendation

There is insufficient evidence to recommend or refute intravenous home therapy for APEs,

and decisions should be made on a case-by-case basis **(LE 5; GR D)**.

Which antibiotic(s) should intravenous therapy for an APE include?

Traditionally, intravenous administration of beta-lactam antibiotics combined with aminoglycosides has been the most commonly used therapeutic regimen in the treatment of APEs in patients with CF.[51,52] Given that *P. aeruginosa* is a pathogen that develops resistance to antimicrobial agents relatively easily,[53] the combination of drugs with different mechanisms of action can contribute to minimizing this risk. In a study conducted in England, the researchers reported a high prevalence of ceftazidime-resistant *P. aeruginosa* strains, possibly due to the practice of monotherapy with this drug in the institution **(LE 4)**.[54]

A systematic review published in 2005[55] included 27 studies comparing monotherapy with combination antibiotic therapy in the treatment of APEs in patients with CF. The studies were mostly of questionable methodological quality and were quite heterogeneous, complicating the analysis and interpretation of results. In contrast, some randomized studies have shown that combination antibiotic therapy is effective in the treatment of APEs in patients with CF **(NE 2a)**.[56,57] American guidelines[47] recognize the deficiency in information but recommend that combination drug therapy be instituted.

Recommendation

There is evidence to recommend the combination of an aminoglycoside and a beta-lactam antibiotic for the treatment of APEs in patients with CF **(LE 2a; GR B)**.

Can (or should) aminoglycosides be used once daily?

Aminoglycosides were originally studied and approved for use as a three times-daily injection regimen.[58] The recognition that the maximum bactericidal effect of aminoglycosides results from the serum peak values achieved motivated researchers in the late 1980s to evaluate once-daily aminoglycoside administration,[59] and this strategy was found to be effective and safe in various clinical settings.[60] In patients with CF, the results of a meta-analysis[61] and of a systematic review[62] indicate that once-daily aminoglycoside administration is effective and safer **(LE 1a)**.

Recommendation

Aminoglycosides should be administered in a single daily dose in order to reduce side effects **(LE 1a; GR A)**.

What should be the duration of intravenous therapy for an APE?

There are no clear guidelines on the optimal duration of intravenous antibiotic therapy in APEs in patients with CF. Treatment duration is currently based on the policies of each referral center and on individual response to treatment. Shorter treatment durations for APEs should improve the quality of life and satisfaction of patients and their families, as well as being less costly. However, this might not be sufficient to reduce the density of *P. aeruginosa* in the lungs significantly, potentially resulting in early recurrence of APE.

Although a systematic review[63] concluded that there are insufficient data to recommend an appropriate treatment duration for an APE in patients with CF, most treatment regimens, in many centers worldwide, last 10-14 days **(LE 4)**.

Two more recent studies have provided some interesting data on the subject. VanDevanter et al.,[64] in a retrospective study involving 95 hospitalized patients treated with two distinct antimicrobial regimens, found that the average time to the highest observed FEV_1 during the hospitalizations was 8.7 days (median = 10 days), and also reported that, in patients who had poor baseline pulmonary function (FEV_1 < 40%), the time to the highest observed FEV_1 was significantly longer **(LE 3b)**. In another recent study (also retrospective), which evaluated more than 10,000 courses of intravenous antibiotic therapy in approximately 1,500 patients with CF, Collaco et al.[43] showed that clinical and functional improvement was observed between day 7 and day 8 of therapy in most cases, indicating that shorter therapy durations can be used in some cases **(LE 3b)**.

Recommendation

There is no clear definition in the literature as to what the duration of therapy for APEs

should be. However, the results suggest that antibiotics should be administered for at least 8-10 days, and patients who have worse baseline pulmonary function might require longer period of intravenous therapy **(LE 3; GR C).**

When should chronic inhaled antibiotic therapy be initiated in CF? Which inhaled antibiotics can be used in the treatment of chronic P. aeruginosa infection in CF?

Chronic *P. aeruginosa* infections have a negative impact on the prognosis of patients with CF, and, since the 1980s, there has been evidence that the use of therapies that decrease the amount of *P. aeruginosa* in the bronchial tree contributes to the stabilization or improvement of the disease.[65,66]

Tobramycin is the most studied inhaled antibiotic, since a specific formulation of tobramycin (Tobi®; Novartis, São Paulo, Brazil) has been developed and tested in randomized, double-blind, placebo-controlled clinical trials involving a large number of patients with CF.[2]

In the initial studies, inhaled tobramycin was compared with inhaled placebo or standard therapy in patients with moderate to severe lung disease (FEV_1 < 70% of predicted), and the largest of them involved a sample of 520 patients **(LE 1).**[67] The three most significant studies had a total number of 619 randomized patients. The results showed statistically significant improvement in FEV_1 in those who received tobramycin, with a 7.8-12.0% increase in pulmonary function (FEV_1; **LE 1b).**[67-69]

In addition, those three studies evaluated the influence of the use of inhaled tobramycin on the frequency of APEs, reporting a reduction in the number of hospitalizations and in the number of hospitalization days for the group treated with inhaled tobramycin **(NE 1b).**[67-69] The frequency of reported adverse events, especially those related to tinnitus, throat problems, and voice changes, was low in all studies.

These results led to inhaled tobramycin being recommended by international guidelines as the primary treatment option for such cases.[2]

Two studies,[38,70] involving a total number of 202 patients, evaluated the use of inhaled tobramycin in patients with CF and mild lung disease (FEV_1 between 70% and 89% of predicted). Gibson et al., in a sample of 21 patients under 6 years of age with CF and *P. aeruginosa* detected by BAL culture, reported that the use of inhaled tobramycin resulted in a reduction in the amount of *P. aeruginosa* in the airways **(LE 2b).**[38] Another study, involving 181 patients (6-15 years of age) with mild lung disease, compared the use of inhaled tobramycin with the use of standard therapy for 56 weeks and found a significant reduction in the occurrence of exacerbations requiring hospitalization (11.0% vs. 25.6%). The study was stopped early because of the magnitude of the observed impact **(LE 1b).**[70] There was no significant improvement in FEV_1, but those treated with inhaled tobramycin showed a significant improvement (10%) in forced expiratory flow values—$FEF_{50\%}$ **(LE 1b).**[70]

The quality of evidence for the use of inhaled tobramycin in patients with mild lung disease remains limited by the number of studies and by sample sizes, and the largest of those studies[70] was stopped early because of the magnitude of the impact observed for respiratory exacerbations.

Other inhaled antibiotics are used in CF patients with chronic *P. aeruginosa* infection, but the amount of scientific evidence remains relatively sparse.[2]

Inhaled colomycin remains the initial drug of choice for nebulization in patients with CF and chronic respiratory infection with *P. aeruginosa* in the United Kingdom.[71] A comparative study of inhaled tobramycin (300 mg twice daily) and nebulized colomycin (1,000,000 IU twice daily) involving 115 patients showed that both therapies reduced the bacterial content of sputum samples and increased FEV_1 values by 6.7% and 0.37%, respectively **(NE 2b).**[72] There have been few studies on the use of other drugs, such as gentamicin, amikacin, and ceftazidime.[2]

New drugs for inhalation have recently been tested in order to expand the range of therapeutic options, with benefits in the areas of tolerability, bacterial resistance, and practicality of administration, impacting patient safety and quality of life.

Inhaled aztreonam, a single-ring beta-lactam antibiotic (a monobactam), is one of the recently introduced drugs.[73] One of the initial studies was a randomized, double-blind, placebo-controlled trial involving 211 patients over 6 years of age with CF, FEV_1 between 25% and 75% of predicted, and chronic *P. aeruginosa* infection, all of whom

were using inhaled tobramycin regularly. The patients received 75 mg inhaled aztreonam or placebo, two or three times daily for 28 days, and were then monitored for another 56 days. The reported positive effects included a 21-day increase in the mean time to next respiratory exacerbation, improvement in mean quality of life scores, a 6.3% increase in VEF_1 ($p = 0.001$), and a reduction in sputum *P. aeruginosa* density. Adverse events were comparable between the groups. There was no change in susceptibility to *P. aeruginosa* for aztreonam **(LE 2b).**[73] More recently, a study has been published that reports data on the use of inhaled aztreonam for a longer period of time (18 months).[74] The study included 274 patients (mean age, 26 years) who had participated in other studies with inhaled aztreonam. It was an open-label study involving two regimens (75 mg two or three times daily) in alternate months. In addition to high adherence to treatment, pulmonary function and quality-of-life data improved with each course of the drug, there being no significant increase in bacterial resistance rates. Patients treated with three times-daily nebulization showed more significant improvement in pulmonary function and respiratory symptoms **(LE 2b).**[74]

A novel dry-powder formulation of tobramycin delivered via an innovative inhaler was compared, in a non-inferiority study, with the commercially available inhaled tobramycin preparation.[75] The study included 517 patients over 6 years of age with CF, FEV_1 between 25% and 75% of predicted, and a history of chronic *P. aeruginosa* infection for the last 6 months. The dry-powder formulation of tobramycin and the inhaled tobramycin preparation had similar efficacy in terms of FEV_1 and microbiological effect, although the former resulted in higher rates of adverse effects, such as dysphonia, cough, and dysgeusia. However, the dry-powder formulation of tobramycin resulted in higher scores on quality-of-life questionnaires **(LE 1b).**[75]

A formulation of levofloxacin (MP-376, Aeroquin) was tested in 151 CF patients with chronic *P. aeruginosa* infection **(LE 2b).**[76] Three different doses (120 mg/day, 240 mg once daily, and 240 mg twice daily) were tested against placebo for 28 days. Sputum *P. aeruginosa* density was reduced by MP-376 treatment at all three different doses, and there was a dose-dependent increase (of up to 8.7%) in FEV_1, as well as a significant reduction in the occurrence of APEs. The drug was generally well tolerated relative to placebo **(LE 2b).**[76]

A systematic review of the literature, published in 2011,[77] summarized the available evidence on the use of inhaled antibiotics in patients with CF. The review made several comparisons using meta-analysis techniques. The conclusion was that inhaled antibiotics improve pulmonary function and reduce the rates of exacerbation of *P. aeruginosa* infection, and that the best evidence supports the use of inhaled tobramycin **(LE 1a).**[77]

Recommendation

It is recommended that inhaled tobramycin be used in patients over 6 years of age with CF, chronic *P. aeruginosa* infection, and moderate or severe lung disease ($FEV_1 < 70\%$; **LE 1; GR A).**

The use of inhaled tobramycin in patients over 6 years of age with CF, chronic *P. aeruginosa* infection, and mild lung disease (FEV_1 between 70% and 89%) is recommended to reduce respiratory exacerbations **(LE 2; GR B).**

The evidence for the use of inhaled tobramycin in the younger population (those under 6 years of age) remains too poor to allow any evidence-based recommendation.

There are still few data on the use of other antibiotics, such as colomycin, gentamicin, and aztreonam, and there is no evidence to recommend that they be widely used.

Does adherence to clinical treatment affect the prognosis of patients with CF?

The treatment of patients with CF is based on the prevention structural lung injury, the management of the nutritional status, with supplementation with enzymes and nutrients, the prevention of exacerbations, and the identification and treatment of comorbidities, allowing a good quality of life.[78] Among daily treatments, respiratory therapy plays a prominent role because of its complexity, since it usually requires the assistance of another individual and it is a procedure that has a significant impact on disease progression.[79,80] Given the complexity of the disease and the various objectives involved, it is clear that complex and aggressive treatment

regimens are frequently used, which is very time-consuming for patients and their families.[81]

In this setting of complex treatments and no set deadline for their completion, adherence to the recommended treatment is a factor that greatly impacts the clinical outcomes and prognosis of such patients.[78]

Nebulizations are the most complex part of the pharmacological treatment, because they are very time-consuming and are increasingly recommended in patients with mild disease.[2] In a recent study involving adult patients with CF, the mean reported time spent on treatment activities was 108 min/day, and nebulized therapies accounted for 41 min of that time.[81] Even in asthma patients, who spend much less time on drug administration, estimates of adherence to inhaled therapies range from 30% to 50%.[82]

One of the reasons for poor adherence to treatment is lack of understanding of physician recommendations by patients and their families, who often also understand the same physician recommendation differently.[83]

There is evidence that the low rates of adherence to medication use in CF are associated with poorer disease control, school absenteeism, and an increase in APEs **(LE 2b).**[84] In general, the onset of adolescence further worsens the scenario, because that is the time when the lung disease usually progresses and is precisely the time when adherence to treatment becomes poorer.[85] There is evidence that adherence is inversely proportional to patient age, as well as being intimately related to a more optimistic view of the disease.[86]

Given that a study evaluating factors associated with poor adherence in children with asthma and CF identified common factors between the two diseases (forgetting, oppositional behaviors toward parents, difficulties with time management for procedures, side effects, difficulties swallowing pills, and taste of some medications), but also described many aspects that are specific to each disease, it is recommended that a disease-specific approach be applied to issues of adherence to treatment **(LE 2b).**[87]

A study involving adult CF patients and self-reported adherence that was conducted in Brazil showed high adherence rates, which were higher than that perceived by the medical staff involved in the treatment of those individuals.[88] Using other tools to measure adherence, such as pharmacy records, Eakin et al.[89] showed that poor adherence was associated with a higher risk of APE requiring the use of intravenous antibiotics **(LE 4).** Analyzing supplemental health care data on reimbursement for the purchase of inhaled tobramycin, Briesacher et al.[90] assessed the impact of adherence to this therapy on the clinical outcomes of patients with CF. Categorizing adherence as "low" (< 2 cycles/year), "medium" (2-3 cycles/year,) and "high" (≥ 4 cycles/year), those authors reported that high adherence was identified in only 7% of patients, and that low adherence was associated with an increased risk of hospitalization, with higher costs to the health care system **(LE 3b).** It is of note that the recommended treatment regimen is at least 6 cycles/year.

Recommendation

Adherence to treatment in CF is related to the great treatment load required and is poorer in adolescence. **Nebulized therapies and respiratory therapy have the worst rates of adherence, and there is evidence that these therapies affect relevant clinical outcomes, such as the need for hospitalization (LE 3; GR C).**

Is azithromycin efficacious in slowing the progression of lung disease in CF patients colonized with P. aeruginosa?

Macrolides are bacteriostatic drugs that act by inhibiting bacterial protein synthesis by binding to the 50S ribosomal unit.[91] In the 1980s, Japanese researchers described their experience in using low doses of erythromycin in diffuse panbronchiolitis, a disease that is accompanied by bronchiectasis and pulmonary suppuration.[92] That initial experience motivated further studies using different macrolides in the treatment of respiratory diseases, such as CF, asthma, and bronchiolitis obliterans.[91]

Possible mechanisms of action of macrolides in CF include actions in the microorganism, such as reduced *P. aeruginosa* virulence, delayed bactericidal effects, reduced bacterial adherence to the respiratory epithelium, decreased bacterial motility, and impaired biofilm production.[91,93] Among the immunomodulatory actions of macrolides in the host are alteration in the neutrophil production of elastase, inhibition of

alveolar macrophage production of inflammatory cytokines, and decreased mucus hypersecretion.[91,93]

Azithromycin is the most commonly used macrolide in patients with CF, and the first encouraging clinical trial was published in 2002: a 15-month randomized double-blind, placebo-controlled crossover trial evaluating 41 patients with CF.[94] The primary outcome measure was change in FEV_1, and azithromycin was dosed by body weight: ≤ 40 kg (250 mg/day) and > 40 kg (500 mg/day). The authors found significant improvement in pulmonary function (5.4%; 95% CI: 0.8-10.5%) in the group receiving azithromycin as compared with the group receiving placebo, and there was no significant difference in sputum bacterial concentration, exercise tolerance, or quality of life. In addition, treatment was well tolerated, with no significant adverse events **(LE 2b).**[94]

Subsequently, a new, multicenter, randomized, double-blind, placebo-controlled trial involving 185 patients over 6 years of age who were chronically infected with *P. aeruginosa* was conducted in the USA.[95] The dose of azithromycin was the same as that of the previous study, although it was administered only three times weekly. The primary outcome measure was also FEV_1, and the authors reported a significant difference between the treatment and placebo groups (6.2%; 95% CI: 2.6-9.8%). Other encouraging results were a 35% reduction in the risk of APE and significant weight gain among the patients receiving azithromycin **(LE 1b).**[95] The same group of authors assessed the effects of azithromycin in CF patients uninfected with *P. aeruginosa*[96]; the use of azithromycin for 24 weeks did not result in significant improvement in FEV_1 when compared with that of placebo, but there was a significant reduction in the occurrence of APEs in the group treated with azithromycin **(LE 2b).**[96]

A recent meta-analysis evaluating the use of macrolides in patients with CF included 6 randomized placebo-controlled trials (654 patients).[97] Treatment with azithromycin resulted in significant improvement in FEV_1 and FVC, especially in patients chronically infected with *P. aeruginosa*. The incidence of side effects was not significantly different between the placebo group and the azithromycin group **(LE 1a).**[97]

A recent systematic review on the use of macrolides in CF included 10 studies (959 patients).[98] Four clinical trials (549 patients) reported significant improvement in pulmonary function by comparing azithromycin with placebo. The mean difference at 6 months was 3.97% (95% CI: 1.74-6.19%). Patients receiving azithromycin had a reduction in the occurrence of APEs, needed oral antibiotics less frequently, had greater weight gain, and had fewer respiratory secretion cultures positive for *S. aureus*. Adverse effects were uncommon, although there was an increase in resistance to macrolides. The authors concluded that azithromycin has a small beneficial effect in the treatment of patients with CF using a three times-weekly regimen for periods of 6 months. However, considering the limited long-term data available and the concern about the development of bacterial resistance to macrolides, the current evidence is not strong enough to recommend that azithromycin be used in all patients with CF **(LE 1a).**[98]

Recommendation

The use of azithromycin in CF patients chronically infected with *P. aeruginosa* causes slight improvement in pulmonary function, reduces the frequency of APEs, and has no significant side effects **(LE 1; GR A).**

Because most studies lasted approximately 6 months, long-term studies are needed to confirm the efficacy and safety of azithromycin.

Is there a good correlation between antibiogram results and clinical response in chronic P. aeruginosa infection?

In initial infection with *P. aeruginosa* in patients with CF, nonmucoid forms are usually quite sensitive, there is a good correlation with antibiogram results, and treatment is usually successful. In chronic infections, mucoid forms of *P. aeruginosa* predominate, and higher concentrations of antibiotics are required; in addition, given the common occurrence of mixed populations of *P. aeruginosa* in the biofilm in the lung, the correlation between antibiogram results and clinical response might not be good.[71]

There are reports of clinical success in the treatment of bacteria that are resistant in vitro, and, in a study involving treatment of APEs, clinical outcomes were not associated with the minimum inhibitory concentration values

for *P. aeruginosa* of the antimicrobial agents used (LE 2b).[99]

In a study addressing multidrug-resistant *P. aeruginosa* isolates, Aaron et al.[100] found no significant differences in clinical or bacteriological outcomes between the antimicrobial regimen chosen on the basis of standard sensitivity testing and that chosen on the basis of multiple combination bactericidal antibiotic testing (synergy testing; LE 2b).

Despite the lack of correlation found between antibiogram results and clinical response in the treatment of *P. aeruginosa* infections, the recommendation is to perform cultures of respiratory secretions from CF patients periodically to detect the initial infection, as well as to monitor changes in sensitivity patterns or the presence of other pathogens, such as *B. cepacia* complex, *Achromobacter xylosoxidans, Aspergillus* spp., etc. (LE 5).[101]

Recommendation

Despite the poor correlation between antibiogram results and clinical response in chronic *P. aeruginosa* infection, it is recommended that cultures of respiratory secretions from CF patients be performed periodically to identify different bacterial species, although *P. aeruginosa* treatment should not be directed solely by the sensitivity pattern in the antibiogram (LE 5; GR D).

Does multidrug-resistant P. aeruginosa infection worsen prognosis?

As the mean survival of patients with CF increases and the population of adults with CF grows, there is increasing concern about multidrug-resistant *P. aeruginosa* infections. Multidrug-resistant *P. aeruginosa* has been defined as resistance to all drugs in at least two of the three following antimicrobial classes: fluoroquinolones; beta-lactam antibiotics; and aminoglycosides.[102]

The major risk factors for multidrug-resistant *P. aeruginosa* infection are diabetes, long-term use of inhaled tobramycin, and frequent APEs requiring hospitalization or intravenous antibiotics. Receiving care at a treatment center with a high prevalence of resistant *Pseudomonas* spp. also increases the risk for acquiring multidrug-resistant *P. aeruginosa* (LE 2b).[103]

A study following 75 adult patients with CF over a 3-year period found that multidrug-resistant *P. aeruginosa* infection was associated with greater lung disease severity, more rapid decline in FEV_1, increased use of intravenous antibiotics, and increased frequency of medical visits (LE 2b).[104]

Recommendation

Multidrug-resistant *P. aeruginosa* infection worsens the prognosis of patients with CF, as well as increasing the need for care and the use of medical and hospital resources (LE 2).

Final considerations

There is a body of evidence that early *P. aeruginosa* colonization has a significant impact on the prognosis of patients with CF, and that eradication strategies should be used, although there is controversy as to what is the best treatment regimen for this purpose. Early diagnosis of *P. aeruginosa* infection remains a challenge in clinical practice, and the role of *P. aeruginosa* serology in routine practice has yet to be established. A major problem for patients with CF, APEs are difficult to identify and treat, which often results in significant functional loss. Maintenance treatment for patients with chronic *P. aeruginosa* infection includes drugs such as azithromycin and inhaled antibiotics and, despite the body of evidence supporting the use of inhaled tobramycin, there is a novel formulation of this drug, as well as other antimicrobial agents with potential for use in such cases.

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