J Bras Pneumol. 2023;49(2):e20230040
https://dx.doi.org/10.36416/1806-3756/e20230040

Brazilian guidelines for the pharmacological treatment of the pulmonary symptoms of cystic fibrosis. Official document of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association)

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Submitted: 19 March 2023.
Accepted: 31 March 2023.

ABSTRACT

Cystic fibrosis (CF) is a genetic disease that results in dysfunction of the CF transmembrane conductance regulator (CFTR) protein, which is a chloride and bicarbonate channel expressed in the apical portion of epithelial cells of various organs. Dysfunction of that protein results in diverse clinical manifestations, primarily involving the respiratory and gastrointestinal systems, impairing quality of life and reducing life expectancy. Although CF is still an incurable pathology, the therapeutic and prognostic perspectives are now totally different and much more favorable. The purpose of these guidelines is to define evidence-based recommendations regarding the use of pharmacological agents in the treatment of the pulmonary symptoms of CF in Brazil. Questions in the Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest (PICO) format were employed to address aspects related to the use of modulators of this protein (ivacaftor, lumacaftor+ivacaftor, and tezacaftor+ivacaftor), use of dornase alfa, eradication therapy and chronic suppression of *Pseudomonas aeruginosa*, and eradication of methicillin-resistant *Staphylococcus aureus* and *Burkholderia cepacia* complex. To formulate the PICO questions, a group of Brazilian specialists was assembled and a systematic review was carried out on the themes, with meta-analysis when applicable. The results obtained were analyzed in terms of the strength of the evidence compiled, the recommendations being devised by employing the GRADE approach. We believe that these guidelines represent a major advance to be incorporated into the approach to patients with CF, mainly aiming to favor the management of the disease, and could become an auxiliary tool in the definition of public policies related to CF.

Keywords: Cystic fibrosis; GRADE approach; Cystic fibrosis/drug treatment; Clinical practice guide.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease that results in dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is a chloride and bicarbonate channel expressed in the apical membrane of epithelial cells in various organs of the human body.[1] Dysfunction of the CFTR protein results in multisystemic manifestations, impairing quality of life and reducing life expectancy.[2]

Although CF is still an incurable pathology, the therapeutic perspective is currently more favorable due to the discovery of CFTR modulators.[3,4] Historically, treatments for individuals with CF were developed to overcome deficiencies or to modify basic aspects of the pathophysiology of the disease.[5-8]

The emergence of CFTR modulators has prompted systematic reviews on the evidence for their beneficial effects on health outcomes for individuals with CF.[3,4,9,10]

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Financial support: This project received partial financial support through unrestricted educational support from Vertex Farmacêutica do Brasil Ltda, São Paulo (SP) Brazil.

When these guidelines were first being devised, the CFTR modulators approved by the Brazilian *Agência Nacional de Vigilância Sanitária* (ANVISA, National Health Regulatory Agency) were ivacaftor[11] and two drug combinations: lumacaftor+ivacaftor[12]; and tezacaftor+ivacaftor.[13,14] At the end of 2020, ivacaftor was incorporated into the Brazilian Unified Health Care System for use in individuals with CF ≥ 6 years of age and with genetic regulation (gating) mutations. In 2022, the Brazilian National Health Regulatory Agency approved triple therapy (elexacaftor+tezacaftor+ivacaftor), which proved to be highly effective for individuals with CF carrying the *F508del* genetic mutation, even for those who are heterozygous for that mutation.[15,16] Because that drug combination was approved so recently, it was not evaluated in these guidelines.

One of classical treatments for CF, dornase alfa,[17] has long been incorporated into the Brazilian Unified Health Care System. However, questions persist regarding its true impact on relevant outcomes, such as mortality and the frequency of pulmonary exacerbations.[18-20]

Management strategies for respiratory infections in CF are quite heterogeneous. An evaluation of the evidence supporting eradication regimens for pathogens such as *Pseudomonas aeruginosa*,[21] methicillin-resistant *Staphylococcus aureus* (MRSA),[22] and strains of the *Burkholderia cepacia* complex[23] could help clarify positions on the risks and benefits of such regimens. Another common practice in the treatment of individuals with CF is suppression therapy for chronic *P. aeruginosa* infection with inhaled antibiotic therapy. Given the impact of this treatment, which imposes long periods of nebulization,[24] the topic was also addressed in the guidelines presented here.

The aim of this special article is to carry out a systematic review and meta-analysis of data from the literature involving aspects of the treatment of individuals with CF regarding the use of CFTR modulators and dornase alfa, as well as strategies for the eradication and suppression of pathogens commonly associated with respiratory infections in such individuals.

METHODS

The steps for developing the guidelines followed the model proposed and approved by the Brazilian Thoracic Association, which employs the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach,[25] together with questions in the **P**atients of interest, **I**ntervention to be studied, **C**omparison of interventions, and **O**utcome of interest (PICO) format.[26] On May 15, 2019, a virtual meeting, involving four coordinators (two CF specialists and two methodologists), one patient, and a committee of experts, was held for the approval

Chart 1. Questions and respective outcomes selected for the preparation of the guidelines.

Question	Critical outcomes	Important outcomes
1. Should we recommend treatment with ivacaftor in patients with CF who carry class III (gating) or class IV (conduction) mutations in the *CFTR* gene?	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
2. Should we recommend treatment with lumacaftor+ivacaftor in CF patients homozygous for the *F508del* mutation?	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
3. Should we recommend treatment with tezacaftor+ivacaftor in CF patients homozygous for *F508del* or heterozygous for *F508del* and with residual function mutations?	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
4. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection?	Mortality Adverse events Time free from *P. aeruginosa* infection	Eradication of *P. aeruginosa* Lung function Exacerbations BMI variation
5. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
6. Should we recommend antimicrobial eradication treatment in CF patients with MRSA colonization of the airways?	Mortality Eradication of MRSA Adverse events Quality of life	Lung function Exacerbations
7. Should we recommend nebulized dornase alfa for CF patients ≥ 6 years of age?	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
8. Should we recommend antimicrobial eradication treatment in CF patients with airway colonization by *Burkholderia cepacia* complex strains?	Mortality Eradication of *B. cepacia* Quality of life Adverse events	Lung function Exacerbations BMI variation

CF: cystic fibrosis; and MRSA: methicillin-resistant *Staphylococcus aureus*.

of the methodology used. The experts formulated PICO questions about the pharmacological treatment of patients with CF. A vote was then taken to select the eight most relevant questions. The outcomes of interest for each question were defined *a priori* and classified as critical or important (Chart 1).

The search for articles and the meta-analysis were carried out by a team of experienced methodologists, hired for the purpose of devising these guidelines. The project was registered on the International Prospective Register of Systematic Reviews (PROSPERO) platform (Protocol no. CRD42020173901). The searches were carried out in the MEDLINE and EMBASE databases. Clinical trials, case-control studies and cohort studies were included, with keywords pre-established by the specialist coordinators, with no date or language restrictions (Chart S1).

We first evaluated the articles on the basis of their titles and abstracts. Two methodologists, working independently, then performed a qualitative analysis of the full texts and selected articles to be included. Their selections were subsequently validated by the specialist coordinators. The reasons for inclusion or exclusion are presented in the supplementary material (Figures S1 to S8).

When appropriate, data on pharmacological interventions were pooled and meta-analyses were performed independently by the team of methodologists. For each of the eight PICO questions, the quality of evidence of each of the studies included in the meta-analyses was assessed by employing the GRADE approach, through the use of evidence tables, with the GRADEpro Guideline Development Tool (McMaster University, Hamilton, ON, Canada).

For any given study, the quality of evidence depends on the design, the implementation, and the risks of bias. As detailed in Charts 2 and 3, the quality of evidence can be classified as high, moderate, low, or very low.[25]

In December of 2021, a working group met to review the evidence and make recommendations for each question according to the GRADE approach. The recommendations were classified as strong or conditional, according to degree of certainty regarding the strength and quality of the evidence. We use the term "recommend" for strong recommendations and "suggest" for conditional recommendations. Chart 4 shows the proposed interpretations of those recommendations,[26,27] which are detailed in Tables S1 to S8.

Chart 2. Interpretation of the quality of evidence employing the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

GRADE quality of evidence	Implications	Examples
High (⊕⊕⊕⊕)	Future research is unlikely to change the level of confidence in the estimated effect; we are confident that we can expect a very similar effect in the population for which the recommendation is intended.	Randomized trials without serious limitations Well-executed observational studies with very large effect sizes
Moderate (⊕⊕⊕◯)	Future research is likely to have a major impact on the level of confidence in the estimated effect and could change this estimate.	Randomized trials with serious limitations Well-executed observational studies with large effect sizes
Low (⊕⊕◯◯)	Future research is likely to have a major impact on the level of confidence in the estimated effect and is likely to change that estimate.	Randomized trials with very serious limitations Observational studies without special strengths or serious limitations
Very low (⊕◯◯◯)	Any estimate of an effect is very uncertain.	Randomized trials with very serious limitations and inconsistent results Observational studies with serious limitations Nonsystematic clinical observational studies (e.g., case series or case reports)

Adapted from Guyatt et al.[27] GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Chart 3. Factors that can affect the quality of evidence.[a]

Quality of evidence	Situations that can lower the grade	Situations that can raise the grade
• High • Moderate • Low • Very low	• Risk of bias • Indirect evidence • Inconsistency • Imprecision • Publication bias	• Strong association, no plausible confounding factors • Evidence of a dose-response relationship • Known plausible confounding factors that reduce the effects

Adapted from Guyatt et al.[27] [a]Quality can be lowered by one or two degrees when a risk of bias, indirect evidence, inconsistency, imprecision, or publication bias is identified. However, it can be raised when there is a strong association without identification of plausible confounding factors or when there is evidence of a dose-response relationship.

Chart 4. Implications of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Target audience	Strong GRADE recommendation		Conditional GRADE recommendation	
	We recommend	We do not recommend	We suggest	We do not suggest
Patients	Most individuals would want the intervention to be indicated, and only a small number would not accept this recommendation.	Most individuals would not want the intervention to be indicated, and only a small number would accept this recommendation.	Most individuals would like the intervention to be indicated, although a considerable number would not accept this recommendation.	Most individuals would not want the intervention to be indicated, although a considerable number would accept this recommendation.
Health professionals	Most patients should receive the recommended intervention.		The professional must recognize that different choices can be appropriate for each patient and should help patients make a decision consistent with their values and preferences.	
Policy makers	The recommendation can be adopted as health policy in most situations.		Substantial debate and stakeholder involvement is required.	

Adapted from Abou Alaiwa et al. and Accurso et al.[28,29]

Question 1. Should we recommend treatment with ivacaftor in CF patients with class III (gating) or class IV (conduction) mutations in the *CFTR* gene?

Ivacaftor is a CFTR modulator. It acts as a CFTR potentiator, aimed at treating the dysfunction underlying this genetic alteration. It regulates the opening of the chlorine channel present in the cell membrane, restoring healthy mucus rheology in the airways.

In 2012, the US Food and Drug Administration approved the use of ivacaftor for CF patients ≥ 12 years of age.[11] It is the first drug approved for CF whose therapeutic action targets the basic problem of the disease, characterized by CFTR protein dysfunction. Various clinical trials were subsequently carried out, the results of which allowed the use of the drug to be extended to patients ≥ 6 years of age.

Evidence

Among the studies analyzed, there were 28 on the use of ivacaftor, for a variety of outcomes,[12,28-54] as shown in Figure S1 and Chart S2. Of those 28 studies, 8 were randomized controlled trials (RCTs).[11,29,32-34,36,44,45] Although not all investigated the same sets of outcomes, the articles collectively demonstrated a beneficial therapeutic effect of ivacaftor in patients with class III (gating) or class IV (conduction) mutations.

A detailed description of the findings can be found in the Supplementary Material (Question S1). The quality of evidence of the selected articles for this question is summarized in Tables S1A and S1B.

In 2020, Volkova et al.[55] evaluated disease progression (real-life study) in CF patients treated with ivacaftor for 5 years. Patients enrolled in US and UK CF registries, which maintain a high degree of data integrity, were evaluated. The authors analyzed 635 cases versus 1,875 controls in the US registry and 247 cases versus 1,230 controls in the UK registry. They observed that, at the end of the 5-year follow-up period, the ivacaftor group patients had better lung function and better nutritional status, as well as a lower frequency of exacerbations and hospitalizations, when compared with their baseline values and with the values obtained for the standard therapy without ivacaftor (control) group.[55]

Recommendation

For patients with CF and at least one class III (gating) or class IV (conduction) mutation, we suggest the use of ivacaftor (conditional recommendation, very low quality of evidence).

Comments

The results obtained in real-life studies of the use of ivacaftor are similar to those obtained in clinical studies, indicating that it has a positive effect as a modifying drug in the natural progression of CF. The very low quality of the evidence found is due to the high heterogeneity of the studies evaluated, given that our systematic review included clinical trials and observational studies. The studies evaluated included only patients ≥ 6 years of age, and it is not possible to extrapolate the recommendation to any younger age group.

Question 2. Should we recommend treatment with lumacaftor+ivacaftor in CF patients homozygous for the *F508del* mutation?

Lumacaftor and ivacaftor are both CFTR modulators. Lumacaftor is a CFTR corrector, which acts in the processing of the protein, correcting its format and consequently increasing in its quantity on the cell membrane.[4]

Combination therapy was evaluated in CF patients aged 6 years or older who were homozygous for the *F508del* class II mutation. The results indicated a reduction in the number of pulmonary exacerbations, a slight increase in FEV_1, improved nutritional status, better quality of life, and a reduction in sweat chloride levels.[12,56-60]

In view of the benefits it presents, the use of lumacaftor+ivacaftor has been approved by various international agencies, including the Brazilian ANVISA.

In addition, that combination has been shown to have an acceptable safety profile, satisfactory patient adherence (the majority of patients completing the prescribed therapeutic regimen), and a low incidence of relevant adverse events.[13,58-60]

Evidence

Using the methodology described, we selected 16 articles.[12,56-69] All of those articles were later included for reading, review, and synthesis of evidence (Figure S2 and Chart S3).

Of the 15 studies selected, only 2 were RCTs.[12,57] Although not all investigated the same sets of outcomes, they collectively demonstrated that lumacaftor+ivacaftor has a beneficial therapeutic effect in patients homozygous for the *F508del* mutation.

A detailed description of the findings can be found in the Supplementary Material (Question S2). For each of the articles, the quality of evidence for this question is summarized in Tables S2A and S2B.

Recommendation

For CF patients with the *F508del* mutation, we do not suggest the use of lumacaftor+ivacaftor (conditional recommendation, very low quality of evidence).

Comments

The combination of a CFTR corrector and a CFTR potentiator can benefit patients homozygous for *F508del*, representing a differential in the treatment of approximately 45% of individuals with CF and that mutation. However, in the present systematic review, we identified no significant results regarding clinical outcomes that were considered critical. The positive findings obtained for the outcomes that were considered important were only marginal. Some patients may benefit from treatment. However, given the very low quality of evidence for most of the outcomes assessed, we do not suggest the use of lumacaftor+ivacaftor for the treatment of CF patients homozygous for the *F508del* mutation. It is important to emphasize that new classes/combinations of modulators, such as tezacaftor+ivacaftor[13] and, more recently, the triple combination (elexacaftor+tezacaftor+ivacaftor),[15] have been approved and have been shown to have better efficacy and safety profiles in this population.

Question 3. Should we recommend treatment with tezacaftor+ivacaftor in CF patients homozygous for *F508del* or heterozygous for *F508del* and with residual function mutations?

Tezacaftor is a CFTR corrector that binds to the protein, improving its processing and trafficking through the cell to the cell membrane.[9]

The use of tezacaftor+ivacaftor was evaluated in phase III studies involving CF patients ≥ 12 years of age who were homozygous for the *F508del* mutation,[13] as well as for patients who were heterozygous for the *F508del* mutation and had a residual function mutation.[14] In those studies, the use of tezacaftor+ivacaftor was found to provide a significant improvement in lung function, a reduction in the number of exacerbations, and nutritional gain, with an adequate safety profile. Similar results were obtained in patients between 6 and 11 years of age.[70-72] Therefore, tezacaftor+ivacaftor was approved for use in patients in several countries, including Brazil.

Evidence

As shown in Figure S3 and Chart S4, 5 articles were selected by using the methodology described: 4 RCTs and 1 observational study.[13,14,70-72] All of the studies assessed more than one outcome, including BMI, quality of life, adverse events, occurrence of exacerbations, lung function, and mortality.[13,14,70-72]

For each of the articles, the quality of evidence for this question is summarized in Table S3. A detailed description of the findings can be found in the Supplementary Material (Question S3).

Recommendation

For CF patients homozygous for *F508del* or heterozygous for *F508del* and with a residual function mutation, we suggest using tezacaftor+ivacaftor (conditional recommendation, very low quality of evidence).

Comments

The use of tezacaftor+ivacaftor was evaluated in CF patients ≥ 6 years of age who were homozygous for *F508del* or heterozygous for *F508del* and with a residual function mutation. The main effect of the drug was on lung function. The gain in FEV_1, albeit modest, seems significant when considered in the context of a disease that leads to a progressive decline in lung function. It is important to point out that the clinical benefits obtained in patients with a residual function mutation seem to be greater than those found in patients homozygous for *F508del*. In all of the studies evaluated, there was no difference between the control and tezacaftor+ivacaftor groups in terms of the occurrence of adverse events. Most of the adverse events observed were mild and did not lead to discontinuation of the treatment. In addition, many of the events reported (such as increased pulmonary secretion and increased coughing) can be attributed to the disease itself, which attests to the adequate safety profile of the drug.[13,14,70-72]

Question 4. Should we recommend eradicating *P. aeruginosa* infection in individuals with CF?

Respiratory tract infections are common in individuals with CF, who are more susceptible to infection with certain microorganisms, including *P. aeruginosa*. Infection with this pathogen is considered a major predictor of morbidity and mortality from CF,[73] as well as of a severe loss of lung function.[74] Since the

1990s, CF referral centers have used regimens for early eradication of *P. aeruginosa*, aiming to delay the progression to chronic infection and its unfavorable outcomes.

Evidence

Using the methodology described, we selected 17 articles, conducted between 1980 and 2019 and published between 1991 and 2020,[75-91] of which 10 were observational studies[75-80,82,83,86,87] and 7 were RCTs.[81,84,85,88-91] The number of individuals included in the studies ranged from 11 to 304, and 12 of the studies had a sample size of less than 200 (Figure S4 and Chart S5).

For each of the articles, the quality of evidence for this question is summarized in Table S4. A detailed description of the findings can be found in the Supplementary Material (Question S4).

Recommendation

For individuals with CF, we do not have sufficient evidence to recommend or not recommend the use of *P. aeruginosa* eradication therapy.

Comments

The association between *P. aeruginosa* infection and poor CF outcomes is well established. In addition, eradication therapy has already been incorporated into the routine of referral centers, making it difficult to carry out new studies on the subject. The literature review made it possible to include a limited number of studies, most of which were observational in nature and, in general, had small sample sizes. Such characteristics can lead to inconsistent results, making it impossible to make an appropriate recommendation on the subject. Despite being a practice recommended in several national and international guidelines, further studies are needed to determine the efficacy and safety of *P. aeruginosa* eradication therapy, especially in the era of CFTR modulator use.

Question 5. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection?

Through complex mechanisms, *P. aeruginosa* adapts to and can remain in the airways of CF patients for long periods. Chronic infection in CF is defined as detection of the pathogen in more than 50% of respiratory secretion samples over a 12-month period.[92] Chronic infection with *P. aeruginosa* can affect up to 60% of patients in adult life and is associated with progression of lung disease and higher mortality.[21,93,94] Inhaled antimicrobials are widely used for the suppression of *P. aeruginosa* in patients with chronic infection, and their use is aimed at reducing the consequences of the presence of the pathogen in the airways. Inhaled drug options for such treatment classically include colistimethate, tobramycin, and, more recently, aztreonam.[93]

Evidence

Using the methodology described, we selected 25 studies carried out between 1995 and 2008.[94-118] Five were observational studies[101-103,109,117] and the others were classified as RCTs. Samples sizes were over 200 in 9 of the studies, of which 2 included more than 500 individuals (Figure S5 and Chart S6).

For each of the articles, the quality of evidence for this question is summarized in Table S5. A detailed description of the findings can be found in the Supplementary Material (Question S5).

Recommendation

For CF patients with chronic *P. aeruginosa* colonization, we suggest chronic suppression therapy with inhaled antibiotics (conditional recommendation, very low quality of evidence).

Comments

Although not all of the studies analyzed exactly the same sets of outcomes, as a whole, they point in favor of the use of inhalation treatment of patients with chronic *P. aeruginosa* colonization, because such treatment can result in functional improvement, better quality of life, and lower mortality in those patients. It should be borne in mind that, despite the potential benefits, there is heterogeneity among the studies evaluated, resulting in a low quality of evidence.

Question 6. Should we recommend antimicrobial eradication treatment in CF patients with MRSA colonization of the airways?

Chronic MRSA infection is associated with worse clinical outcomes in CF patients.[119] There are various antimicrobial regimens for eradicating this pathogen, including combinations of oral, topical, and inhaled drugs. There is also great variability regarding treatment time, and some authors argue that combined treatment is more effective than is monotherapy.[120,121] However, there is still no consensus in the literature and it is questionable whether there is robust scientific evidence that MRSA eradication is beneficial for CF patients.[122,123]

Evidence

Using the methodology described, we selected 8 studies (Figure S6 and Chart S7).[120-127] Of those, only 2 are RCTs[123,126] and the other 6 are observational studies.[120-122,124,125,127]

For each of the articles, the quality of evidence for this question is summarized in Tables S6A and S6B. A detailed description of the findings can be found in the Supplementary Material (Question S6).

Recommendation

For CF patients, we do not have enough evidence to recommend or not recommend the use of MRSA eradication therapy.

Comments

Although all of the studies assessed the eradication rate, they employed different treatment protocols, as well as different means of assessing eradication (short- vs. long-term follow-up). All of the studies evaluated had sample sizes of less than 70 individuals. It is possible that further studies, especially studies with larger patient samples, will result in a change in the confidence level of this recommendation.

Question 7. Should we recommend nebulized dornase alfa for CF patients ≥ 6 years of age?

In CF patients, chronic inflammation and infection results in extracellular DNA from leukocytes being constantly released into the airways and accumulating in lung secretions.[18] Consequently, there is an increase in the viscosity and adhesion of mucus. Dornase alfa is an enzyme capable of cleaving the extracellular DNA contained in mucus, reducing its viscosity and promoting greater clearance of secretions.[128]

Dornase alfa is administered by inhalation, at the usual dose of 2.5 mg once a day, and should be used in conjunction with other airway clearance techniques.[17,128]

In phase I and II studies, the use of nebulized dornase alfa in CF patients proved to be safe and led to an increase in FEV_1 in the short term, together with improvements in symptoms and quality of life.[129,130] Subsequent studies demonstrated the maintenance of benefits in the long term, with sustained improvement in FEV_1, a reduced risk of exacerbations, and a good safety profile.[128]

Evidence

We selected 32 studies,[17,131-161] 18 of which were RCTs that compared the use of dornase alfa with placebo,[17,131-135,140-142,144,145,149,151-154,159,160] and 14 were observational studies,[136-139,143,146-148,150,155-158,161] as illustrated in Figure S7 and Chart S8.

For each of the articles, the quality of evidence for this question is summarized in Tables S7A and S7B. A detailed description of the findings can be found in the Supplementary Material (Question S7).

Recommendation

For CF patients, we suggest the use of inhaled dornase alfa (conditional recommendation, very low quality of evidence).

Comments

The differences in mortality rates between the intervention and placebo groups were not significant, because few patients died. Two RCTs evaluated adverse effects[17,149] and found no significant differences in terms of the frequency of adverse events. One RCT and two observational studies[131,155,156] assessing quality of life demonstrated improvements in the intervention groups.

Nine RCTs,[17,131,141,142,144,149,152,154,160] evaluated collectively, showed that FEV_1 values were 5% higher among patients receiving dornase alfa than among those receiving a placebo. Although that is a modest improvement, FEV_1 is a proxy for mortality in population studies. In addition, 2 RCTs[17,152] demonstrated that the rate of exacerbations was 7% lower in the intervention groups than in the placebo groups. This outcome is important, because a reduction in exacerbations is associated with favorable lung function outcomes and, indirectly, with lower mortality.

The search of the literature for these guidelines did not include studies involving children under 6 years of age. Therefore, it is not possible to extrapolate this recommendation to any younger age group.

Question 8. Should we recommend antimicrobial eradication treatment in CF patients with airway colonization by *B. cepacia* complex strains?

The *B. cepacia* complex comprises 22 species,[162] the most common of which in CF are *B. multivorans* and *B. cenocepacia*. The clinical picture is quite variable, ranging from chronic, oligosymptomatic infection to severe cases, with necrotizing pneumonia, respiratory failure, and sepsis (cepacia syndrome).[163] The *B. cepacia* complex has a peculiar bacterial resistance profile, which makes the choice of antibiotic treatment difficult, and a combination of antimicrobial drugs is commonly suggested, preferably guided by antimicrobial susceptibility testing.[164]

Evidence

Using the methodology described, we selected 3 studies,[23,165,166] as illustrated in Figure S8 and Chart S9. Only 1 study was characterized as an RCT.[165]

For each of the articles, the quality of evidence for this question is summarized in Tables S8A and S8B. A detailed description of the findings can be found in the Supplementary Material (Question S8).

Recommendation

For CF patients, we do not have enough evidence to recommend or not recommend the use of eradication therapy for *B. cepacia* complex.

Comments

None of the selected studies showed any benefits of eradication therapy for *B. cepacia* complex when evaluating the many critical outcomes considered important in the methodology of these guidelines. Only a few studies on the subject were found in the literature. Most of those studies had low methodological quality, and there was considerable heterogeneity among them. The eradication regimens described were not standardized. The higher rates of adverse events found with the use of inhaled aztreonam cannot be extrapolated to other therapeutic regimens, especially because that antibiotic is not commonly recommended for this type of infection. Therefore,

our guideline committee decided that it is not possible to make a recommendation either for or against this therapy, given the scarcity of published information. Further studies are needed in order to evaluate this issue in greater detail.

FINAL CONSIDERATIONS

A summary of the recommendations for the pharmacological treatment of respiratory disease in CF is presented in Chart 5.

It is up to the prescribers to determine which treatments are appropriate for a given patient or group of patients, and that it is up to them to help patients and their families make consistent and well-founded decisions, consistent with the strength of the recommendations and the quality of existing evidence. Cost analyses and pharmacoeconomic aspects were not considered in these recommendations.

Although there is still no drug with curative capacity in CF, the present guidelines suggest several interventions with potential benefits for the treatment of the disease. Some drugs, such as dornase alfa, and strategies to control chronic infection by *P. aeruginosa* have been approved for more than a decade and are considered standard therapy in the management of CF. However, those interventions work to control the consequences of the disease, such as increased mucus viscosity and recurrent infectious exacerbations. More recently, a new class of drugs, CFTR modulators, has initiated a new phase in the treatment of CF by acting on the underlying cause of the disease.[9] Substantial gains in lung function and reduction in exacerbation rates were found when ivacaftor was used in patients with class III mutations[11] and when tezacaftor+ivacaftor was used in patients with residual function mutations.[14] However, despite the statistically significant benefits, such results were not achieved in CF patients homozygous for the *F508del* mutation who were treated with lumacaftor+ivacaftor[12] or tezacaftor+ivacaftor.[13] These data indicate the need for an adequate assessment of the benefits of each treatment according to the population evaluated. Treatment with CFTR modulators can be considered a targeted therapy, and CFTR modulators are chosen according to the action of different drugs on specific groups of CFTR mutations. A new triple combination of CFTR modulators (elexacaftor+tezacaftor+ivacaftor) appears to be an effective and safe option for patients with at least one *F508del* allele.[15,16]

In view of the many advances in the management of CF in recent years, it is recommended that even proven effective treatments, such as dornase alfa and chronic *P. aeruginosa* suppression therapy, be reassessed in the future, given the greater access to CFTR modulators in eligible patients.

Regarding the other interventions evaluated, the expert panel was not able to issue an evidence-based recommendation because of the low quality of the evidence obtained for the eradication of *P. aeruginosa*, MRSA, and *B. cepacia* complex. More studies on the topic are needed in order to make a

Chart 5. Summary of recommendations for pulmonary pharmacological treatment in cystic fibrosis.

Question	Recommendation	Grade of recommendation	Quality of evidence
1. Should we recommend treatment with ivacaftor in patients with CF who carry class III (gating) or class IV (conduction) mutations in the *CFTR* gene?	We suggest the use	Conditional	Very low
2. Should we recommend treatment with lumacaftor+ivacaftor in CF patients homozygous for the *F508del* mutation?	We do not suggest the use	Conditional	Very low
3. Should we recommend treatment with tezacaftor+ivacaftor in CF patients homozygous for *F508del* or heterozygous for *F508del* and with residual function mutations?	We suggest the use	Conditional	Very low
4. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection?	No recommendation		
5. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection	We suggest the use	Conditional	Very low
6. Should we recommend antimicrobial eradication treatment in CF patients with MRSA colonization of the airways?	No recommendation		
7. Should we recommend nebulized dornase alfa for CF patients ≥ 6 years of age?	We suggest the use	Conditional	Very low
8. Should we recommend antimicrobial eradication treatment in CF patients with airway colonization by *Burkholderia cepacia* complex strains?	No recommendation		

CF: cystic fibrosis; and MRSA: methicillin-resistant *Staphylococcus aureus*.

formal recommendation. However, clinical physicians must evaluate the particularities of each patient and recognize the possible benefits of these therapies in selected cases.

It should be borne in mind that these guidelines sought to answer questions regarding only eight of the main pharmacological interventions for the treatment of the respiratory consequences of CF. Other therapies, such as nebulization with hypertonic saline and long-term use of macrolides, were not evaluated in these guidelines. That does not mean that such therapies do not present clinical benefits or that they cannot be used according to their own eligibility criteria. Nonpharmacological care, including vaccination, physical activity, respiratory physiotherapy, and pulmonary rehabilitation, is also essential in the management of CF. Finally, because CF is a multisystemic disease, the patient must be cared for in a multidisciplinary way, involving gastrointestinal, endocrinological, and otolaryngological aspects that were not within the scope of these guidelines.[7]

It is important to clarify that the very low quality of evidence for some recommendations does not mean that they should not be considered or implemented. In these guidelines, it was decided that RCT and observational studies should be included, with the aim of better evaluating the effect of some therapies approved many years ago for CF. This strategy allows the evaluation of a large sample of patients with high external validity. However, it increases the uncertainty of the results because of the biases inherent to the different study designs. It is important to emphasize that the consistent finding of results in RCT and observational studies favors the clinical applicability of these interventions for a greater proportion of patients with CF. In addition, our recommendations are in line with those of other international guidelines.[8]

We believe that these guidelines constitute an important tool to be incorporated into the approach to patients with CF, mainly aiming to favor its management, as well as helping define public policies related to the disease.

ACKNOWLEDGMENTS

We would like to thank Dr. Anna Menezes and Dr. Fernando Wehrmeister for the methodological and statistical support during the development of this project.

AUTHOR CONTRIBUTIONS

All of the authors actively participated in the process of devising these guidelines and were involved in the formulation of the questions, the choice of outcomes to be evaluated, and the reviewing of the obtained results. All of the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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