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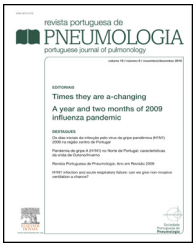

REVIEW

New advances in the therapy of non-cystic fibrosis bronchiectasis

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Abstract Non-cystic fibrosis bronchiectasis remains a common and important respiratory disease to date. It is a chronic pathology and consequently the patients usually require continuous treatment.

In recent decades therapies that do not have scientific evidence of their benefits have been commonly used in non-cystic fibrosis bronchiectasis. Cystic fibrosis has provided the experience to extrapolate therapeutic approaches to other bronchiectasis patients. Finally, in the last few years some trials have been carried out specifically in non-cystic fibrosis bronchiectasis which aim to assess the efficacy of some of the treatments which are commonly used but sometimes without clear indication.

This review will discuss the recent results from these trials, namely mucoactive, anti-inflammatory and antibiotic therapy. Several trials are ongoing and we hope they will be able to add clarification to the management of these patients.

PALAVRAS-CHAVE
Bronquiectasia não-fibrose cística;
Avanços;
Mucoactivo;
Anti-inflamatório;
Antibiótico;
Terapia

Novos avanços no tratamento da Bronquiectasia não-fibrose cística

Resumo As bronquiectasias não-fibrose quística continuam a ser uma doença respiratória comum e importante. Trata-se de uma patologia crónica e, consequentemente, os doentes geralmente precisam de um tratamento contínuo.

Nas últimas décadas, tratamentos sem evidência científica dos seus benefícios foram comumente usadas nas bronquiectasias não-fibrose quística. A fibrose quística serviu de experiência para extrapolar a abordagem terapêutica para outros doentes com bronquiectasias. Finalmente, nos últimos anos, foram realizados alguns ensaios bronquiectasias não-fibrose quística que visam avaliar a eficácia de alguns dos tratamentos que são comummente usados mas por vezes sem uma clara indicação.

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Nesta revisão serão apresentados os resultados recentes destes ensaios, nomeadamente sobre o tratamento mucoactivo, anti-inflamatório e antibiótico. Diversos estudos estão a decorrer e esperamos que estes venham a esclarecer a abordagem mais adequada destes doentes.

Introduction

Bronchiectasis (BE) is an abnormal and irreversible dilation of the bronchi, which has numerous causes. Its frequency depends on the patient's age and sex, social and economic conditions and the degree of applied investigation.

There was little interest in the investigation of non-cystic fibrosis BE, this includes therapeutic approaches, in the last few decades, probably due to supposedly low prevalence and the assumption that treatment is the same for all patients and that little can be done to change the symptoms and evolution.

The publication of diagnosis and treatment reviews in the last few years[1,2] demonstrates a growing interest in this pathology. The level of evidence for most recommendations however is low, because of the absence of large double-blind, placebo-controlled trials.[3,4]

The existence of strong evidence supporting the use of some drugs in patients with cystic fibrosis (CF) does not mean that they will be good for patients with BE of another etiology. So, it is not correct to extrapolate the CF trial results to the non-CF patients.

In CF, the forced expiratory volume in 1 s (FEV1) is one of the most important trial end-points. In non-CF BE it has been difficult to establish appropriate end-points to evaluate the effect of new therapeutic interventions. To date it seems that improvement in quality of life is one of the most important outcome measures.[5]

BE is characterized by a vicious cycle of infection, inflammation and further sputum production. In this review we decided to focus on three important pharmacological groups that aim to interfere with each part of the cycle and in which there have been relevant advances. Nevertheless, BE treatment should be embraced and specific therapies for the underlying cause as well as interventions like physiotherapy, pulmonary rehabilitation, nutritional support and, in selected patients, surgical intervention need to be kept in mind.

Mucoactive therapy

Regardless of the cause, BE is mainly characterized by bronchial infection and persistent inflammation which could be the cause and consequence of impaired airway mucous clearance. The mucus progressively becomes viscous due to the presence of inflammatory cells, microorganisms and large polymers and turns into sputum, overwhelming the ciliary clearance capacity.[6]

The mucus clearance requires a balance between periciliary liquid volume, mucus composition and volume and normal ciliary beat frequency.[6] One of these steps could be more particularly affected depending on the cause of BE; the therapeutic intervention should ideally be focused on the main mechanism.[7] Unfortunately in many cases this is not clear and there is probably a mix of mechanisms involved so the development of combined therapies would be more appropriate.

Table 1 Comparison between mannitol and hypertonic saline.

Hyperosmolar agent	Mannitol	Hypertonic saline
Dose	400 mg bid	6 or 7% bid
Delivery	By an inhaler	By nebulizer
Duration of effect	Sustained (up to 24 h)	Short

The pathogenesis process mostly accepted in CF indicates a relative dehydration and a reduction in airway surface liquid volume.[8] Therefore airway hydration is an important goal in the overall therapeutic management of this disease. However, it is generally accepted that even in the absence of dehydration the increase in water improves mucus clearance by decreasing surface interactions.[9] In this context the most recent advances in the treatment of mucociliary dysfunction are targeted at increasing hydration on airway surface by inhaled hyperosmolar agents, like mannitol and hypertonic saline (Table 1). Both the agents increase the osmolarity of the airway surface fluid causing influx of water into the airway and reducing the viscoelastic properties of the mucus by breaking some of the mucin bonds.[10]

As inhalation of hyperosmolar agents may induce airway narrowing and a reduction in FEV1 of about 15% in sensitive subjects, an assessment of bronchial hyperresponsiveness is recommended before starting treatment.[11,12]

Mannitol

Mannitol is a nonionic sugar alcohol, commonly used as an osmotic agent, which increases mucus clearance. The precise mechanism of this action is unknown.[9] Studies have demonstrated that the effect of mannitol is acute rather than cumulative but it has a sustained effect for up to 24 h. The mucociliary clearance effect was also found in all regions of the lung, including the peripheral region.[13]

Mannitol capsules (40 mg) which contain dry powder for inhalation using an inhaler device are commercially available.[12] They have been approved for the treatment of CF in adults aged $\geq$18 years. The recommended dose is 400 mg (which requires the inhalation of the content of