Review Article

Inhaled antibiotics in bronchiectasis

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ABSTRACT

The presence of chronic infections in patients with respiratory diseases has led to an increased interest in inhaled antibiotics. Their utility has been demonstrated in cystic fibrosis (CF) and extended their use to chronic obstructive pulmonary disease and non-CF bronchiectasis (BE). We have seen a development of new inhaled formulations and nebulizers in the last years. The main objective is to reduce the airway bacterial load, symptoms and the rate and severity of exacerbations. Actual BE guidelines recommend inhaled antibiotics when a patient has 3 or more exacerbations per year. Recent meta-analysis shows an overall benefit for BE patients with inhaled antibiotics. Nowadays, there are different nebulizer systems such as ultrasonic nebulization, "jet" nebulizer, and vibrating mesh system. In addition, there are several antibiotic formulations for nebulization and some dry powder formulations. We review the current evidence available for inhaled antibiotics in BE patients and the systems designed for the inhalation of antibiotics.

Key words: Bronchiectasis, inhaled antibiotics, nebulizer

INTRODUCTION

The interest on inhaled antibiotics has been constantly increasing in the last years due to diffusion of their use for the treatment of respiratory infections. So much interest is possibly due to multiple factors like the important role of chronic infections in patients with respiratory diseases (cystic fibrosis [CF], bronchiectasis (BE), and chronic obstructive pulmonary disease [COPD]) and the growing development of antibiotic formulations for inhaled administration and more effective and faster devices for inhaled medications.

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The use of inhaled antibiotics together with systemic medications is already a practice largely diffused in the intensive care units for the treatment of severe respiratory infections (nosocomial pneumonia, immunocompromised patients, etc.) although the evidence level is modest due to the lack of randomized clinical trials and the complexity of critical patients.[1]

On the other hand, at the end of 70's, it has been demonstrated that the use of inhaled antibiotics in CF could significantly improve the natural history of the disease.[2,3] These findings generate the hypothesis to extend their use to other chronic respiratory infections such as in non-CF BE or COPD.[4]

Finally, we have seen in the last decade the progressive development of new formulations specifically created for the inhaled administration (nebulizer solution or dry powder) contrary to the intravenous formulation that has been used for nebulizing in the past.

Nowadays, the inhaled antibiotics appear as an old treatment with new perspectives and their indications possibly will be updated in the nearly future with optimization of their tolerance and more scientific evidence.

INHALED ANTIBIOTICS IN BRONCHIECTASIS

Bronchiectasis are an anatomic and pathologic alteration of the bronchial structure, more frequent than those associated with CF although limited epidemiological data are currently available (prevalence: CF, 1:5000 in newborns; BE, 1:1900[5] in general population or 1:90 in population >65 years old in USA).[6] In some regions, the prevalence of BE is particularly high possibly due to socioeconomics factors and the high prevalence of pulmonary tuberculosis or limited access to health system (Korea, 9.1% of adults; Australia, 2% of aboriginal children).[7,8]

The BE have many different causes (postinfectious, immunodeficiencies, ciliary dyskinesia, and rheumatoid arthritis) but frequently, it is not possible to identify a clear cause in up to 50% of the causes and they are often classified as idiopathic.[9-12]

Despite the different etiologies of BE, they are usually characterized by chronic symptoms (cough, expectoration, recurrent respiratory infections, hemoptysis, asthenia, etc.), poor quality-of-life (QOL)[13-15] and frequent chronic respiratory infections that are reported in 60% of main BE series (*Pseudomonas aeruginosa*, *Haemophilus influenzae*, etc.).[16,17] In particular, the chronic infection by *P. aeruginosa* has been described as a factor that increases 4 times (odds ratio: 3.61) the risk of mortality.[18] And in the last years, an increased rate of *P. aeruginosa* has been described both in Europe and Northern America and, in particular, a rising concern has grown about the emergence of multi-resistant strains as a consequence of the frequent antibiotic use, specially quinolones (ciprofloxacin), for the treatment of exacerbations.[16,17]

On the other hand, several studies have confirmed that chronic airways infection is associated with a higher degree of local and systemic inflammation, as well as with worse outcomes (exacerbations, functional deterioration, and mortality).[18-23] For the opposite, Chalmers *et al*. described that the antibiotic therapy, in short- or long-term, can attenuate the local or systemic inflammation and positively influence disease process.[24] In addition, epidemiological data described a major sociosanitary impact with a mean cost per BE hospitalization of 2700 pounds according to an English audit in 2011.[25] In addition, a North-American study has calculated an annual cost of 13,244 US dollars per patient, higher than the expected mean expense for COPD.[5] Moreover, it has also been calculated that 9% of patients died during 9 years follow-up, a mortality rate similar to multiple sclerosis.[26]

Is a fact that many patients labeled during years as COPD, as "chronic bronchitis" has finally been diagnosed of BE with a delay of >15 years in many cases.[27] In the last years, different studies have described that patients with both COPD and BE have a worse long-term prognosis suggesting the importance to identify this clinical entity through specific factors (frequent exacerbations, *P. aeruginosa* etc.) in order to optimize treatment and long-term clinical management.[4,28-30]

For all these reasons and based on the good experience in CF, the use of inhaled antibiotics in short- and long-term has been extended to patients with BE.

The impact of chronic infection in natural history of BE has been described in several studies in terms of increased symptoms and exacerbation rate, deterioration of lung function over time, worse QOL and functional limitation, increased long-term mortality, and healthcare expenses.[5,17,18,20,23]

Accordingly, inhaled antibiotics have been used in order to control chronic airway infections through high local (airways) concentrations, low risk of antibiotic resistance, and minimal systemic effects.

The main objective is primarily to reduce the bacterial load as a cause of the increase in local and systemic inflammation, symptoms and to reduce the rate and severity of exacerbations. Currently, there are no studies that clearly define if exacerbations are consequences of a new infection or a result of increased bacterial load of a strain chronically present. Even so, it is commonly assumed that many exacerbations are caused by the chronically "colonizing" pathogen, and the initial empiric treatment should always cover it.[9,11]

Among the different therapeutic options (pharmacological or not) for the long-term control of bacterial load, the inhaled antibiotics are an essential tool in order to reduce symptoms, exacerbations, use of systemic antibiotics, functional decline, and health care spending.

Therefore, clinical guidelines (BTS, SEPAR), despite the lack of an approved treatments, recommend the use of inhaled antibiotics when 3 or more exacerbations per year occur, or in case of fewer exacerbations but with a significant morbidity (subjects with severe bronchorrhea and limitation of activities of daily living).[9,11] In fact, the few data available from Spanish and American registries report that approximately 10% of BE patients are currently on inhaled antibiotics.

Similarly to CF, nebulized tobramycin was one of the first antibiotics evaluated for treatment of chronic infection in BE with a good microbiological response and a reduction of the usual symptoms. However, tobramycin trials described no apparent changes in lung function (spirometry), several cases of intolerance and side effects (such bronchospasm and cough), and some cases of antibiotic resistance (increase in

minimal inhibitory concentration [MIC] of tobramycin); nonetheless, the small number of cases investigated so fare makes difficult to achieve definitive conclusions about the risk of long-term antibiotic resistance with this antibiotic.[31-34]

In the last years, the use of inhaled colistin has spread vastly, mainly for two reasons that facilitate its administration:

1. Its good tolerance, mainly due to its administration by the "I-Neb" (a nebulizer of new generation with a vibratory mesh), and
2. Also the limited cases of microbial resistance to this drug. As a confirmation of it, the audit carried out in Great Britain between 2010 and 2011 about the use of inhaled antibiotics in clinical practice has described that 76% of patients were or had taken nebulized colistin.[25]

Most trials with colistin described good microbiological response and a substantial reduction in sputum production and the risk of hospitalization[35,36] and in some cases, a sustained eradication of infection by *P. aeruginosa* was also obtained when colistin was administered in combination with another systemic antibiotic.[37]

It is possible that new inhaled formulations (dry powder) will be assessed in future in parallel as has been done in CF with promising results.[38]

Other antibiotics have been evaluated in BE including "old generation" drugs as gentamicin that used for 12 consecutive months showed a significant reduction in the frequency of exacerbations with an eradication rate above expectations, 30.8% eradication in those infected with *P. aeruginosa* and 92.8% eradication in those infected with other pathogens.[39]

A European multicenter phase II trial has evaluated the efficacy of a formulation of ciprofloxacin powder administered 2 times a day for a month compared to placebo.[40] The study has clearly demonstrated a reduction in bacterial load (-3.62 $\log_{10}$ CFU) and a rate of side effects similar to placebo. Unfortunately, the short duration of the study (1-month) cannot allow conclusions about the most relevant clinical outcomes in BE as QOL and the frequency of exacerbations but showed a non-significant trend toward a better QOL (-3.6 points in questionnaire Saint George) and to a reduction of exacerbations. To fill this gap, a new long-term trial (48 weeks) with this formulation of ciprofloxacin dry powder is expected by 2017 (NCT01764841).

Other formulations are also being investigated such as the liposomal ciprofloxacin (LC) in order to improve its absorption and tolerance (one administration daily). An Australian/New Zealand phase II trial investigated the use of LC during 3 cycles of treatment (28 days on/28 days off) in subjects with ciprofloxacin-sensitive *P. aeruginosa* chronic infection.[41] The trial achieved the primary outcome of a significant reduction of bacterial sputum load (LC, -4.2 vs. placebo -0.1 $\log_{10}$ CFU) at day 28 and also a delayed time to first pulmonary exacerbation (134 vs. 58 days). No significant differences were observed in forced expiratory volume 1, Saint George questionnaire or 6 min walk test distance. In addition, no differences in MIC and rates of side effects were described between the two groups showing LC was safe and well-tolerated.[41]

Finally, aztreonam for inhalation solution (AZLI) was assessed (75 mg 3 times daily) in Gram-negative organism infection in BE patients based on the excellent results described in CF with the primary objective to investigate possible changes in QOL. AIR-BX1 and AIR-BX2 were two double-blind randomized phase 3 that showed no significant differences in QOL between AZLI group and placebo (it improved similarly in both arms of treatment), and the treatment-related adverse events were more common in AZLI group.[42] Some issues that could explain this result could be the heterogeneity of patients from USA and Europe, differences in etiologies distribution, different Gram-negative pathogens, etc.

Clearly, despite the general positive trend, more investigation is needed to define protocols of intervention with inhaled antibiotic (specific indications according to pathogens and patients characteristic) in BE.

Recent meta-analysis show however an overall benefit for BE patients treated with inhaled antibiotics.[43,44]

NEBULIZERS

A key aspect for treatment with inhaled antibiotics is the fulfillment of treatment, especially in children and working adults for whom a correct drug inhalation can be difficult to reconcile with the daily routine.

Furthermore, the tolerance and efficacy of inhaled antibiotic treatment are strictly linked to drugs' characteristics (density, viscosity, surface tension, pH between 6.5 and 7.5, osmolarity between 159 and 550 mOsm/kg, aerodynamic diameter of the particles between 1 and 5 μm) and to nebulizer. In fact, there are several formulations for nebulization (levofloxacin, aztreonam, tobramycin, colistimethate sodium), several nebulizers (ultrasonic, jet, and vibrating mesh) and some dry powder formulations (ciprofloxacin, tobramycin, and colistin); although the availability of both formulations vary from country to country.

It is, therefore, important to know how to choose the most appropriate nebulizer based on availability and formulation of the drug and the characteristics and tolerance of the patient. A general recommendation is usually to check the patient's ability to take the medication and its tolerance at the beginning of each treatment.

Other factors influence the drug deposition into the lungs such as the respiratory pattern, airway anatomy, and size of inhaled particles. We obtain a range or very different particle diameter with each nebulization. It is important to know the geometric standard deviation as a measure of dispersion of particles diameter obtained and that particles of diameter <1 μm can easily be absorbed in the alveoli and into the blood (with possible systemic effects), while particles >5 μm particles are deposited almost exclusively in the mouth, trachea, and main bronchi with no therapeutic effect. However, it is important to remember that the drug deposition in the lungs usually not exceed 20% of the inhaled drug even using the best available nebulizer.

Currently, there are different nebulizer systems such as ultrasonic nebulization (which is not usually used with antibiotics because of the risk of heat denaturation), and the "jet" nebulizer with high flows and vibrating mesh.

Jet nebulizer is distinguished in:

1. Constant debit nebulizers that nebulize continuously (inspiratory and expiratory phase) with loss of at least 70% of the drug and risk of environmental contamination and requires a minimum of 30-40 min for complete nebulization process (preparation, nebulization, and cleaning);
2. Jet nebulizer with Venturi effect that is only active during inspiration and in some cases with expiratory valves and lower loss drug (Ventstream, Pari LC Plus); and
3. Dosimetric jet nebulizer (Akita) that fit the patient's expiratory flow with almost no loss drug.

Finally, vibrating mesh nebulizers "E-Flow" type offer the advantage of nebulization times between 2 and 5 min (7-10 min with preparation and cleaning). The effectiveness of this nebulizer is superior to jet nebulizers because of the greater uniformity in the diameter of therapeutic particles obtained (1-5 μm) allowing a greater pulmonary distribution of the drug. On the other hand, we have to remember that in case of nebulized bronchodilators (such as salbutamol) we should reduce the dose by the risk of major side effects (tremor, tachycardia, etc.) secondary to their greater absorption.

The last generation of vibrating mesh nebulizer is represented by the device called "I-Neb AAD" (Phillips Respironics) that combine mesh technology and dosimetric release, and is currently available only for inhaled colistin (Promixin, Zambon-Praxis) and for Iloprost (Ventavis) for the treatment of pulmonary hypertension. This device has small dimensions and does not need a power source or long time for nebulization (2-4 min). Its internal microchip is able to memorize the breathing pattern of patient to adapt the dispensing of the drug to the inspiratory time to facilitate lung deposition of the drug and prevent its loss in the expiratory phase.

Finally, there are some dry powder inhaled antibiotics (Novartis Pulmosphere technology, Tobi, Ciprofloxacin phase II) that can be administered similar to inhalers used in chronic respiratory diseases (bronchodilators, corticosteroids, etc.).

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