**Inhaled antibiotics in non-cystic fibrosis bronchiectasis: better than oral antibiotics?**

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**SUMMARY**

Non-cystic fibrosis (non-CF) bronchiectasis is a chronic disorder of the major airways characterized by permanent dilation and destruction [1]. The origin of bronchiectasis varies, but the presence of microbial infection and a persistent inflammatory response are characteristic for the disease [2,3].

Recently Quint et al [4] studied the incidence of bronchiectasis in the UK during the period between 2004 and 2013. Across all age groups, the incidence in women increased from 21.2 per 100000 person-years in 2004 to 35.2 per 100000 person-years in 2013 and in men from 18.2 per 100000 person-years in 2004 to 26.9 per 100000 person-years in 2013. Moreover, bronchiectasis is also associated with a markedly increased mortality. The reasons for the overall increased incidence are not clear, but may be due to improved diagnosis rates, with increased use of computed tomography (CT) scans to assess patients with lung disease.

Colonisation of the airway by bacteria stimulates an inflammatory response, which can become chronic if the infection is not eradicated [5]. Chronic inflammation causes host-mediated lung damage leading to a vicious cycle of events and decline in lung function[5]. This vicious cycle of infection and inflammation periodically develops into pulmonary exacerbations that are characterized by the following symptoms: changes in sputum production and purulence, increased dyspnoea, cough, wheezing, fever and fatigue. These exacerbations maybe associated with changes in chest sounds, radiographic abnormalities, but also lead to a decreased exercise tolerance and lung function decline6. Bacteria isolated from the sputum of patients with bronchiectasis include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and other gram-negative bacteria including *Pseudomonas aeruginosa*[7]. *P. aeruginosa* may appear later in the disease and causes more extensive and severe symptoms than the other bacteria [8]. Non-CF bronchiectasis patients with *P. aeruginosa* infection have more hospitalizations, a worse quality of life (QoL), and a more rapid decline in lung function than patients with other lung infections [9-11]. For other Gram-negative bacteria the progression of bronchiectasis as disease is less well known. Treatment of patients with non-CF bronchiectasis consists of postural physiotherapy, therapy with bronchodilators if reversible airflow obstruction is present, and sometimes inhaled corticosteroids as a local anti-inflammatory agent. Treatment of recurrent respiratory infections is the cornerstone in patients with chronic suppurrative lung disease. In the past, different studies with long-term oral antibiotic therapy were performed. These studies reported controversial outcomes [12].

For decades, long-term macrolide treatments have been reserved for patients with relatively uncommon conditions such as cystic fibrosis and diffuse panbronchiolitis and perhaps the odd bronchiectasis patient with unusually severe symptoms. The work of action is unclear, but long-term macrolide has been considered as immunomodulating therapy and not as antimicrobial therapy [13].

Three RCTs were performed looking at the long-term effect of macrolides in non-CF bronchiectasis [14-16]. They found that prolonged therapy with azithromycin or erythromycin provides benefit, especially in reducing the risk of future exacerbations and hospitalisations. In the BAT trial also an effect on health-related Quality of Life and lung function has been demonstrated [14]. The used
antibiotics were well tolerated without significant differences in side effects. However, antibiotic resistance is a matter of concern.

Antibiotics frequently fail to eradicate lung infections despite intensive therapy. In addition, relapse may occur when the antibiotics are stopped, and resistance frequently occurs with long-term use of systemic antibiotics [9]. An attractive alternative is the use of an inhaled antibiotic that delivers drug in high concentrations directly to the site of infection, eliminating the need for high systemic concentrations and reducing the risk of systemic toxicity or gastrointestinal side effects.

Different kind of inhaled antibiotics (solution or liposomal) has been studied: tobramycin, gentamycin, amikacin, aztreonam, ciprofloxacin, colistin and ceftazidime) [17].

Most studies included only patients with positive sputum cultures for *Pseudomonas aeruginosa* (PA) and were initiated by pharmaceutical companies. Tobramycin inhalation solution (TIS) has been introduced for the long-term management of chronic PA infection, with a Cochrane review suggesting some benefit from TIS in terms of lung function and pulmonary exacerbation rate but also concern regarding an increase in antibiotic resistance [12].

Three meta-analysis were performed with the conclusion that these antibiotics can effectively reduce the sputum bacterial density, increase PA eradication, and attenuate the risk of exacerbation [17-19]. However, these inhaled antibiotics are associated with a higher risk of cough and bronchospasm.

Dry powder inhalers (DPIs) are primarily developed delivering antibiotics for the suppressive treatment of PA in cystic fibrosis. It is an increasingly replacing time-consuming nebuliser therapy [20].

Non-inferiority studies in CF have shown that the efficacy of inhaled tobramycin delivered by DPI was similar to that of wet nebulisation. However, there are many differences between inhaled antibiotic therapy delivered by DPI and by nebuliser. The question is whether and to what extent inhalation technique and other patient-related factors affect the efficacy of antibiotics delivered by DPI compared with nebulisers.

Only one clinical study with DPIs in non-CF patients with bronchiectasis has been performed. Wilson et al. [21] used dry powder ciprofloxacin and found a significant reduction of sputum bacterial load from baseline to day 28. In 35% of the ciprofloxacin group, PA was eradicated at the end of treatment. The rates of bronchospasm were low. Further investigations with different inhaled antibiotics are necessary to evaluate the effect on the exacerbation rate, lung function and health-related Quality of Life. One have to keep in mind that DPIs require training to optimise the inhalation manoeuvre.

Non-CF bronchiectasis has regained more attention during the last decade. Patients with this disease have often poor Quality of Life, increase health care use, and poor outcome. However, a better understanding of exacerbations has gained. Newer tools evaluating severity (LRTI-VAS) and Quality of Life (QOL-B) have also been studied [22-23]. Antibiotic treatment has been used in exacerbations, but is more and more used as long-term treatment.

Several studies examining the benefits of chronic macrolide therapy and inhaled antibiotics were performed with promising results. Further studies of better quality are needed and should be appropriate powered and of adequate duration. They should have standardised endpoints and report baseline characteristics, extent of disease, disease burden and co-morbidities.
REFERENCES

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