The role of antibiotics in acute exacerbations of chronic obstructive pneumonology disease

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According to the “British hypothesis”, which was first put forward in the 1950s, both recurrent infections of the airways and excessive secretion of mucus were considered to be major causes of chronic obstructive pneumonology disease (COPD). It has not been possible to correlate the rate of acute exacerbations of COPD (AE-COPD) with the secretion of mucus and airway obstruction, but the isolation of bacteria in the mucus of patients with COPD was shown to be significant in both stable COPD and AE-COPD. The infection itself was thought to play only a limited role in the pathogenesis of COPD. In the last two decades, molecular and immunological studies and cytological evidence have shown that infection is a major cause of COPD exacerbations and plays an important role in the pathogenesis of the disease.

It is estimated that 50% of AE-COPD are caused by a bacterial infection. Specifically, *Haemophilus influenzae* is responsible for nearly 20-30% of COPD exacerbations, *Streptococcus pneumoniae* for 10-15%, *Moraxella catarrhalis* for 10-15% and *Pseudomonas aeruginosa* for 5-10%. In addition, viral infections cause almost 50% of exacerbations in patients with COPD and specifically, rinovirus (RV) causes 20-25% of exacerbations, parainfluenza virus 20-25%, influenza virus 5-10%, respiratory syncytial virus (RSV) 5-10%, and various other viruses at lower rates. Atypical infections (*Chlamydia pneumoniae, Mycoplasma pneumoniae*) are found responsible in 4-7% of COPD exacerbations.

It should be mentioned that an infection does not always cause an exacerbation of COPD. The result depends on the interactions between the infective agent and the host protective mechanisms; for example, certain strains of *Haemophilus* that may cause AE-COPD have increased ability to adhere to epithelial cells, unlike the strains of *Haemophilus* that do not lead to exacerbations. The host immunity status also plays an important role. Host immune deficiency in COPD is responsible for the establishment of a bacterial population in the airways.

Bacteria are not present in the airways and the alveoli of normal individuals because of effective local immune mechanisms. In patients with COPD, however, these protective mechanisms appear to be weakened. A major problem is impaired mucociliary clearance, which is a characteristic of smokers. The mucus that covers the respiratory epithelium is rich in antimicrobial peptides (cationic proteins, etc.). The concentration of proteins...
A and D in the surfactant is reduced in smokers. In other patients the reduced level of lysozyme in saliva is correlated to frequent exacerbations. The alveolar macrophages may have impaired activity against *Haemophilus* and a reduced response against its antigens.

The epithelial cells of the Airways have a double protective action; they act as a physical barrier and they orchestrate immune mechanisms, together with the macrophages. Certain pathogens have increased the ability to adhere to the impaired epithelial cells in the oropharynx of smokers.

Specific receptors for the pathogens are utilized to identify microbes, such as the TLR receptors. A reduction in the expression of TLR-2 receptors is a characteristic of the alveolar macrophages of patients with COPD. In general, it can be said that the presence of various microbes (bacteria, viruses, fungi) leads to impaired function of the immune mechanisms that play an important role in the immune response in COPD, resulting in airway inflammation and increased mucus production. In this way infection of the lower respiratory tract is started.

The resulting inflammatory response allows the local aggregation of more bacteria, the outcome of which is microbial colonization of the Airways. *H. influenzae* and *Ps. aeruginosa*, in particular, are bacteria which are more usually found in COPD, causing increased mucus production and leading to impairment of mucociliary clearance and destruction of the epithelium.

An important question, therefore, is what is the role of antibiotics in AE-COPD?

Undoubtedly, antibiotics are widely used in the treatment of patients with COPD, but it is well known that almost half of acute exacerbations of COPD are caused by viral infections. A specific mechanism to explain the initiation of an AE-COPD by viral infection has not yet been ascertained, but there is evidence that rhinoviruses affect alveolar cells, and viral infections produce inflammatory mediators and cytokines. As a rule, antibiotics should be used only if the patient produces purulent sputum, or when sputum production is increased, or when dyspnoea is intensified. A meta-analysis of studies of AE-COPD conducted between 1966 and 1992 provided the data on which the above recommendations are based. It appears that the use of antibiotics reduces mortality and increases the possibility of curing the exacerbation. The most important study in the field was accomplished by Anthonisen and co-workers, according to which 3 types of exacerbations of COPD can be identified: Type A, characterized by an increase in dyspnoea, mucus production and the presence of purulent sputum, Type B characterized by the presence of two of the above symptoms, and Type C characterized by one of the above symptoms, plus fever or inflammation of the upper Airways. The administration of antibiotics is beneficial especially in type A exacerbations, but no significant results can be achieved in type C. It is considered that only types A and B of AE-COPD can benefit from the use of antibiotics.

Purulent sputum is an important criterion for the prescription of antibiotics, but the patients themselves may not be objective in the evaluation of their sputum production and colour. Inflammatory markers, such as C-reactive protein (CRP) and procalcitonin, may increase in an acute exacerbation in patients with COPD, and can be used to evaluate the need for antibiotics.

On an outpatient basis, the use of amoxicillin, tetracycline or amoxicillin/clavulanic acid is common and effective. Ciprofloxacin or levofloxacin are indicated in cases of suspected infection with *Ps. aeruginosa*.

According to Wilson and colleagues, moxifloxacin has an effect similar to that of amoxicillin/clavulanic acid. Moxifloxacin produces improved results only in the case of a positive mucus culture, when the use of antibiotics may also protect from a future COPD exacerbation.

The use of other therapeutic options needs to be considered when considering the use of antibiotics. It is known that the use of inhaled corticosteroids, with or even without β2-agonists can reduce the possibility of a future exacerbation.

Are antibiotics essential in all COPD exacerbations? They are considered not to be essential. The colour of the mucus needs to be taken into consideration. White mucus indicates non purulent mucus production, in which case antibiotic use can be avoided. Administration of antibiotics should not be initiated in the early stages of COPD and patients could benefit from the use of inhaled corticosteroids and β2-agonists.

For those patients who do not show improvement after a short 4-day period antibiotics should be added. Prolonged use of antibiotics should be avoided. Finally, the cost of treatment needs to be taken into consideration, as well as the possibility of development of resistant bacterial strains.

REFERENCES

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