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General review

Probiotics: A new way to fight bacterial pulmonary infections?

Les probiotiques : une nouvelle arme thérapeutique contre les infections respiratoires ?

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Abstract

Antibiotics, of which Fleming has identified the first representative, penicillin, in 1928, allowed dramatical improvement of the treatment of patients presenting with infectious diseases. However, once an antibiotic is used, resistance may develop more or less rapidly in some bacteria. It is thus necessary to develop therapeutic alternatives, such as the use of probiotics, defined by the World Health Organization (WHO) as "micro-organisms which, administered live and in adequate amounts, confer a benefit to the health of the host". The scope of these micro-organisms is broad, concerning many areas including that of infectious diseases, especially respiratory infections. We describe the rational use of probiotics in respiratory tract infections and detail the results of various clinical studies describing the use of probiotics in the management of respiratory infections such as nosocomial or community acquired pneumonia, or on specific grounds such as cystic fibrosis. The results are sometimes contradictory, but the therapeutic potential of probiotics seems promising. Implementing research to understand their mechanisms of action is critical to conduct therapeutic tests based on a specific rational for the strains to be used, the dose, as well as the chosen mode and rhythm of administration.

Keywords: Cystic fibrosis; Hospital-acquired pneumonia; Immunomodulation; Probiotics

Résumé

Les antibiotiques, dont Fleming a identifié le premier représentant, la pénicilline, en 1928, ont permis une amélioration spectaculaire de la prise en charge des patients atteints de maladies infectieuses. Cependant, dès lors qu'un antibiotique est utilisé, des résistances sont mises en évidence plus ou moins rapidement chez certaines bactéries. Aussi il apparaît indispensable de développer des alternatives thérapeutiques, telles que l'utilisation des probiotiques, définis par l'Organisation mondiale de la santé (OMS) comme des « micro-organismes qui, administrés vivants et dans des quantités adéquates, confèrent un bénéfice à la santé de l'hôte ». Le champ d'application de ces micro-organismes est vaste, touchant de nombreux domaines dont celui des maladies infectieuses et en particulier des infections respiratoires. Après avoir exposé l'origine de l'utilisation des probiotiques dans les infections de l'appareil respiratoire, nous détaillerons ici les résultats de différentes études cliniques menées à propos de l'utilisation des probiotiques dans la prise en charge d'infections des voies respiratoires comme celles des pneumonies nosocomiales ou communautaires, ou sur des terrains particuliers comme la mucoviscidose. Les résultats sont certes parfois contradictoires mais le potentiel thérapeutique semble prometteur : la recherche approfondie des mécanismes d'action est essentielle pour construire des essais thérapeutiques reposant sur des données précises concernant la ou les souche(s) utilisée(s), les quantités de bactéries administrées, les voies et les rythmes d'administration choisis.

Mots clés : Immunomodulation ; Mucoviscidose ; Probiotiques ; Pneumonies nosocomiales

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1. Introduction

Microbiology in general and bacteriology in particular have long been used in the medical world via the search for pathogenic bacteria implicated in the etiology of infectious diseases. The discovery of antibiotics by Fleming in 1928 allowed fighting effectively against number of these pathogens and thus considerably improving public healthcare and saving numerous lives. Nevertheless, the massive and sometimes inappropriate use of antibiotics in human, veterinarian, and agronomic practices, for more than 50 years, has promoted the emergence of a great variety of multiresistant bacterial strains throughout the world [1,2]. Even if antibiotics remain today mandatory arms to fight against bacterial infections, the sharp increase of various types of resistance, associated to the low number of new antibiotic agents put on the market, makes it essential to develop new therapeutics approaches.

Today, the knowledge acquired on some microbial ecosystems allows better understanding of the complexity of host to commensal microbiota interactions and their impact on the host's health. Thus the human commensal microbiotas — from the Latin cum, with and mensa, table, literally "table companion" — include a number of species that, integrating in a mutual relationship, have an impact on the host's physiology and participate in maintaining homeostasis [3].

In this context, probiotics (and more precisely the bacteriocin producing strains) could be used for prophylaxis or therapy to fight against bacterial infections [4,5]. The advantages of probiotics compared to antibiotics are their specificity of action and lesser pressure of selection on bacteria. The concept of probiotics is based on a hypothesis made by Elie Metchinikoff, the Nobel Prize winner in physiology and medicine in 1908, in his book *The Prolongation of Life: Optimistic Studies* published in 1907. This hypothesis was that the ingestion of great quantities of lactic acid bacteria, by consuming fermented dairy products, would increase life expectancy by protecting the body from various diseases. The definition of probiotics, first limited to the ingestion of live micro-organisms having a beneficial effect on the host's health by improving the balance and the stability of its intestinal microbiota, has changed in time to adapt to the broadening of organ target and modes of administration. Currently, according to the WHO, probiotics are "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host" [6]. Hence, the use of probiotics has considerably increased and their potential domain of application in human clinical care is extremely wide: allergy, oncology, bowel inflammatory diseases or infectious diseases. In this review, we focused on the contribution of probiotics for the management of respiratory tract infections.

2. Probiotics and their adequate use for respiratory tract infections

The recent use of probiotics in the prophylactic treatment of respiratory tract infections was not due only to the increased resistances of pathogens to antibiotics and to the need to look for alternatives to these agents. Indeed, the use of probiotics in this domain relies of three main factors:

- a better knowledge of the respiratory tract microbiota;
- a better understanding of the mechanisms of action associated to the inhibition of pathogens by probiotics;
- the innocuity of these micro-organisms.

2.1. The respiratory tract microbiota

The knowledge of the respiratory tract microbiota, i.e. all the micro-organisms living in a specific environment, is crucial to take into account the complexity of interactions between the micro-organisms (including probiotics) which make it up as well as interactions between these micro-organisms and their host. The recent molecular biology tools, no longer requiring culture of micro-organisms, has greatly modified our knowledge of the respiratory tract microbiota. Thus, while the lung was still considered very recently as sterile in healthy individuals, it was demonstrated, after analyzing respiratory samples collected at various levels in six healthy individuals (pyrosequencing and quantitative PCR), that bacteria were also present in alveoli and bronchioles [7]. The bacterial communities were identical to those found in the upper respiratory tracts but in much lower levels (2 to 4 logarithmic decrease of concentrations). This similar bacterial population suggests that alveolar bacteria could come from the upper respiratory tracts, and that the colonization of lower airways could be caused by a micro-inhalation mechanism. The authors of another study of the oral microbiota in healthy individuals by pyrosequencing, demonstrated the presence of a common phylogenetic core among individuals, while the others phylotypes were specific for each individual [8].

At the same time, and with the same tools, the pulmonary microbiota was described in patients presenting with various diseases: pneumonia [9], cystic fibrosis [10,11], chronic obstructive bronchitis [12], demonstrating a microbial complexity little studied until now. This understanding of various predominant bacterial phylotypes in healthy individuals and in patients should allow studying the modifications induced in a given microbiota after administrating probiotics.

2.2. The mechanisms of action associated to the inhibition of pathogenic bacteria

In the current state of knowledge, it is estimated that the protective effects of probiotics against pathogenic bacteria relies on the implementation of three types of biological process:

- direct antimicrobial activity;
- reinforcement of the epithelium barrier function;
- immunomodulation (Fig. 1).

This evidence was mostly provided by the authors of numerous studies on the activity of probiotics in the digestive tract, research concerning their use for the respiratory tract having barely been initiated. Nevertheless, some authors have already demonstrated mechanisms of the actions associated with the