International Journal of Infectious Diseases 51 (2016) 113–122

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Bacteria in the respiratory tract—how to treat? Or do not treat?

Cristina Prat [a,b,*], Alicia Lacoma [a,b]

[a] Microbiology Department, Hospital Universitari Germans Trias i Pujol, Institut d'Investigació Germans Trias i Pujol, Universitat Autònoma de Barcelona, Ctra del Canyet s/n, 08916 Badalona, Barcelona, Spain
[b] CIBER Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

ARTICLE INFO

Article history:
Received 18 July 2016
Received in revised form 30 August 2016
Accepted 4 September 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Lower respiratory tract infection
Bacterial colonization
Novel therapeutic approaches
Alternatives to antibiotics
Prudent use of antibiotics

SUMMARY

Background: Acute and chronic respiratory tract infections are a common cause of inappropriate antimicrobial prescription. Antimicrobial therapy leads to the development of resistance and the emergence of opportunistic pathogens that substitute the indigenous microbiota.
Methods: This review explores the major challenges and lines of research to adequately establish the clinical role of bacteria and the indications for antimicrobial treatment, and reviews novel therapeutic approaches.
Results: In patients with chronic pulmonary diseases and structural disturbances of the bronchial tree or the lung parenchyma, clinical and radiographic signs and symptoms are almost constantly present, including a basal inflammatory response. Bacterial adaptative changes and differential phenotypes are described, depending on the clinical role and niche occupied. The respiratory tract has areas that are potentially inaccessible to antimicrobials. Novel therapeutic approaches include new ways of administering antimicrobials that may allow intracellular delivery or delivery across biofilms, targeting the functions essential for infection, such as regulatory systems, or the virulence factors required to cause host damage and disease. Alternatives to antibiotics and antimicrobial adjuvants are under development.
Conclusions: Prudent treatment, novel targets, and improved drug delivery systems will contribute to reduce the emergence of antimicrobial resistance in lower respiratory tract infections.

1. Introduction—a daily clinical and microbiological challenge

As a medical microbiologist, reporting the results of susceptibility testing of a non-primary pathogenic microorganism isolated from the respiratory tract may be discouraging, both when it is susceptible and when it is multidrug-resistant (MDR). The clinical consequence of such a report is often the prescription of antimicrobial treatment, even without clinical symptoms. Therapeutic decisions are a daily clinical challenge. What is the clinical role of a MDR *Pseudomonas aeruginosa* or a methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from the sputum of a chronic pulmonary obstructive disease (COPD) patient with a moderate exacerbation, or when isolated from the endotracheal aspirate of a ventilated patient who simultaneously presents *Escherichia coli* bacteremia?

Huge progress has been made in imaging and bronchoscopic techniques and these have improved the diagnosis of neoplasia, lower respiratory tract infections (LRTI), and tuberculosis. In addition, the development of highly sensitive molecular biology assays and mass spectrometry have increased the detection of respiratory pathogens. However, the clinical role of bacteria whose normal ecological niche is the airways, where healthy carriage dominates over disease, is still an unresolved issue,[1] and very sensitive techniques need to be interpreted with caution. Many efforts have also been directed at identifying novel therapeutic approaches, but it is first crucial to clearly establish when it is really necessary to treat and what the adequate duration of treatment is. The unnecessary use of extended-spectrum antibiotics in patients infected with non-resistant organisms and the inappropriate use of first-line antibiotics in patients infected with resistant organisms contribute to the emergence and spread of resistance.[2,3] Acute and chronic respiratory tract infections are the most frequent causes of antimicrobial prescription in primary care, the hospital setting, and health care facilities.[4] The respiratory tract

* Corresponding author. Tel.: +34 93 497 88 94.
E-mail address: crisprat2010@gmail.com (C. Prat).

http://dx.doi.org/10.1016/j.ijid.2016.09.005

has become one of the biggest reservoirs of MDR variants of microorganisms such as *S. aureus* and *P. aeruginosa*.

Antibiotic resistance is the evolutionary response to the strong selective pressure that results from exposure to the use of these drugs in the clinic and in livestock feed, and it needs to be curtailed.[5] There is a correlation between antimicrobial usage and resistance, increasing from north to south in Europe,[6] although some situations such as the emergence of community-acquired (CA) MRSA epidemics are not so easy to explain.[7] The availability of antibiotics has enabled revolutionary medical interventions such as cancer chemotherapy, organ transplantation, and all major invasive surgeries,[5] but patients are exposed to infections by MDR bacteria, which impacts on morbidity and mortality. The presence of a MDR microorganism is troublesome even when only colonizing, because of its social and economic impact due to the required contact isolation measures.

Antimicrobial usage in LRTI also leads to the emergence of opportunistic pathogens that substitute the indigenous microbiota, such as constitutively resistant non-glucose-fermenting Gram-negative bacilli, Aspergillus, *Actinomycetales*, and environmental mycobacteria.[5] Finally, even when an apparently appropriate therapy is prescribed, the respiratory tract has areas that are potentially inaccessible to antimicrobial entry due to collapse or oedema, but also because of microbial adaptation mechanisms such as biofilm formation and intracellular persistence. Considering all the aforementioned reasons, respiratory tract infections are often mismanaged regarding the correct diagnosis, indication, dosage, and duration of antimicrobial treatment. In addition, the immunity of several opportunistic pathogens adapted to the respiratory tract is not completely understood, so vaccine development remains challenging.[8,9]

2. Microbiological detection: bronchial colonization or respiratory tract infection?

The respiratory tract is not a sterile site,[10] and the composition of the indigenous microbiota evolves in relation to factors such as the hormonal environment, ecological disturbances, and antimicrobial use.[11] The resident microbiome includes microorganisms that are also potential aetiological agents of respiratory tract infections, such as *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, and *S. aureus*. Airway inflammation, altered mucus production, and diminished mucociliary clearance contribute to colonization in several situations. *S. aureus* carriage in the upper airways may be occasional or persistent,[12] and its success as a component of the respiratory flora is determined by its ability to scavenge iron and coordinate gene expression, as well as the horizontal acquisition of useful genetic elements.[13] *S. pneumoniae*[1] and *H. influenzae*[14] are present in the nasopharynx (a highly oxygen-exposed region) of up to 60% of preschool children, as well as in patients with underlying pulmonary diseases. The establishment of colonization is a prerequisite for the development of pneumococcal disease through a combination of virulence factor activity and the ability to evade the early components of the host immune response to compete with other microorganisms.[15] Colonization by *P. aeruginosa* requires an underlying pathology,[16] but it is also possible without active infection.

Quantitative measurements of bacterial load have failed to clear up the situation: respiratory samples are heterogeneous and often not comparable one to another, although bacteriological response is a parameter used in clinical trials to assess efficacy. The validity of microbiological tests is improved by strict case definition and adequate radiographic review, but in the absence of positive blood cultures, a gold standard is lacking and the variability of sputum quality and contamination with oropharyngeal bacteria is still determinant, even when molecular detection is positive.[17] Even a positive urinary antigen detection may be the result of colonization.[18,19] Comprehensive molecular testing including bacterial load quantitation significantly improves pathogen detection and may improve early antimicrobial de-escalation,[20] but PCR is able to detect dead as well as viable bacteria and a clinical improvement is sometimes observed without a decrease in the bacterial inoculum. The recently published hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) guidelines recommend non-invasive sampling with semiquantitative cultures, since the evidence suggests that clinical outcomes are similar regardless of whether specimens are obtained invasively or non-invasively, and whether cultures are performed quantitatively or semiquantitatively, although a lower risk of inadequate initial antibiotic coverage may be observed and facilitates antibiotic de-escalation.[21]

Microorganisms may persist in the respiratory tract for a long time even when prescribed antimicrobials have been expected to be active based on conventional in vitro susceptibility testing.[22] As reviewed below, members of the indigenous microbiota and even newly acquired microorganisms have evolved to adapt,[16] at least temporarily, to the anatomical site and nutrient environment where they secure a niche. A hypothesis is that lymphatic tissue associated with the respiratory tract allows the immune system to contain pathogens and confine them to their carrier niche, and occasional failure and disturbances in homeostasis result in disease.[1]

Infection is the establishment of a microorganism within a host, while infectious disease applies when the interaction causes damage or an altered physiology resulting in clinical signs and symptoms.[23] The distinction is particularly difficult in patients with chronic pulmonary diseases and structural disturbances of the bronchial tree (bronchiectasis) or the lung parenchyma (pulmonary neoplasia, lobectomy/pneumonectomy, or tuberculosis scars) in whom clinical and radiographic signs and symptoms are almost constantly present, including a persistent systemic inflammation.[24]

Several new assays and technologies have come into clinical use, such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and gene expression profiling.[25] This last approach using microarrays has potential value as a diagnostic test, once validated through multi-cohort analyses to identify diagnostic gene sets,[26] since it uses the host response to pathogens as a means of diagnosing infection, rather than direct pathogen detection, or response through a specific biomarker, generating a snapshot of the immune response.[25]

3. Bacterial adaptation to the respiratory tract

For opportunistic pathogens that can either reside asymptomatically or cause symptomatic infections, the definition of success becomes increasingly complex.[27] Bacteria develop adaptative mechanisms to the respiratory tract in order to survive in hostile environments related to factors such as co-infecting species and antimicrobial therapies, as well as lung conditions such as inflammatory response, hypoxia, or nutrient deficiency[16] (Figure 1). Adaptation mechanisms include exopolysaccharide production (mucoid phenotypes), loss in motility, formation of small colony variants (SCV), and an increased mutation rate, as well as changes in quorum sensing (QS) and in the consequent production of virulence factors.

In many cases, especially those associated with indwelling medical devices such as an orotracheal tube, the formation of biofilm may explain the persistent isolation of *S. aureus*, *H. influenzae*, or *P. aeruginosa*. In fact, the natural state of many bacteria is one where they are associated with surfaces, in which acting as a ‘community’ increases their possibility of survival. Biofilm-associated bacteria tend to be less susceptible to treatments