Respiratory Medicine 117 (2016) 190–197

Contents lists available at ScienceDirect

Respiratory Medicine

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

Review article

The effect of *N*-acetylcysteine on biofilms: Implications for the treatment of respiratory tract infections

Francesco Blasi [a], Clive Page [b], Gian Maria Rossolini [c, d, e, f], Lucia Pallecchi [e], Maria Gabriella Matera [g], Paola Rogliani [h, i], Mario Cazzola [h, *]

[a] Department of Pathophysiology and Transplantation, University of Milan, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
[b] The Sackler Institute of Pulmonary Pharmacology, Institute of Pharmaceutical Science, King's College London, United Kingdom
[c] Department of Experimental and Clinical Medicine, University of Florence, Careggi University Hospital, Florence, Italy
[d] Clinical Microbiology and Virology Unit, Careggi University Hospital, Florence, Italy
[e] Department of Medical Biotechnologies, University of Siena, Santa Maria alle Scotte University Hospital, Siena, Italy
[f] Don Carlo Gnocchi Foundation, Florence, Italy
[g] Department of Experimental Medicine, Unit of Pharmacology, Second University of Naples, Naples, Italy
[h] University of Rome Tor Vergata, Department of Systems Medicine, Rome, Italy
[i] University Hospital Tor Vergata, Unit of Respiratory Medicine, Rome, Italy

ARTICLE INFO

Article history:
Received 9 March 2016
Received in revised form
12 June 2016
Accepted 15 June 2016
Available online 16 June 2016

Keywords:
N-acetylcysteine
Biofilm
Airways infections
Topical administration
Inhaled formulation

ABSTRACT

Objectives: In airway infections, biofilm formation has been demonstrated to be responsible for both acute and chronic events, and constitutes a genuine challenge in clinical practice. Difficulty in eradicating biofilms with systemic antibiotics has led clinicians to consider the possible role of non-antibiotic therapy. The aim of this review is to examine current evidence for the use of *N*-acetylcysteine (NAC) in the treatment of biofilm-related respiratory infections.

Methods: Electronic searches of PUBMED up to September 2015 were conducted, searching for 'biofilm', 'respiratory tract infection', '*N*-acetylcysteine', 'cystic fibrosis', 'COPD', 'bronchiectasis', 'otitis', and 'bronchitis' in titles and abstracts. Studies included for review were primarily in English, but a few in Italian were also selected.

Results: Biofilm formation may be involved in many infections, including ventilator-associated pneumonia, cystic fibrosis, bronchiectasis, bronchitis, and upper respiratory airway infections. Many in vitro studies have demonstrated that NAC is effective in inhibiting biofilm formation, disrupting preformed biofilms (both initial and mature), and reducing bacterial viability in biofilms. There are fewer clinical studies on the use of NAC in disruption of biofilm formation, although there is some evidence that NAC alone or in combination with antibiotics can decrease the risk of exacerbations of chronic bronchitis, chronic obstructive pulmonary disease, and rhinosinusitis. However, the usefulness of NAC in the treatment of cystic fibrosis and bronchiectasis is still matter of debate. Most of the studies published to date have used oral or intramuscular NAC formulations.

Conclusions: Evidence from in vitro studies indicates that NAC has good antibacterial properties and the ability to interfere with biofilm formation and disrupt biofilms. Results from clinical studies have provided some encouraging findings that need to be confirmed and expanded using other routes of administration of NAC such as inhalation.

Contents

* Corresponding author.
E-mail address: mario.cazzola@uniroma2.it (M. Cazzola).

http://dx.doi.org/10.1016/j.rmed.2016.06.015
0954-6111/

1. Introduction

Bacteria can exist as single, independent cells (planktonic) or can be organized into sessile aggregates called biofilms. A biofilm is a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface. Acute infections are assumed to involve planktonic bacteria, which are generally treatable with antibiotics, although successful treatment depends on accurate and fast diagnosis, and treatment with an appropriate antibiotic. However, in cases where the bacteria succeed in forming a biofilm within the human host, the infection is often resistant to standard treatment regimes and will therefore develop into a chronic state. Recent advances have demonstrated that biofilms account for most human infections [1,2] and are related to exacerbation or relapse of symptoms. Characteristic features of chronic biofilm-based infections are increased resistance to host defenses and decreased susceptibility to antimicrobial agents. These features make persistent infections difficult or impossible for the immune system to clear and to be eradicated with antibiotics [2,3].

In airway infections, biofilm formation has been demonstrated to be responsible for both acute and chronic events and is a real challenge in clinical practice [1,2]. The observation that systemic antibiotics are not unequivocally effective in eradicating biofilms has led to an increased interest in non-antibiotic therapies. In this review, we discuss the role of biofilms in respiratory infections and current management strategies, focusing on the current evidence regarding the effects of NAC on biofilms.

2. Literature search methodology

Literature searches, conducted in the period August–September 2015, were performed using the PubMed database (with no date limitations), searching with the terms 'biofilm', 'respiratory tract infection', '*N*-acetylcysteine', 'cystic fibrosis', 'COPD', 'bronchiectasis', 'otitis', and 'bronchitis' in titles and abstracts, and restricting the results primarily to articles written in English. A few publications in Italian were also included. The authors examined the resulting lists of abstracts and excluded those that did not fit within the scope of the present review.

2.1. Biofilms in respiratory tract infections

2.1.1. Device-related infections

In ventilator-associated pneumonia (VAP), biofilms are responsible for microbial persistence and impaired response to treatment. Biofilm formation within the first 24 h after intubation has been demonstrated in 95% of endotracheal tubes. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are the most frequent bacteria that colonize the devices [4–6].

2.1.2. Tissue-related infections

2.1.2.1. Cystic fibrosis (CF). In CF, the incidence of bacterial lung infections is high since the mucoid polysaccharidic material that accumulates on the respiratory epithelium due to impaired mucociliary clearance in the bronchi of such patients favors biofilm formation. *P. aeruginosa* is the most common bacterial species involved in respiratory tract infection in CF patients and can be found in about half of all cases and in up to 70% of adults (Cystic Fibrosis Foundation Patient Registry. Annual data report 2013 Cystic Fibrosis Foundation, Bethesda, MD). The ability of *P. aeruginosa* to form biofilms is thought to be the primary reason for its survival in the CF lung, despite an exuberant inflammatory response and intensive antibiotic treatment [7,8]. Other pathogens such as *Burkholderia cepacia* complex, *Staphylococcus aureus*, *Achromobacter xylosoxidans*, and *Stenotrophomonas maltophilia* have also been identified in CF and are related to biofilm formation [9].

2.1.2.2. Chronic obstructive pulmonary disease (COPD). A role of biofilms in patients with COPD has not been directly demonstrated but has been hypothesized considering the evidence indicating that the airways of these patients are frequently colonized by pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. COPD is characterized by frequent exacerbations and resistance to antibiotics. Even if direct evidence of biofilms *in vivo* is lacking, biofilms may reasonably be considered to be involved in the vicious cycle of infection/inflammation leading to disease progression in patients with COPD [10–12]. However, the role of biofilms in acute exacerbations needs to be further investigated (i.e. acute episodes caused by new strains or species compared to those accounting for chronic colonization).

2.1.2.3. Non-cystic fibrosis bronchiectasis. In bronchiectasis not due to CF, infections cause a change in the muscular and elastic components of the bronchial wall, which become distorted and enlarged. Airways slowly become unable to clear mucus, leading to serious lung infections that in turn cause more damage to bronchi. Biofilm formation has recently been demonstrated *in vivo* and is assumed to play a relevant role in the pathophysiological cascade of this disease [13–15]. Bacterial biofilm formation by *P. aeruginosa* or *Klebsiella pneumoniae* is common in bronchiectasis and could be an important factor that makes infections in bronchiectasis intractable. Other pathogens such as *Veilonella* sp., *Prevotella* sp. and *Neisseria* sp. have also been recently identified in patients with bronchiectasis [16,17].

2.1.2.4. Bronchitis. Protracted bacterial bronchitis may be caused by chronic infections of the airways. Especially in children, the condition appears to be secondary to impaired mucociliary clearance that creates an environment favorable for bacteria to become established, often in the form of biofilms [18]. The most commonly involved bacteria include *H. influenzae* (30–70%), *S. pneumonia*, and *M. catarrhalis*.