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Review article

Do orally administered antibiotics reach concentrations in the middle ear sufficient to eradicate planktonic and biofilm bacteria? A review

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ABSTRACT

Introduction: Infectious conditions of the middle ear are a common and significant cause of morbidity and mortality worldwide. Systemic antibiotics are frequently used, but their effectiveness will depend on whether an adequate antibiotic concentration is achieved in the middle ear; this is especially important in biofilm infections such as otitis media with effusion (OME), where high antibiotic concentrations are typically required for effective treatment.
Objective: This review examines what antibiotic levels can be reached in the middle ear with oral administration, as a means of guiding rational antibiotic choice in the clinic and future research, and to determine whether levels high enough for biofilm eradication are reached.
Methods: A literature search of studies measuring levels of antibiotics in the plasma and in the middle ear after oral administration was conducted. These levels were compared to the minimum inhibitory concentrations (MIC) provided by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) to determine if antibiotic doses were reaching sufficient levels to inhibit planktonic bacteria. The middle ear concentrations were then calculated as a multiple of the MIC to determine if the concentrations were reaching biofilm eradication concentrations (typically up to 1000 × MIC).
Results: The highest antibiotic levels against *Staphylococcus aureus* reach 8.3 × MIC, against *Moraxella catarrhalis* 33.2 × MIC, against *Haemophilus influenzae* 31.2 × MIC, and against *Streptococcus pneumoniae* 46.2 × MIC. The macrolide antibiotics reach higher levels in the middle ear than in plasma.
Conclusions: Orally administered antibiotics reach levels above the MIC in the middle ear. However, they do not reach levels that would be likely to eradicate biofilms.

Contents

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1. Introduction

Infections of the middle ear such as acute otitis media (AOM) and otitis media with effusion (OME) are a significant cause of morbidity and mortality worldwide. Successful treatment with systemic antibiotics relies on being able to achieve a sufficiently high concentration in the middle ear fluid to have the desired antimicrobial effect. This is important in the case of free-floating planktonic bacteria, and even more so when one is trying to deal with a biofilm infection such as in OME. A variety of antibiotics are used to treat middle ear infections. This article reviews the antibiotic levels that can be achieved in the middle ear with systemic administration, summarising the various published articles, with the aim of guiding rational antibiotic use especially when biofilm infections are the target. In addition, this information would be useful for researchers contemplating future studies of antibiotic use in middle ear infectious conditions.

AOM and OME are related conditions [1], with AOM being an acute infection (viral or bacterial) with signs and symptoms of inflammation [2], whereas OME is defined by the presence of an effusion with no signs or symptoms of acute inflammation [3]. At least 50–85% of children will have one episode of AOM by three years of age [1], and the treatment of OME with ventilation tubes is one of the commonest surgical procedures in children [4].

1.1. Antibiotics for OME

The aetiology of OME is multifactorial. The main organisms responsible include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. Other organisms such as *Staphylococcus aureus*, streptococci and gram-negative rod bacteria have also been implicated [5–8]. Viruses such as respiratory syncytial virus may contribute to pathogenesis, but are especially important in AOM [9]. Additional aetiological factors include genetic and environmental factors, and Eustachian tube function [10].

Antibiotics are often prescribed for AOM (with clear guidelines in place), and are effective. However, much research has examined the use of antibiotics in OME, but whilst they may be effective in the short term, antibiotics do not appear to affect the long-term outcome of OME [11–13]. This may be because bacterial biofilms are important in the aetiology of OME [14,15]. Biofilms are functional communities of microorganisms attached to a surface (such as mucus or middle ear mucosa) and are surrounded by an exopolysaccharide matrix [16]. One of the defining features of a biofilm is that antibiotic levels 10–1000 higher than the levels sufficient to eradicate free planktonic bacteria are required [17,18]. This is termed recalcitrance and is influenced by a variety of factors (Fig. 1).

Topical antibiotic therapy is often the preferred route of administration when the tympanic membrane is perforated or infection is in the ear canal, as it achieves a localised high antibiotic level with reduced systemic exposure. However, in OME the tympanic membrane is intact, so if antibiotics are required then the route of delivery has to be systemic. This article discusses antibiotic levels that can be achieved with oral administration, as this route is simplest, most convenient, and most acceptable to patients. Furthermore, there is no advantage to using an antibiotic intravenously if it is available orally and has high bioavailability [19]. Therefore, although intravenous administration of some antibiotics may achieve higher levels, the drawbacks of intravenous administration led us to focus on the oral route.

Antibiotics will be effective only if they actually reach sufficiently high levels in the middle ear. Inhibition of planktonic bacteria requires levels above the minimum inhibitory concentration (MIC), which by definition is the minimum concentration of an antimicrobial required to inhibit growth of an isolate in planktonic culture. Simply, MIC is the lowest concentration of antimicrobial that will inhibit visible growth of the bacterial isolate after 24 h incubation on an agar plate in the microbiology laboratory. The MIC of an organism will either be below or above a breakpoint, which correlates with sensitivity or resistance, respectively. MICs of individual isolates of a particular species can be determined in the laboratory setting, but several organisations have set species-specific MICs levels that divide resistant from susceptible isolates; these levels are the MIC breakpoints.

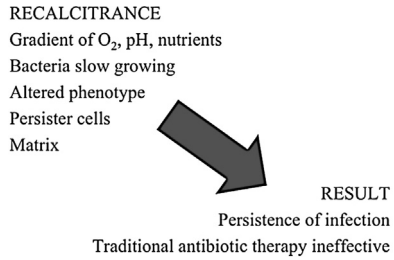

Fig. 1. Factors influencing biofilm recalcitrance. The main factor in recalcitrance is now considered to be the phenotypic modification of bacterial metabolism resulting from enforced slow replication. Energy generation and transport inside the bacteria is critically low, and non-essential functions are down–regulated. In this dormant state, bacterial targets for common groups of antibiotics are no longer active, and anti-cell wall synthesis drugs (betalactams, vancomycin), anti-protein synthesis drugs (aminoglycosides, macrolides, tetracyclines, etc.) and anti-DNA replication agents (quinolones) are orders of magnitude less effective. Matrix refers to the exopolysaccharide matrix of the biofilm.

Achieving levels above the MIC does not guarantee clearance of all bacteria, however. Dagan et al., demonstrated that even though azithromycin reached levels above the MIC in the middle ear for *H. influenzae* and *S. pneumoniae*, this did not correspond with bacteriological cure [20]. In the case of a biofilm being present, achieving the MIC at the target site may not be sufficient for eradicating biofilm. The minimum biofilm—eradicating concentration (MBEC) is typically up to 1000 times higher than MIC. Importantly, antibiotic levels below MBEC (in the case of biofilm infections) not only fail to eradicate biofilms but can promote bacterial resistance. Therefore, this article aims to review articles in the literature that have measured antibiotic levels in the plasma and in the middle ear to determine if the antibiotics prescribed for middle ear infections reach sufficient levels to eradicate planktonic and biofilm bacteria.

2. Defining minimum inhibitory concentrations of otitis media pathogens

2.1. Standardising MIC values

Standardised MIC values (breakpoints) for different organisms have been developed by several bodies worldwide, including the Clinical Laboratory Standards Institute (USA), European Committee on Antimicrobial Susceptibility Testing (EUCAST), and British Society for Antimicrobial Chemotherapy (BSAC; United Kingdom). The breakpoints aim to correlate MIC with clinical outcome [21] by categorising isolates as clinically susceptible, intermediate, or resistant. The clinical breakpoints, which separate MIC values that indicate sensitivity and resistance, distinguish between infections that are likely to respond (sensitive) to antibiotics and those that may not (resistant) [22]. MIC breakpoints are influenced by the pharmacodynamics of the drug, the distribution of susceptibility of the microorganism (ie bacterial populations that acquire resistance mechanisms or are innately resistant), and clinical outcomes (i.e. how often does an isolate determined as susceptible, respond to standard treatment?) [23]. Likewise, reaching antibiotic levels under the MIC, meaning levels that will not inhibit sensitive