

Antibiotic Concentration after Delivery to Middle Ear for Chronic Suppurative Otitis Media

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Abstract

Chronic suppurative otitis media (CSOM) with a non-intact eardrum is a common diagnosis in otolaryngology clinics. Otological fluoroquinolones (e.g. ciprofloxacin) are a mainstay for treatment. Despite the emergence of ciprofloxacin-resistant microorganisms, current clinical practice is predicated on the assumption that in vivo concentrations in the middle ear are much higher than the minimum inhibitory concentration used to determine resistance. However, a previous study by our group demonstrated poor outcomes for resistant bacteria treated with ciprofloxacin drops alone. One possible explanation for these findings is that the concentrations actually delivered to the middle ear are insufficient to overcome the bacterial resistance. This study will investigate the feasibility of accurately measuring in vivo ciprofloxacin concentrations in patients with CSOM.

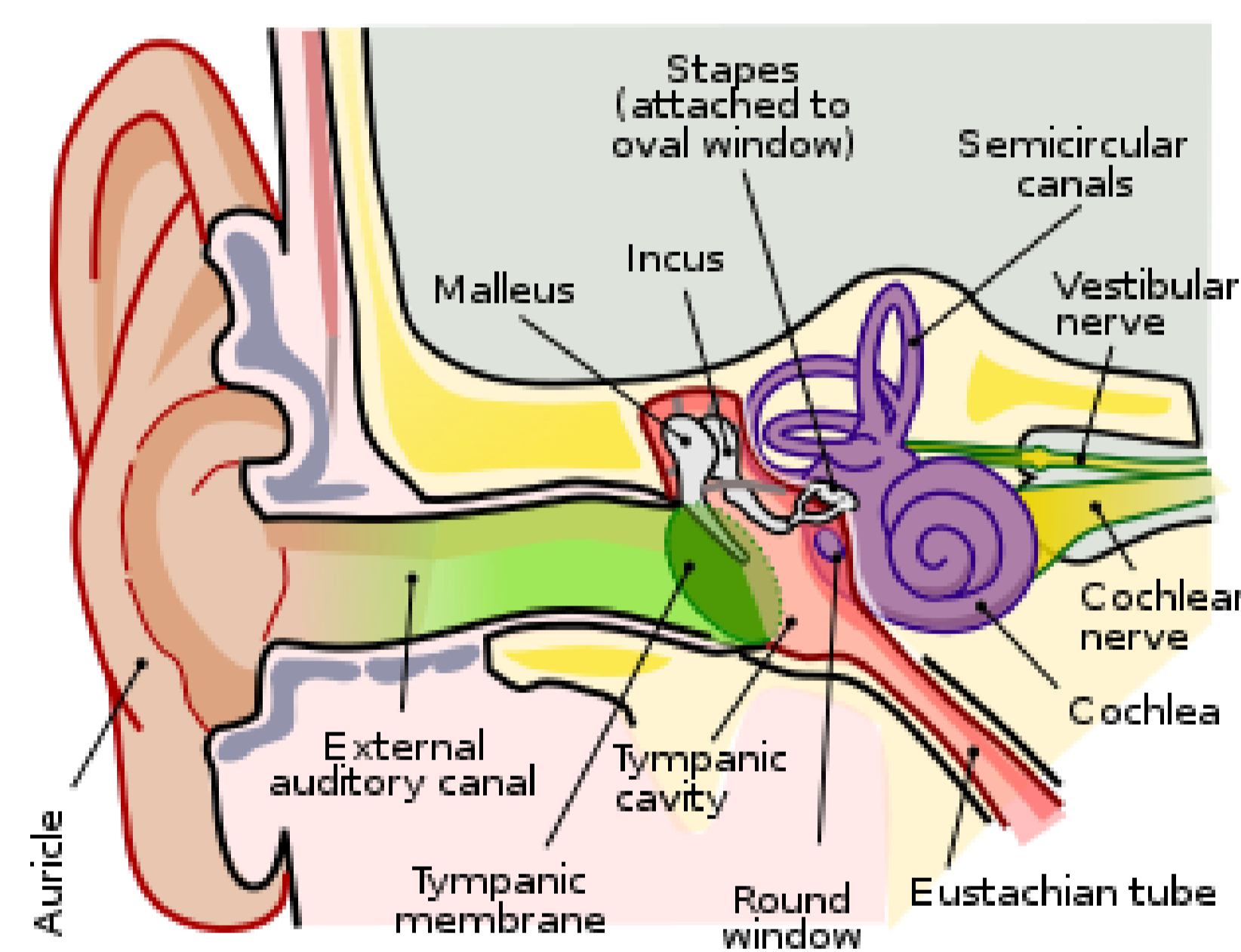


FIGURE 1: The middle ear spans from the tympanic membrane to the inner ear and contains the ossicles, round and oval windows, and the Eustachian tube. Source: *Wikipedia "Middle Ear"*

Introduction and Background

Chronic suppurative otitis media (CSOM) is characterized by chronic inflammation of the middle ear (Figure 1) with persistent discharge and is notably associated with a significant burden of disease worldwide (1, Figure 2). Topical fluoroquinolones are first line therapy (2-5), yet resistance has been increasing (6-8). Recently, ciprofloxacin-resistant otitis media has been described with poor outcomes with necessary alternative therapy such as IV antibiotics (9, 10).

These findings contradict the previously accepted thought by many practicing otolaryngologists that the high concentrations as high as 3000 mcg/m obtained with topical antibiotic preparations would sufficiently overcome all minimum inhibitory concentration (MIC) levels and bactericidal concentrations of resistant strains commonly seen in chronic otitis media (4,11). However, even the elevated MICs measured in ciprofloxacin-resistant bacteria were found to be generally well below the concentration of the otological solution (12), suggesting that poor clinical outcomes could be a combination of MICs and failure to reach the necessary inhibitory concentration at the tympanic membrane.

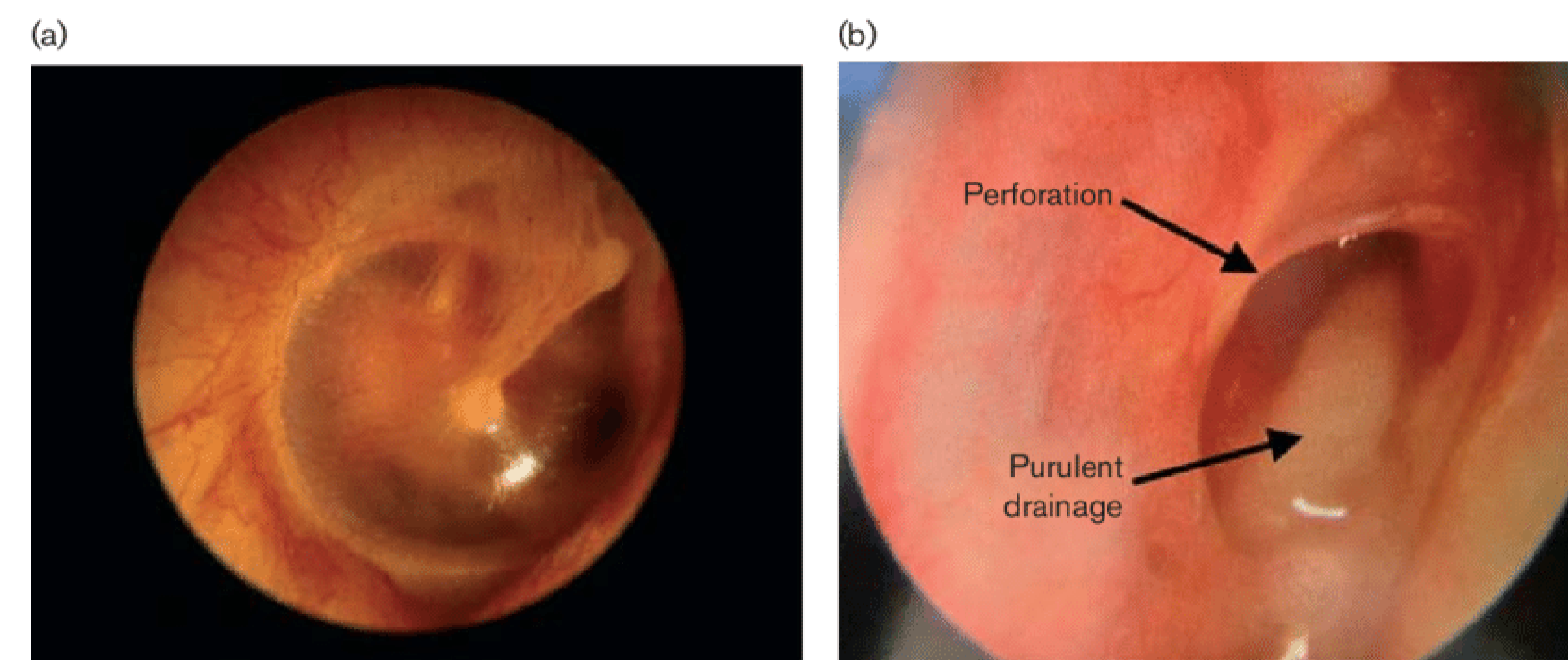


FIGURE 2: a) shows a healthy intact tympanic membrane with no drainage, whereas b) shows obvious tympanic membrane perforation with purulent drainage that is characteristic of chronic suppurative otitis media. Source: Mittal et. al. (17)

Methods and Materials

This study is a prospective study of adult patients being diagnosed with CSOM at a tertiary care hospital, Dartmouth-Hitchcock Medical Center. Subjects will be prescribed the standard-of-care ciprofloxacin droplets with written instructions for self-administration to administer three times daily for ten days. After three to ten days, the subject will be asked to administer the drops in the affected ear one hour prior to their appointment. Microscopic aspirate of fluid at the level of tympanic membrane will be collected using an aseptic technique with a modified Juhn Tym-Tap specimen trap with subsequent analysis of ciprofloxacin concentration using a reverse-phase liquid chromatography with tandem mass spectrometry (LC-MS/MS). This data will be analyzed using Fisher's exact test due to small sample size. Additional data collected will include otologic diagnosis, bacteria culture results, presenting symptoms, amount and type of drainage, external ear canal volume estimates, configuration of the external auditory canal, prescribed treatment, treatment outcome, and duration of infection.



FIGURE 3: a) Otological antibiotic therapy is delivered through self-administration. Our study team believes that otological variation in delivery explains the discrepancy found in known bactericidal concentrations and high concentration droplets. b) Juhn-Tym tap aspirator will be used to aspirate the ear during the follow-up visit to obtain ciprofloxacin concentration at the tympanic membrane. Source a: RXList "Ciprodex"; Source b: DOTmed

Discussion and Future Results

The potential role of ineffective otological delivery of fluoroquinolones and antibiotic resistance in patient outcomes has yet to be elucidated. Topical antibiotic therapy is demonstrating unexpected complexity with clear necessity for elucidation. Only one study by Ohyama et. al. has reported on drug concentration of otological solutions at the level of the middle ear, which illustrated high variations of concentration (13). These results allude to the variety of patient factors that can influence drug penetration and the availability in the middle ear, including volume of otorrhea, the narrowness of the ear canal, differences in surface tension affecting fluid dynamics, and size of the tympanic membrane. However, these factors are ill defined within the literature and the magnitude of such individual effects is largely unknown. As such, our study presents an opportunity to develop this body of knowledge for the first time

Many authors have advocated for a more complex assessment of fluoroquinolone resistance that includes both the relative resistance of the organism, the available concentration at the tissue level and duration of drug exposure to those tissues (14, 15). By using liquid chromatography-tandem mass spectrometric (LC-MS/MS) method (16), we expect to find an association of tissue-level antibiotic concentration directly with patient outcomes. Should our hypothesis be correct, we would conduct a higher powered study to better describe the variables that contribute to otological therapy in order to improve it with new principles of understanding.

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