Treatment of methicillin-resistant *Staphylococcus aureus* otorrhea

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Incidence of MRSA otorrhea in chronic suppurative otitis media

The emergence of antibiotic resistance in humans and animals is primarily due to excessive and often unnecessary use of antibiotics. Risk factors for the spread of resistant bacteria in hospitals and the community include overcrowding, lapses in hygiene and poor infection control practices. Increasing antibiotic resistance in bacteria has been exacerbated by the slow pace in antibiotic development.

Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and multiresistant ciprofloxacin-resistant *Pseudomonas aeruginosa* (CRPA) are spread primarily by direct or indirect person-to-person contact. Independent risk factors for MRSA include the use of broad spectrum antibiotics and the presence of decubitus ulcers and prosthetic devices, while those for VRE include prolonged hospitalization and treatment with glycopeptides or broad spectrum antibiotics. For the spread of resistant Gram-negative bacteria, risk factors include urinary catheterization, excessive use of antibiotics and contamination of humidifiers and nebulizers.

Chronic suppurative otitis media (CSOM) is characterized by irreversible inflammatory changes in the middle ear cavity and mastoid process. Purulent otorrhea is a common symptom in patients with CSOM. Patients with CSOM generally have a chronic inflammation of the middle ear and mastoid, with a persistent perforation of the tympanic membrane associated with recurrent otorrhea. If purulent otorrhea persists the mucous membrane may become ulcerated, polypoid or granulomatous. Prolonged infection may be associated with resorption of the ossicles and mastoid bone by demineralization and osteoclastic activity.

The first strains of MRSA were identified in 1961 [1]. Since then, the proportion of nosocomial MRSA isolates has increased worldwide from 2% in 1974 to 50% in 1997 [2]. There has been a steady increase in the number of cases of MRSA otorrhea [3–8]. For example, studies monitor staphylococcal isolates in cases of chronic otitis media have reported MRSA incidence rates of 22.3% in Japan [9] and 25% in Taiwan [6]. In Korea, 70% of *S. aureus* strains have been MRSA since the mid-1990s, and it is one of the most common isolated bacteria in chronic otitis media, with an incidence of about 30% [10]. The normal bacterial flora in patients with external otitis media consists predominantly of *S. epidermidis*, *S. auricularis*, *S. capitis* and *Corynebacterium* sp. [11]. Nosocomial infection is the most common route of MRSA infection, defined as more than 48 h of hospitalization, recent (<1 year) hospital stay, multiple medical visits for a chronic condition such as dialysis or a family member with a recent history of hospital-acquired MRSA [12,13]. Community-acquired MRSA infection has been linked to intravenous drug abuse, cystic fibrosis, chronic disease and repeated antimicrobial therapy [13–15]. Recently, however, the prevalence of community-acquired MRSA infections in adults and children without identified risk factors has increased [16, 17].

The incidence of MRSA infection after middle ear surgery has recently increased. Lee et al. [18] investigated a reciprocal transmission between medical personnel and patients in a molecular study. Surveillance bacterial cultures of medical personnel were performed from the anterior nares and from the fingertips. Molecular epidemiological studies, ribotyping and pulsed-field gel electrophoresis (PFGE) were used to compare 12 MRSA strains obtained from carriers among medical personnel with the 60 strains identified from patient's otorrhea. Six different MRSA strains were identified from ribotyping, and three subtypes were evident from PFGE. There was a particular subtype that was the most frequently identified strain found in both medical carriers and patients. Postoperative MRSA infection rates after the treatment of medical carriers and application of preventive procedures decreased from 11.9% to 5.7%. The results of the study suggested that the MRSA transmission can occur between medical personnel and patients.

Approximately 30% of children who undergo tympanostomy tube placement develop acute otorrhea. *Haemophilus influenzae* and *Streptococcus pneumoniae* are responsible for 40%–45% of these cases, particularly in children under 2-years-of-age and in those who develop symptoms during the winter months. The other 55%–60% of cases are caused by pathogens from the external canal, most commonly *S. aureus* and *P. aeruginosa*. These patients tend to be older, to develop symptoms during warmer months and to have a malodorous discharge (in contrast to the nasopharyngeal pathogens, which are odorless). There appears to be a contribution from water in the ear, which triggers an inflammatory response. Topical fluoroquinolones (particularly ofloxacin and ciprofloxacin) are being used more frequently, with the increased recognition that staphylococcus and pseudomonas also contribute to the microbiology of this disease. Even in young children, otic preparations are often considered superior to oral antibiotics because they are active against all four of the main pathogens, safely achieve high concentrations in the middle ear and are less likely to contribute to the emergence of resistance because they are not given systemically. Furthermore, the problem of noxious
taste is eliminated. However, with the emergence and increasing prevalence of CA-MRSA posttympanostomy tube otorrhea, the topical quinolone treatment strategy is more prone to failure.

**Treatment**

Many otolaryngologists routinely use topical antibiotics for purulent otorrhea. A recent study documented good in vitro MRSA activity of topically-applied ciprofloxacin [19]. However, ciprofloxacin otic drops do not have a clinical effect against MRSA because the increasing incidence of fluoroquinolone resistance [7, 20, 21]. Recently, we have noted an increasing number of patients presenting with ciprofloxacin-resistant MRSA otorrhea. In vitro susceptibility of MRSA to clindamycin, trimethoprim-sulphamethoxazole, erythromycin and tetracycline has been frequently reported [22, 23]. In vitro antibiotic efficacy is not always indicative of in vivo efficacy, as has been so well-established with β-lactam antibiotics.

While intravenous vancomycin remains the first choice for MRSA otorrhea, it is inconvenient to admit patients for an antibiotic that cannot be given orally. An otic preparation of vancomycin, which is currently unavailable commercially, results in a smaller amount of drug administered, compared with parenteral administration. We have treated patients with MRSA otorrhea as outpatients using a locally prepared otic solution of vancomycin [7]. In this approach, a 500-mg vial of vancomycin powder is reconstituted with 20 ml of sterile distilled water to yield a working solution with a vancomycin concentration of 25 mg/ml. Our more recent experience has included the use of a more diluted vancomycin eardrop solution of 16.67 mg/ml prepared in 30 ml of sterile distilled water. The preparation is stored in a refrigerator following preparation and when not being used. All patients who use the eardrops are required to wash their hands prior to drop application.

An organism must maintain a fairly constant pH to survive. Most bacteria grow the best in a narrow range of pH from 6.5–7.5. The low pH therapy using dilute vinegar solution is definitely effective in the management of intractable otorrhea. Diluted vinegar irrigation is good for the inhibition of MRSA growth in the middle ear and the external auditory canal. Presently, after self-irrigation using a dilute vinegar solution, fortified vancomycin otic drops were applied. Patients were instructed to administer the fortified vancomycin otic drop while maintaining the head in a position for 5 min that allowed drainage of the drops into the ear canal. Following treatment, most of the patients displayed complete or partial cessation of drainage, a dry cavity and no sign of infection within 3–4 weeks. If a patient displayed persistent discharge, the use of dilute vinegar irrigation with topical vancomycin otic drops could be prolonged. Upon cessation of drainage, a mupirocin ointment dressing was used. Furukawa et al. [24] reported the clinical effectiveness (overall cure rate of 40%) of an ototopical application of mupirocin ointment in MRSA otorrhea. However, we think that irrigation with dilute vinegar followed by the topical application vancomycin is therapeutically superior than topical mupirocin ointment only. Trimethoprim-sulfamethoxazole oral antibiotics [25] and fucidic acid ointment [26] have also been recommended, but the numbers of patients examined in the study were too small to allow for any statistical significance to be assigned. Moreover, fusidic acid resistant MRSA are increasing in prevalence.

After ototopical treatment of vancomycin and diluted vinegar irrigation, most of the patients display thickened middle ear mucosa through the perforation. Mupirocin ointment applied to the tympanic membrane is typically softened and melted prior to delivery to the middle ear mucosa for eliminating MRSA. A successful protocol for MRSA otorrhea is shown in Figure 1.
For MRSA-associated skin and soft tissue infections, trimethoprim-sulfamethoxazole, linezolid, or even intravenous vancomycin are usually effective. However, these agents are often ineffective or are associated with relapse as soon as therapy is discontinued when a foreign body such as a tympanostomy tube is involved, because of the lack of blood supply and the formation of biofilms. A recent study [27] compared the in vitro efficacy between vancomycin and linezolid by minimal inhibitory concentration (MIC). All the isolated organisms were uniformly susceptible to both the antibiotics. Vancomycin MICs were higher than those of linezolid. Linezolid can be used for vancomycin-resistant S. aureus (VRSA). However, we have not encountered VRSA in cases of chronic suppurative otitis media.

Bacterial biofilm formation has been implicated in the high rate of persistent otorrhoea after tympanostomy tube insertion [28–30]. Once a staphylococcal biofilm has formed on an implanted medical device or damaged tissue, it is difficult to disrupt. Biofilm-infected implants must often be removed and replaced, placing the patient at increased risk of complications [31]. Current antimicrobial therapies for biofilms have proven largely unsuccessful [32]. Reduction in biofilm contamination could substantially reduce the incidence of otorrhoea. Chole and Hubbell [33] reported a decreased incidence of otorrhoea with the use of silver oxide-coated silicone tympanostomy tubes, compared with plain silicone tympanostomy tubes. However, silver oxide-coated tubes are also susceptible to biofilm formation [34, 35]. We have observed MRSA biofilm formation on silver-treated tympanostomy tubes, which may explain the resistance of MRSA to silver oxide. Prevention of MRSA biofilm formation has been reported using tympanostomy tubes coated with vancomycin using chitosan [36]. Ion-bombarded silicone tympanostomy tubes and phosphorylcholine-coated tubes have also been reported to resist biofilm formation [37, 38], but, so far, not the development of MRSA biofilms.

References


