Methicillin-Resistant *Staphylococcus aureus* Otorrhea After Tympanostomy Tube Placement

James M. Coticchia, MD; Joseph E. Dohar, MD, MS

**Objective:** To compare a retrospective cohort of non-hospitalized children with methicillin-resistant *Staphylococcus aureus* (MRSA) otorrhea with those with methicillin-sensitive *S aureus* (MSSA) otorrhea to determine the risk factors predisposing to MRSA otorrhea and the treatments used.

**Design:** Retrospective case-controlled series.

**Setting:** Tertiary pediatric care facility.

**Patients:** Seventeen children with MRSA otorrhea after bilateral myringotomy with tympanostomy tube insertion (BM&T) and 19 age- and sex-matched control subjects who demonstrated MSSA otorrhea. The average age at culture in MRSA patients was 52 months; in MSSA patients, 54 months. There were 8 boys and 3 girls in the MRSA group and 8 boys and 4 girls in the MSSA group.

**Interventions:** Oral, topical, and intravenous antimicrobial agents.

**Main Outcome Measures:** Antibiotic exposure and history of otitis media and routine antibiotic administration (topical, oral, or intravenous).

**Results:** The following findings were statistically significant (*P* ≤ 0.06, Mann-Whitney test): (1) longer duration of antibiotic treatment after BM&T for patients with MRSA vs those with MSSA; (2) increased number of episodes of acute otitis media before BM&T in patients with MRSA vs those with MSSA; and (3) increased number of courses of antibiotics after BM&T in patients with MRSA vs those with MSSA.

**Conclusions:** Methicillin-resistant *S aureus* otorrhea is commonly seen as a community-acquired infection in otherwise healthy pediatric outpatients. Risk factors for development of MRSA otorrhea include the number of episodes of acute otitis media before BM&T and number of treatment courses and duration of antibiotic therapy after BM&T.

developed a resistance to penicillinase-resistant penicillins.\(^{15}\) This class of antibiotics includes methicillin sodium, nafcillin sodium, oxacillin sodium, cloxacillin sodium, and dicloxacillin sodium.\(^{14}\) Three different mechanisms have been described by which \(S\) aureus develops resistance to the penicillinase-resistant penicillin class of antibiotics. The first mechanism is by alteration of penicillin-binding proteins, which results in a decreased affinity for penicillinase-resistant penicillins.\(^{15}\) The second mechanism is tolerance due to decreased production of autolytic enzymes. The result is a minimum bactericidal concentration at least 32 times greater than the minimum inhibitory concentration. The third mechanism is production of increased amounts of \(\beta\)-lactamase.\(^{15}\) It is notable that higher antibiotic concentrations can often effectively treat these resistant strains.

Methicillin was introduced as a new antibiotic agent in 1959, and shortly thereafter reports of \(S\) aureus resistance appeared in the literature. Methicillin-resistant \(S\) aureus was first described by investigators in Europe in 1961 as a common organism in nosocomial infections.\(^{16}\) In 1968, Barrett et al\(^{17}\) reported the first case of nosocomial infections with MRSA at Boston City Hospital. Since the first report by Barrett et al,\(^{17}\) many articles have shown that MRSA is an increasingly common pathogen in hospital-acquired infections. For instance, Peacock et al\(^{18}\) demonstrated that MRSA accounted for up to 38% of nosocomial infections at the University of Virginia Medical Center.

Numerous risk factors have been associated with nosocomial MRSA infections; these include prolonged hospitalization, multiple-antibiotic therapy, prolonged duration of antibiotic use, and in-dwelling catheters.\(^{19-22}\) A study by Asensio et al\(^{23}\) evaluated risk factors associated with 192 patients with MRSA (compared with 175 random control subjects) and found that MRSA colonization was correlated with previous hospitalization, coma, invasive procedures, and prolonged hospital stays.

A nationwide trend being reported is community-acquired MRSA infection. One hundred sixty-five patients with community-acquired \(S\) aureus infection underwent evaluation by Saravolatz et al\(^{24}\) and were found to have an increased prevalence of this illness. Microbiologic surveillance demonstrated that only 3% of community-acquired \(S\) aureus infections were methicillin resistant, but this number eventually increased to 38%. They demonstrated an association between intravenous drug abuse, serious illness, and previous hospitalization. These investigators also showed a concomitant increase in the number of nosocomial infections (30.6%) attributed to MRSA. These investigators concluded that MRSA may originate in the community as well as the hospital.

Infection with MRSA is of concern, but of equal concern is MRSA colonization. Hicks et al\(^{25}\) followed up 35 families (mothers and infants) discharged from a maternity hospital colonized with MRSA. After 4 weeks, swabs detected that 22 of these families continued to carry MRSA. These families were then treated as outpatients with mupirocin calcium nasal ointment twice daily and hexachlorophene and chlorhexidine gluconate for 5 days. Follow-up surveillance demonstrated that despite treatment, 50% of the patients were still colonized with MRSA.

### METHODS

This study is a retrospective case-controlled series of 17 patients with MRSA otorhea after BM&T. All patients were instructed to wear plugs during water exposure. We compared the 17 MRSA patients with 19 age- and sex-matched controls with methicillin-sensitive \(S\) aureus (MSSA) otorhea after BM&T. We also evaluated history of recurrent acute otitis media (AOM) and oitis media with effusion before tube placement (Table 1). Microbiological cultures were obtained at initial presentation to our clinic. Most of the patients were receiving antibiotics at the time of culture. Culture techniques used followed the procedure of the National Committee for Clinical Laboratory Standards. A limited number of the cultures underwent resin-binding techniques in an attempt to subtract out middle ear effusion levels of antibiotics.

We used the Mann-Whitney test to determine statistical significance for all comparisons (\(P \leq .06\)). The average age of these patients at culture was 52 months for MRSA patients and 54 months for MSSA patients. The sex distributions were 8 boys

<table>
<thead>
<tr>
<th>Variable</th>
<th>MRSA</th>
<th>MSSA</th>
<th>MRSA+</th>
<th>MSSA+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of AOM episodes</td>
<td>10.2 (4.8)†</td>
<td>2.6 (3.2)</td>
<td>3.3 (2.5)</td>
<td>0.6 (1.3)</td>
</tr>
<tr>
<td>No. of COME episodes</td>
<td>0.3 (0.5)</td>
<td>0.8 (0.5)</td>
<td>0.3 (0.6)</td>
<td>1.0 (0.0)</td>
</tr>
<tr>
<td>No. of antibiotic courses</td>
<td>10.7 (4.5)</td>
<td>5.1 (4.8)</td>
<td>3.3 (2.5)</td>
<td>3.6 (3.4)</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>3.5 (1.3)</td>
<td>1.9 (1.9)</td>
<td>1.3 (0.6)</td>
<td>1.2 (1.1)</td>
</tr>
<tr>
<td>Augmentin,‡ cephalosporins, penicillins</td>
<td>6.0 (2.8)</td>
<td>1.8 (2.2)</td>
<td>2.0 (2.6)</td>
<td>1.4 (1.7)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>2.3 (2.1)</td>
<td>0.3 (0.8)</td>
<td>0.0 (0.0)</td>
<td>0.04 (0.9)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Ototopical</td>
<td>0.0 (0.0)</td>
<td>0.6 (1.7)</td>
<td>0.0 (0.0)</td>
<td>0.6 (0.9)</td>
</tr>
<tr>
<td>Duration of antibiotic therapy, d</td>
<td>106 (45)</td>
<td>59 (55)</td>
<td>33 (25)</td>
<td>28 (34)</td>
</tr>
</tbody>
</table>

Abbreviations: AOM, acute otitis media; BM&T, bilateral myringotomy and tympanostomy tube insertion; COME, chronic otitis media with effusion; MRSA, methicillin-resistant \(S\) aureus; MRSA+, MRSA and \(P\)seudomonas aeruginosa or penicillin-resistant \(S\) taphylococcus pneumoniae; MSSA, methicillin-sensitive \(S\) aureus; MSSA+, MSSA and \(P\) aeruginosa or penicillin-resistant \(S\) pneumoniae.

† Difference was statistically significant (\(P \leq .06\)).
‡ Indicates a combination of amoxicillin and clavulanate potassium.
Table 2. Episodes of MRSA and MSSA After BM&T*

<table>
<thead>
<tr>
<th>Variable</th>
<th>MRSA</th>
<th>MSSA</th>
<th>MRSA+</th>
<th>MSSA+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of AOM episodes</td>
<td>4.5 (4.6)</td>
<td>3.3 (2.1)</td>
<td>4.8 (3.3)</td>
<td>5.0 (3.3)</td>
</tr>
<tr>
<td>No. of AOM episodes with otorrhea</td>
<td>3.3 (3.6)</td>
<td>2.4 (0.6)</td>
<td>3.8 (3.2)</td>
<td>3.6 (2.1)</td>
</tr>
<tr>
<td>Duration of drainage, d</td>
<td>19.6 (4.5)</td>
<td>16.7 (7.7)</td>
<td>23 (15.0)</td>
<td>21.4 (10.5)</td>
</tr>
<tr>
<td>No. of CSOM episodes</td>
<td>0.5 (0.5)</td>
<td>0.1 (0.3)</td>
<td>0.0 (0.0)</td>
<td>0.8 (0.8)</td>
</tr>
<tr>
<td>No. of antibiotic courses</td>
<td>14.4 (14.7)†</td>
<td>6.7 (4.7)</td>
<td>14.2 (9.8)</td>
<td>14.0 (13.3)</td>
</tr>
</tbody>
</table>

Abbreviation: CSOM, chronic suppurative otitis media. For other abbreviations, see Table 1.
*Unless otherwise indicated, data are expressed as mean (SD).
†Differences were statistically significant between MRSA and MSSA.
‡Indicates a combination of amoxicillin and clavulanate potassium.

and 3 girls in the MRSA group and 8 boys and 4 girls in the MSSA group (Table 2). Data are given as mean values unless otherwise indicated.

RESULTS

In the year before BM&T, patients who developed MRSA otorrhea had 10.2 episodes of AOM, compared with 2.6 episodes of AOM for patients who developed MSSA otorrhea (Table 1). This difference was statistically significant. When we compared the incidence of chronic otitis media with effusion (unresolved middle ear effusion for ≥3 months), patients with MSSA were almost 3 times more affected. In the preceding 12 months, patients with MRSA otorrhea received approximately 11 courses of oral antibiotics compared with approximately 5 courses of oral antibiotics for patients with MSSA otorrhea. During that time, antibiotic duration for patients who developed MRSA was 106 days, compared with 59 days for patients who developed MSSA.

After BM&T, both groups of patients had similar numbers of episodes of AOM with otorrhea (AOMT) and similar numbers of days of drainage (19.6 for those with MRSA otorrhea and 16.7 for those with MSSA otorrhea). We found significant differences in the number of antibiotics prescribed and the duration of antibiotic use (Table 2). Ototopical drops used were fluoroquinolones as a first line of choice. Oral antibiotics were used after treatment failure of 1 to 2 weeks, at which time cultures were obtained. Oral antibiotics were chosen on the basis of sensitivities obtained from organisms cultured (Table 1). Patients with MRSA otorrhea after BM&T had 14.4 courses of antibiotics (oral, intravenous, and ototopical antibiotics). The total duration of antibiotic treatment was 160 days. Patients with MSSA otorrhea after BM&T had 6.7 courses of antibiotics (oral, intravenous, and ototopical antibiotics). The numbers of courses of antibiotics were significantly greater for patients with MRSA otorrhea compared with patients with MSSA otorrhea. The total duration of this antibiotic treatment was 67 days. Likewise, the duration of antibiotic therapy (160 days) was significantly greater for patients with MRSA otorrhea.

The total number of episodes of MRSA otorrhea was 15, compared with 14 episodes of MSSA otorrhea (Table 3). There were no statistically significant differences between groups with respect to courses of intravenous, oral, or ototopical antibiotics necessary to resolve the infection, duration of drainage, complications, or need for subsequent sets of tympanostomy tubes. Of note, 23 (79%) of the 29 episodes were cured with ototopical antibiotics alone without the need for systemic therapy. This finding suggests that the clinical presentation and severity of these infections were similar, although culture results may have altered standard treatment protocols.

Eight children had MRSA otorrhea coexisting with P aeruginosa or penicillin-resistant Streptococcus. Hence, the designation MRSA+ was used to denote MRSA otorrhea with either or both of these pathogens. Similarly, the designation MSSA+ was used to denote MSSA otorrhea with either or both of these pathogens. The average age of these patients at culture and the sex distribution was the same for both groups.

Patients with MRSA+ otorrhea also had significantly more episodes of AOM before BM&T (Table 1). No other premorbidity differences were found with respect to frequency of chronic otitis media with effusion, number of courses of antibiotics, or total duration of antibiotic treatment.
After BM&T, those patients who developed MRSA otorrhea had a somewhat increased incidence of AOMT (mean ±SD, 4.5 ±4.6 vs 3.3 ±2.1), an increased number of courses of antibiotics (mean ±SD, 14.4 ±14.7 vs 6.7 ±4.7), and a longer duration of antibiotic treatment (mean ±SD, 160 ±176 vs 67 ±56 days) compared with those with MSSA otorrhea. The number of courses of antibiotics and duration of antibiotic treatment was significantly greater for patients with MRSA otorrhea. Although both groups of patients had a somewhat similar number of episodes of AOMT, the patients who developed MRSA otorrhea were treated with twice the number of courses of antibiotics. In these same patients, MRSA required 3 times the duration of antibiotic therapy. This finding underscores the importance of the judicious use of appropriate antibiotic therapy and the risks associated with prolonged use.

At present, intravenous administration of vancomycin hydrochloride remains the drug of choice to treat MRSA-infected patients. As of March 1993, no vancomycin-resistant strain of MRSA was reported in the literature. Unfortunately, in September 2002, a laboratory in Pennsylvania recorded the world’s second case of vancomycin-resistant S aureus. Fortunately, new antibiotics such as combined quinupristin and dalfopristin (Synercid) and linezolid (Zyvox) have some activity against vancomycin-resistant S aureus, although resistance to these agents has been detected. Vancomycin is often combined with other antibiotics in such cases. These other antibiotics include rifampin, novobiocin sodium, ciprofloxacin hydrochloride, combined trimethoprim sulfate and sulfamethoxazole, minocycline, and fusidic acid. In fact, 1 study found that patients with MRSA otorrhea received more than 1 type of antibiotic more frequently than did those with MSSA otorrhea. That notwithstanding, mere topical antibiotic therapy suffices in most cases of MRSA AOMT. It is the opinion of one of us (J.E.D.) that ototopical quinolones...
such as ofloxacin and ciprofloxacin are first-line agents, given their lack of ototoxic effects. Not uncommonly, cultures are obtained from these children, who are clinically indistinguishable from those with pathogens other than MRSA, and the children are empirically treated with topical quinolone ear drops. By the time the culture and sensitivity results are returned, the patient's status is improved. It is likely that the higher, often 1000-fold concentrations of these broad-spectrum antibiotics accounts for this. Although some data suggest that the third- and fourth-generation quinolones such as moxifloxacin may have enhanced activity against MRSA systemically, no such data exist for a topical use. It is unlikely, owing to the large concentrations delivered topically, that there are significant clinical differences between different generations of quinolones. This experience has been reported by other investigators as well. Hartnick et al concluded that pediatric patients with MRSA-positive cultures as a result of post–tympanostomy tube otorrhea can often be successfully treated with ototopicals.

As we know from previous investigations, there may be regional differences in the development of multidrug-resistant organisms. It is important for us to carefully characterize these trends, to understand risk factors and consequences associated with infections, and to be able to identify regional differences in clinical practice that may influence these trends. As this and other studies point out, it may not be enough to treat the AOMT and ignore persistent carriage. This is especially true during an outbreak within a health care facility. Obviously, identification and treatment of those carrying MRSA is needed. At this time, total eradication of MRSA from a specific population is not deemed to be prudent, not only because of the cost but also because resistant organisms—potentially more dangerous than MRSA—may develop.

Although vancomycin is effective in treating infections caused by MRSA, unfortunately, it may not eradicate the carrier state. One should consider a combination of topical and oral antibiotic administration, because carriage through nasal secretions is a predominant mode of MRSA transmission, and because oral administration frequently does not allow a bactericidal concentration to be reached in certain areas of the body (eg, nasal vestibule). Bacitracin zinc, vancomycin, and mupirocin topical ointments have been reported to eliminate the carrier state.

Other systemic drugs, such as combined trimethoprim-sulfamethoxazole, novobiocin, and ciprofloxacin, have also been used. Caution must be exercised, however, because there is a potential for even more highly resistant organisms to be selected while failing to eliminate MRSA colonization. In fact, bacitracin and vancomycin were reported to suppress, but not eliminate, MSSA. It is possible and, in the senior author's experience, likely that persistent and recurrent disease may only be able to be successfully managed by eliminating colonization, especially in the setting of ongoing eustachian tube dysfunction. Surveillance cultures were obtained from patients in whom infection progressed to chronic suppurative otitis media or from patients who underwent reculture and in whom treatment was considered a failure. We recognize the limitation of this report, given the retrospective study design and relatively small number of cases statistically compared. We nonetheless believe that such a study is important to report because it adds to the existing body of evidence that MRSA infections are occurring with increased frequency in otherwise healthy children from our communities and that, unlike other pathogens commonly isolated from AOMT, persistent and recurrent infection appears to be more likely and may require additional treatment to adjacent colonized sites.

There are numerous guidelines for controlling MRSA infection in various health care settings and clinical scenarios (eg, burns and urinary tract infections). When such patients are seen, gowns, masks, and gloves should be considered by those in contact with the child. In an outpatient clinic, physicians and other health care personnel must wash their hands between patients. A new pair of gloves should be used for each patient, and equipment should be disposed of or sterilized after use.

Within the home, measures such as diligent sanitary habits are important to prevent household contacts. This is equally important in daycare–type settings. One method of decolonization that is recommended is frequent bathing.

CONCLUSIONS

Antibiotic-resistant bacterial pathogens are an increasing problem in the United States and abroad, especially in pediatric patients. This study clearly demonstrates the risks associated with the indiscriminate use of antimicrobials. Patients who went on to develop MRSA otorrhea had an increased exposure to broad-spectrum antibiotics of long duration. We also demonstrated that if MRSA otorrhea was identified, this clinical episode could be handled with ototopical therapy. However, despite our ability to treat these episodes with ototopical antibiotics, these patients may be at a somewhat increased risk of developing new episodes of AOM. Although the first description of MRSA was 37 years ago, MRSA is increasing in frequency and remains a therapeutic challenge.

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REFERENCES


