Community-Acquired Methicillin-Resistant Staphylococcus aureus in Children and Adolescents

Changing Trends

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Objective: To identify current trends in antibiotic sensitivity patterns of community-acquired methicillin-resistant Staphylococcus aureus (CA MRSA) infections of the head and neck in children and adolescents and evaluate outcomes after therapy.

Design: Retrospective review of cases consisting of a medical record review with telephone follow-up.

Setting: Two tertiary university medical referral centers.

Patients: Pediatric patients (age <18 years).

Main Outcome Measures: Number of cases, sensitivities of cultured organisms, treatments used, and outcome of treatments.

Results: Seven patients were identified with CA MRSA in a 4-month period. Superficial abscesses (3 patients [43%]) and suppurative lymphadenitis (3 patients [43%]) were the most common causes. An erythromycin-resistant, clindamycin-sensitive pattern was observed in 6 (86%) of the 7 isolates. All infections resolved with prescribed treatments; there were no complications.

Conclusions: A high prevalence of erythromycin-resistant, clindamycin-sensitive CA MRSA was noted. This new resistance pattern is indicative of inducible macrolide-lincomycin-streptogramin-B resistance. Basic science data suggest that these strains of bacteria could develop resistance to clindamycin during therapy despite appearing susceptible on initial laboratory testing. In our small series, clindamycin was used alone and effectively in 2 such cases. This appears to support its continued use as initial, empiric therapy in suspected cases of CA MRSA.


STAPHYLOCOCCUS AUREUS is a common pathogen observed in head and neck infections. Over the past 20 years, methicillin-resistant S. aureus (MRSA) has become an important source of such infections. A study from the VA Medical Center in Dallas, Tex (1988), reported methicillin resistance in 61% of S. aureus isolates.1 Patients with chronic or recurrent infections such as otitis media or sinusitis are at a higher risk of contracting MRSA as the result of repeated antimicrobial therapy.2,3 Thus, the practicing otolaryngologist should be acutely aware of this pathologic entity.

Early reports of MRSA focused primarily on nosocomial acquisition; however, the incidence of community-acquired MRSA (CA MRSA) infections has been increasing in recent years. These infections have been more commonly described in adult patients.4,5 Intravenous drug abusers,6 nursing home residents,7,8 and chronically ill patients9 have been identified as “high-risk” populations. Researchers have now noted an increase in CA MRSA in the pediatric population.10,11 At the University of Chicago Children's Hospital, Chicago, Ill, the prevalence of CA MRSA infections in children without identified predisposing risk factors increased from 10 per 100 000 admissions in 1988 through 1990 to 259 per 100 000 admissions in 1993 to 1995.12 More recent data by the same group in a follow-up, prospective assessment performed in 1998-1999 show this incidence remaining high.13

Resistance to penicillins is presumed to be independent of the development of macrolide resistance.14 Nosocomial strains of MRSA tend to be uniformly resistant to macrolides, such as clindamycin and erythromycin, making vancomycin the drug of choice.15 However, a 1999 study observed a high correlation between CA MRSA infections and clindamycin susceptibility.16 Isolates that were susceptible to clindamycin were usually
susceptible to erythromycin as well. Other studies reported similar patterns of susceptibility in hospitalized children and recommended treatment of CA MRSA with clindamycin because of high percentages of susceptible organisms. In contrast to vancomycin, which is a large molecule and does not penetrate areas of poor blood supply, clindamycin is thought to be concentrated in phagocytes, which subsequently transport the drug to the site of infection.

A recent study alluded to the changing susceptibility of CA MRSA and found that while 93% of CA MRSA cases were susceptible to clindamycin, only 64% were susceptible to erythromycin. This showed increasing resistance to erythromycin compared with earlier studies. The present study was prompted by an increase in the number of pediatric CA MRSA cases seen at our institutions and the emergence of MRSA isolates that were clindamycin sensitive but erythromycin resistant.

### METHODS

The Otolaryngology Department at the University of Texas Health Science Center, Houston, identified 7 pediatric patients (age <18 years) with CA MRSA head and neck infections at 2 tertiary level teaching institutions between June 21, 2001, and October 4, 2001. All cases were discovered spontaneously through requested consultations; no specific or additional efforts were made to identify MRSA infections, such as review of infection control records.

From the available medical records, demographic information, including age, sex, and race was extracted. Dates of admission and discharge, underlying medical conditions, antibiotic therapy, clinical course and the antibiotic susceptibilities of MRSA isolates were identified. Patient outcomes were determined from follow-up clinic visits and telephone survey. Isolates were classified as community acquired if they were obtained in an outpatient clinic or identified within 48 hours of hospitalization and the patient had not been hospitalized in the preceding 3 months.

Susceptibility testing of S aureus isolates was performed with the VITEK system (bioMérieux Inc, Hazelwood, Mo) in the microbiology division of the respective institutions. The isolates were identified by coagulase testing and confirmed with the Vitek system. Each S aureus isolate was inoculated into a gram-positive susceptibility minimal inhibitory concentration card containing 1% sodium chloride and placed into the Vitek instrument for incubation and reading. An isolate was further evaluated by disk diffusion testing when the Vitek testing revealed that it was resistant to oxacillin. Disk diffusion testing was performed as recommended by the National Committee for Clinical Laboratory Standards.

### RESULTS

All of the cultures were taken from infections of the head and neck (ie, facial abscesses [2], suppurative lymphadenitis [3], superficial neck abscess [1], and acute mastoiditis [1]) (Table 1). All patients were younger than 18 years, with 4 patients younger than 14 months. All patients had community-acquired infections.

The susceptibility profiles of the MRSA isolates are similar with a few key differences (Table 2). All the cultures grew MRSA that was resistant to oxacillin, penicillin G, and ampicillin. Similarly, all of the cultures were sensitive to gentamicin, levofloxacin, rifampin, trimethoprim-sulfamethoxazole, and vancomycin, except for 1 isolate that was resistant to levofloxacin.

Six (86%) of the 7 cultures were resistant to erythromycin. Of the 6 cultures resistant to erythromycin, all were susceptible to clindamycin. Only 1 (14%) of the 7 cultures was susceptible to erythromycin and clindamycin (no macrolide-lincomycin-streptogramin-B [MLSb] resistance). A clindamycin-sensitive, erythromycin-resistant isolate that was resistant to levofloxacin.

### Abbreviations
- **Clinda**: clindamycin
- **Eryth**: erythromycin
- **Oxac**: oxacillin
- **Rif**: rifampin
- **T-S**: trimethoprim-sulfamethoxazole
- **Vanco**: vancomycin

### Table 1. Profiles of Pediatric Patients With Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Site</th>
<th>Comorbidities</th>
<th>Sensitivities</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo/F</td>
<td>Suppurative LAD</td>
<td>None</td>
<td>Inducible MLSb resistance</td>
<td>Clinda (PO, 7 d)</td>
<td>Resolved</td>
</tr>
<tr>
<td>4 mo/M</td>
<td>Suppurative LAD</td>
<td>None</td>
<td>Inducible MLSb resistance</td>
<td>Vanco (IV, 1 d)</td>
<td>Resolved</td>
</tr>
<tr>
<td>6 mo/M</td>
<td>Superficial neck abscess</td>
<td>None</td>
<td>Inducible MLSb resistance</td>
<td>Rif/T-S (PO, 7 d)</td>
<td>Resolved</td>
</tr>
<tr>
<td>13 mo/F</td>
<td>Suppurative LAD</td>
<td>None</td>
<td>No MLSb resistance</td>
<td>Clinda (IV, 14 d)</td>
<td>Resolved</td>
</tr>
<tr>
<td>6 y/M</td>
<td>Mastoiditis</td>
<td>Chronic otitis media</td>
<td>Inducible MLSb resistance</td>
<td>Vanco (IV, 7 d)</td>
<td>Resolved</td>
</tr>
<tr>
<td>15 y/F</td>
<td>Nasal dorsum abscess</td>
<td>None</td>
<td>Inducible MLSb resistance</td>
<td>Rif/T-S (PO, 10 d)</td>
<td>Resolved</td>
</tr>
<tr>
<td>16 y/M</td>
<td>Cheek abscess</td>
<td>Juvenile detention</td>
<td>Inducible MLSb resistance</td>
<td>Clinda (IV, 1 d)</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

### Table 2. Resistance Profiles of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections in Pediatric Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinda</th>
<th>Eryth</th>
<th>Oxac</th>
<th>Rif</th>
<th>T-S</th>
<th>Vanco</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
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<tr>
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<td>S</td>
<td>R</td>
<td>R</td>
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<td>S</td>
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</tr>
<tr>
<td>4</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

Abbreviations: Clinda, clindamycin; Eryth, erythromycin; Oxac, oxacillin; R, resistant; Rif, rifampin; S, susceptible; T-S, trimethoprim-sulfamethoxazole; Vanco, vancomycin.
resistant pattern was observed in 6 (86%) of the 7 isolates (inducible MLSB resistance).

All infections resolved with the prescribed antibiotic treatments presented in Table 1. Of the 7 patients, 5 were initially treated with intravenous antibiotics, which included clindamycin, vancomycin, and rifampin, and 6 were discharged with oral antibiotic treatments. One patient who was not discharged with an oral antibiotic regimen had been treated with a definitive, 2-week course of intravenous antibiotics. Three patient’s oral regimen included trimethoprim-sulfamethoxazole and rifampin; the other 3 were treated with oral clindamycin. Two cases of erythromycin-resistant, clindamycin-sensitive MRSA treated with oral clindamycin alone resolved without complication.

The incidence of CA MRSA infections is increasing. Gottlieb et al20 documented 15 head and neck cases of CA MRSA in 1992, accumulated over a period of 3 years. Our 7 patients were identified in the course of 4 months. In keeping with previous reports,5,7,10,12 most cases were soft-tissue infections. However, one of the patients presented with acute mastoiditis, which underscores the broad spectrum of infections this pathogen can produce.

Most MRSA strains identified in our study were clindamycin sensitive and erythromycin resistant (6 [86%] of the 7 cultures). Previous authors have reported most strains to be clindamycin and erythromycin sensitive and advocated treating CA MRSA infections with clindamycin.10,12,17,18 The present study found only 1 (14%) of the 7 cultures to be susceptible to both clindamycin and erythromycin.

Macrolide-lincomycin resistance in clinical isolates has been recognized for several decades.21 Methylation of an adenosine residue of bacterial 23S ribosomal RNA is the most common mechanism of acquired resistance to macrolides (ie, erythromycin), lincosamides (ie, clindamycin), and streptogramin-B and confers cross-resistance to all MLSB antibiotics (the MLSB phenotype). The methylated RNA has a lower affinity for MLSB antibiotics than unmethylated RNA, and thus the antibiotics are unable to efficiently inhibit protein translation. This resistance is plasmid mediated, and the resistance is encoded on transposons.

Expression of MLSB resistance in staphylococci is either constitutive or inducible. When it is constitutive, bacteria exhibit resistance to all MLSB antibiotics. When resistance is inducible, staphylococci are resistant to 14- and 15-membered macrolides, such as erythromycin, but retain susceptibility to 16-membered macrolides and linosamides, such as clindamycin. This dissociated resistance arises from differences in inducing capacities of MLSB antibiotics. Erythromycin is a more effective inducer of MLSB resistance than is clindamycin.21 The phenotype of “erythromycin-resistant, clindamycin sensitive” is indicative of inducible MLSB resistance.

Panagea et al24 studied the rate at which staphylococci developed resistance to clindamycin using strains resistant to erythromycin and sensitive to clindamycin. Resistance developed rapidly in vitro, leading them to recommend that clindamycin be avoided in the treatment of infections caused by staphylococci exhibiting inducible MLSB resistance, even when they appear to be susceptible on laboratory testing. Constitutive mutants may emerge during the course of therapy. Similar findings led other authors to recommend initial empiric therapy with vancomycin in critically ill patients, as opposed to clindamycin in cases of CA MRSA.23

Others have been critical of this approach, since favorable pharmacokinetics, intraphagocyte concentrations, and the ability of clindamycin to inhibit staphylococcal toxins usually result in clinical improvement of MRSA infections.25 In the present series, 2 patients with inducible MLSB resistance were treated definitively with oral clindamycin alone. Thus, the antimicrobial activity of clindamycin may outpace the development of resistance.

Most CA MRSA isolates in the our study demonstrated resistance profiles consistent with inducible MLSB resistance. We have identified this emerging resistance profile, which is different from previous reports. Although these bacteria have the potential to develop resistance to clindamycin, no adverse outcomes were encountered when clindamycin alone was used in the treatment of patients with the inducible MLSB phenotype.

Because of our small sample size and the retrospective nature of this series, we cannot make definitive recommendations about using clindamycin in these infections. Clindamycin appears to be appropriate for such infections as long as the patient’s clinical course can be closely monitored. In the current series, a combination of trimethoprim-sulfamethoxazole and rifampin was used as alternate therapy because all specimens were susceptible to these 2 antibiotics. The 3 patients treated with this regimen had complete resolution of their infections. However, if the patient is critically ill, we recommend parenteral vancomycin, since it is the “gold standard.”

Our data show that CA MRSA infections are increasing in incidence in the pediatric population. Diligent surveillance is needed to more accurately assess the prevalence and sensitivities of this infectious pathogen. At present, we support the use of clindamycin as initial empiric therapy in the treatment of CA MRSA infections that demonstrate sensitivity profiles consistent with inducible MLSB resistance. When clindamycin is used, we recommend close clinical monitoring until complete resolution of the infectious process. This is based on a combination of our limited clinical experience with this pattern of resistance and basic science data that appear to advocate cautious use of clindamycin.

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REFERENCES


