Failure of Clindamycin Treatment of Methicillin-Resistant *Staphylococcus aureus* Expressing Inducible Clindamycin Resistance In Vitro

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We report a case of a surgical site infection caused by clindamycin-susceptible, erythromycin-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) that did not respond to treatment with clindamycin. The MRSA isolate obtained after treatment was resistant to clindamycin but was found to be identical by pulsed-field gel electrophoresis to the clindamycin-susceptible isolate obtained before treatment. A post hoc erythromycin-induction test (D test) confirmed the presence of in vitro inducible macrolide–lincosamide–streptogramin B resistance (iMLS) in the pretreatment isolate. Erythromycin induction testing confirmed in vitro iMLS in 90 (56%) of 161 erythromycin-resistant, clindamycin-susceptible clinical *S. aureus* isolates overall and in a significantly higher proportion (78%) of methicillin-susceptible *S. aureus* isolates from pediatric patients. Our clinical laboratory currently tests all *S. aureus* isolates for iMLS before reporting clindamycin susceptibility.

**Case report.** A 5-year-old girl underwent anterior cranial expansion for craniosynostosis related to Crouzon syndrome in July 2001. The surgical scalp wound was complicated by recurrent breakdown that was unresponsive to cephalexin and topical treatments. Debridement and revision were required on 2 separate occasions. No specimens from these procedures were cultured. The patient’s mother was treated for a surgical wound infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) during the same time period.

Two months later, recurrent breakdown of the patient’s scalp wound required debridement and placement of a skin graft. The underlying bone appeared normal at the time of surgery. Debridged material from this operation revealed a moderate number of polymorphonuclear leukocytes and a few gram-positive cocci on Gram stain, and MRSA grew on a culture of this material. The organism was susceptible to vancomycin (MIC, 1 μg/mL), clindamycin (MIC, 0.5 μg/mL), and tetracycline (MIC, 2 μg/mL) but was resistant to erythromycin (MIC, >4 μg/mL) and gatifloxacin (MIC, >4 μg/mL). Contrast CT of the head revealed no collections and no bony changes that would suggest osteomyelitis.

The patient was treated with vancomycin, and the inflammation and discharge at the wound site resolved. Only 7 days of a planned 10-day course of vancomycin was completed because of loss of intravenous access. Two weeks later, the patient

![Figure 1. Double-disk diffusion test (D test) demonstrating erythromycin disk induction of clindamycin resistance; a blunting of the zone of inhibition around the clindamycin disk is produced that forms a D shape (arrow).](image-url)
developed purulent drainage from the scalp wound, from which MRSA with an antibiotic susceptibility profile identical to that of the previous isolate was cultured. Oral clindamycin was prescribed, but drainage and breakdown progressed.

By day 10 of clindamycin therapy, the patient was readmitted to the hospital for surgical debridement. At the time of surgery, softening of the underlying bone was noted that was consistent with osteomyelitis. MRSA grew on cultures of samples obtained intraoperatively; these isolates had a susceptibility profile similar to that of previous isolates, except that they were resistant to clindamycin (MIC, >2 μg/dL). PFGE of the preclindamycin wound isolate and postclindamycin operative isolate revealed that these 2 organisms were genetically identical (data not shown). Erythromycin induction testing (D testing) of the wound isolate confirmed the presence of inducible clindamycin resistance (figure 1).

After surgical debridement, the patient received a 6-week course of vancomycin and rifampin therapy. Over the following year, she received no antibiotic treatment and experienced no recurrence of infection or inflammation of the scalp.

**Discussion.** Increasing frequency of MRSA infections among children and changing patterns in antimicrobial resistance have led to renewed interest in the use of clindamycin therapy to treat such infections [1]. MRSA strains that are susceptible to clindamycin but resistant to erythromycin, however, may have the phenotype of in vitro inducible macrolide–lincosamide–streptogramin B (iMLS) resistance due to the presence of erythromycin ribosomal methylase (erm) genes. For these strains, there is a high rate of mutation to constitutive resistance, which would then be selected during clindamycin therapy. In other strains, the same erythromycin/clindamycin susceptibility pattern may be produced by strains that harbor msrA, which encodes an ATP-dependent efflux pump. This resistance determinant confers resistance only to 14- and 15-membered ring macrolides and type B streptogramins and not to lincosamides, such as clindamycin [2]. For infections due to these strains, clindamycin may be an important therapeutic option.

In vitro iMLS can be detected in erythromycin-resistant *S. aureus* through the use of a double-disk diffusion assay (D test) [3]. In brief, clindamycin (2 mg) and erythromycin (15 mg) disks (Becton Dickinson) are placed 15–20 mm apart on Mueller-Hinton agar that has been inoculated with a standardized (0.5 MacFarland) suspension of *S. aureus*. The presence of iMLS results in a D-shaped blunting of the circular zone of inhibition around the clindamycin disk on the side facing the erythromycin disk (figure 1). If there is no distortion of the zone of inhibition around the clindamycin disk, then the erythromycin resistance can be attributed to macrolide-specific efflux mechanisms, such as the presence of msrA.

Rates of in vitro iMLS among MRSA isolates from pediatric patients with discordant erythromycin/clindamycin susceptibility vary widely, from 8% of community-acquired MRSA isolates in Houston [4] to 94% of MRSA isolates in Chicago [1]. Because clindamycin is frequently used to treat serious staphylococcal infections in children, we studied the rate of in vitro...
The frequency of in vitro iMLS (43%–78%) observed in this evaluation, all S. aureus isolates—including MSSA and MRSA—with the pattern of erythromycin resistance/clindamycin susceptibility currently undergo D testing at our institution before clindamycin susceptibility is reported.

There have been relatively few reports of clindamycin treatment failure in infections due to MRSA with in vitro inducible clindamycin resistance in adults [5, 6] or children [1, 7]. In only 1 adult and 1 pediatric case were PFGE-identical clindamycin-resistant MRSA recovered from persistent or recurrent infection. We would like to add our case to this small but growing body of evidence supporting the clinical relevance of in vitro inducible clindamycin resistance. The high frequency of MSSA isolates with in vitro iMLS at our institution raises concern that clindamycin treatment failures may occur with MSSA as well as with MRSA infections. Such failures may be uncommon, because β-lactam antibiotics are more commonly used to treat MSSA infections; furthermore, we did not actively investigate unreported clindamycin treatment failures in the present study. The proportion of S. aureus with in vitro inducible clindamycin resistance may vary by region, age group, and methicillin susceptibility. We believe that clinical laboratories should report in vitro inducible clindamycin resistance in S. aureus isolates and that clinicians should be aware of the potential for clinical failure when clindamycin is used to treat
serious infections due to *S. aureus* (MRSA or MSSA) with in vitro inducible clindamycin resistance.

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**References**