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

George K. Siberry,[1] Tsigereda Tekle,[2] Karen Carroll,[2] and James Dick[2]

[1]Division of Pediatric Infectious Diseases, Department of Pediatrics, and [2]Division of Clinical Microbiology, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland

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. Debrided 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)*.

Received 21 February 2003; accepted 6 May 2003; electronically published 3 October 2003.

Reprints or correspondence: Dr. George K. Siberry, Pediatric Infectious Diseases, Park 256, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287 (gksiberr@jhmi.edu).

Clinical Infectious Diseases 2003; 37:1257–60

1058-4838/2003/3709-0018$15.00

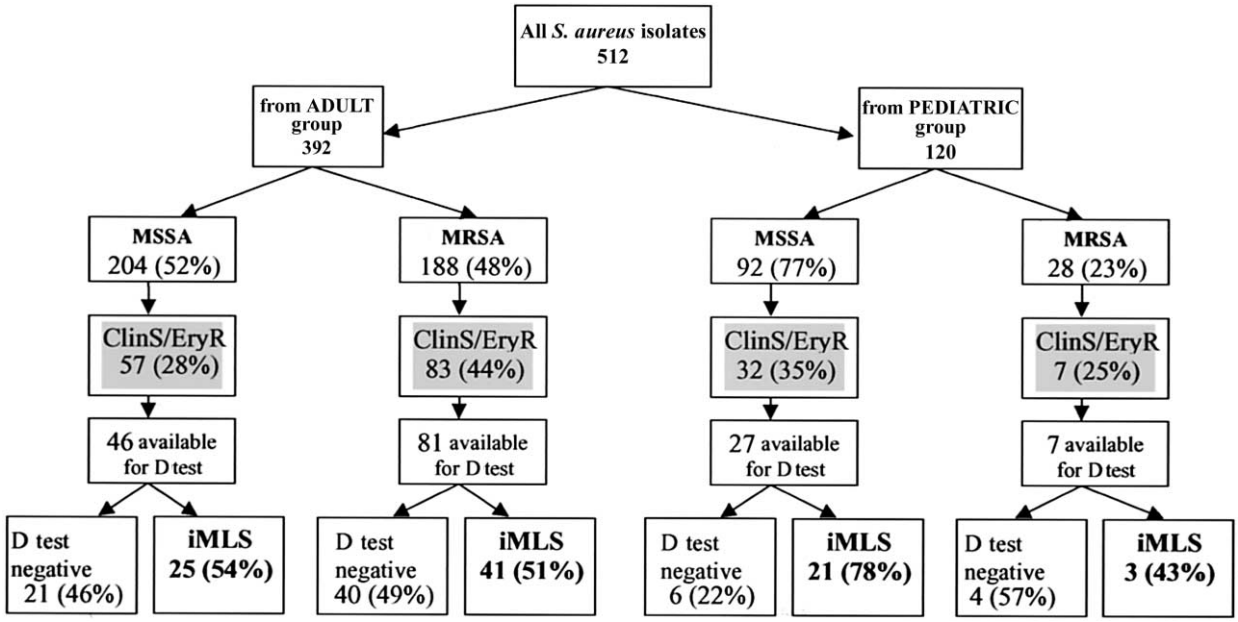

Figure 2. Flow chart for testing of 512 clinical isolates. ClinS/EryR, clindamycin susceptible and erythromycin resistant on initial testing; iMLS, inducible macrolide–lincosamide–streptogramin B resistance seen on D test; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S. aureus*.

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 (MLS_B) resistance (iMLS) 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

Table 1. Inducibility of clindamycin resistance among erythromycin-resistant and clindamycin-susceptible *Staphylococcus aureus* isolates, by population age group and methicillin susceptibility.

Population age group, isolate susceptibility	No. of isolates	No. (%) of ClinS/EryR isolates	Inducible clindamycin resistance, *n/N* (%)[a]	
			Present	Absent
Adult and pediatric				
MRSA and MSSA	512	179 (35)	90/161 (56)	71/161 (44)
MSSA	296	89 (30)	46/73 (63)	27/73 (37)
MRSA	216	90 (42)	44/88 (50)	44/88 (50)
Adult only				
MRSA and MSSA	392	140 (36)	66/127 (52)	61/127 (48)
MSSA	204	57 (28)	25/46 (54)	21/46 (46)
MRSA	188	83 (44)	41/81 (51)	40/81 (49)
Pediatric only				
MRSA and MSSA	120	39 (33)	24/34 (71)	10/34 (29)
MSSA[b]	92	32 (35)	21/27 (78)	6/27 (22)
MRSA	28	7 (25)	3/7 (43)	4/7 (57)

NOTE. ClinS/EryR, clindamycin susceptible and erythromycin resistant; MRSA, methicillin-resistant *S. aureus;* MSSA, methicillin-susceptible *S. aureus*.

[a] No. of isolates with indicated D test result/no. available for testing.

[b] This was the only category in which statistical significance was achieved ($P = .045$). The difference in distribution between presence and absence of in vitro inducible clindamycin resistance was tested for the adult/MRSA, pediatric/MRSA, and pediatric/MSSA groups, compared with the reference group of adult/MSSA, using the χ^2 test.

iMLS among *S. aureus* isolates from our patient population. We undertook a 6-week retrospective analysis of in vitro iMLS in all MRSA and methicillin-susceptible *S. aureus* (MSSA) isolates recovered from pediatric and adult patients (figure 2). Of 512 *S. aureus* isolates, 216 (42%) were MRSA and 179 (35%) had discordant erythromycin/clindamycin susceptibility. Double-disk diffusion testing of 161 available isolates with discordant erythromycin/clindamycin susceptibility demonstrated that 90 (56%) expressed iMLS in vitro. Among the 42% of MRSA with discordant erythromycin/clindamycin susceptibility, iMLS was demonstrated in vitro in 50%, whereas, of the 30% of MSSA with discordant erythromycin/clindamycin susceptibility, 63% demonstrated in vitro iMLS ($P = .098$ for all MRSA vs. all MSSA, by χ^2 test). Among 120 isolates from pediatric patients (<18 years old), 28 (23%) were MRSA and 92 (77%) were MSSA. Of all isolates from pediatric patients, 33% had discordant erythromycin/clindamycin susceptibility, and 71% of those isolates had in vitro iMLS. The proportion of isolates with in vitro iMLS was significantly higher among MSSA from pediatric patients that had discordant erythromycin/clindamycin susceptibility than it was among discordant MSSA isolates from adult patients (78% vs. 54%, respectively; $P = .045$, by χ^2 test), whereas rates of in vitro iMLS among discordant MRSA isolates from adult patients (51%) and from pediatric patients (43%) were not statistically significantly different from that among discordant MSSA isolates from adult patients (table 1). Given 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.

Acknowledgment

We thank Tracy Ross for performing the PFGE analysis.

References

1. Frank AL, Marcinak JF, Mangat D, et al. Clindamycin treatment of methicillin-resistant *Staphylococcus aureus* infections in children. Pediatr Infect Dis J **2002**; 21:530–4.
2. Eady EA, Ross JI, Tipper JL, Walters CE, Cove JH, Noble WC. Distribution of genes encoding erythromycin ribosomal methylases and an erythromycin efflux pump in epidemiologically distinct groups of staphylococci. J Antimicrob Chemother **1993**; 31:211–7.
3. Weisblum D, Demohn V. Erythromycin-inducible resistance in *Staphylococcus aureus:* survey of antibiotic classes involved. J Bacteriol **1969**; 98:447–52.
4. Sattler CA, Mason EO, Kaplan SL. Prospective comparison of risk factors and demographic and clinical characteristics of community-acquired, methicillin-resistant *versus* methicillin-susceptible *Staphylococcus aureus* infection in children. Pediatr Infect Dis J **2002**; 21:910–6.
5. Rao GG. Should clindamycin be used in treatment of patients with infections caused by erythromycin-resistant staphylococci? J Antimicrob Chemother **2000**; 45:715.
6. Drinkovic D, Fuller ER, Shore KP, Holland DJ, Ellis-Pegler R. Clindamycin treatment of *Staphylococcus aureus* expressing inducible clindamycin resistance. J Antimicrob Chemother **2001**; 48:315–6.
7. Faden H, Ferguson S. Community-acquired methicillin-resistant *Staphylococcus aureus* and intrafamilial spread of pustular disease. Pediatr Infect Dis J **2001**; 20:554–5.