

Erythromycin-induced Resistance to Clindamycin in *Staphylococcus aureus*

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Abstract

Purpose: To describe the incidence of erythromycin-induced resistance to clindamycin in a sample of *Staphylococcus aureus* isolates.

Methods: 100 erythromycin-resistant and clindamycin-sensitive *S. aureus* were collected as a convenience sample from February to August 2003. Inducible clindamycin resistance was identified using the D-zone disc method.

Results: Of the 100 *Staphylococcus aureus* isolates, 64 were methicillin sensitive (MSSA) and 36 were methicillin resistant (MRSA). Of the 64 MSSA isolates, 22 (34%) had inducible resistance. Of the 36 MRSA isolates, 4 (11%) had inducible resistance. Overall, 26% of these clindamycin sensitive *S. aureus* isolates, exhibited inducible resistance to clindamycin.

Conclusions: In this sample, MSSA isolates were almost three times more likely to have inducible MLS resistance compared to MRSA isolates. Inducible resistance may compromise the efficacy of clindamycin. The frequency of inducible resistance in this series of "clindamycin sensitive" *S. aureus* isolates is 26%. It is likely that the true percentage of clindamycin resistance is being underestimated since testing for inducible resistance is not routinely performed.

Introduction

Rates of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) carriage and infections have been increasing. Transitioning to oral outpatient treatment of such infections, especially in children, is often limited to clindamycin since erythromycin, tetracycline, and quinolone antibiotics have limited efficacy or undesirable side effects. A recent article

concluded that clindamycin was effective in treating children with invasive infections caused by susceptible community-acquired-MRSA isolates¹. However, it should be noted that hospital acquired MRSA isolates are more commonly clindamycin resistant.

Macrolides (e.g., erythromycin), lincosamides (e.g., clindamycin; trade name Cleocin), and streptogramins (e.g., quinupristin-dalfopristin; trade name Synercid) are antimicrobial agents active against Gram-positive bacteria and some Gram-negative cocci. Streptogramins are commonly used in the cattle industry (e.g., virginiamycin). These three groups are collectively known as "MLS" (macrolide-lincosamide-streptogramin) antibiotics. They are chemically distinct, but alike in their mode of action, which inhibits protein synthesis by binding to the 50S ribosomal subunits². Since the introduction of erythromycin, macrolide-resistant *S. aureus* have appeared along with acquired macrolide-resistance and resistance to other MLS antibiotics³. Resistance to antimicrobial therapy has become an increasing concern among physicians. Clindamycin is more commonly employed for the outpatient treatment of infections with suspected *Staphylococcus aureus*, since methicillin/oxacillin and cephalosporin resistance rates are rising.

The mechanism of macrolide resistance is briefly described in the footnote below*. But of clinical importance, is that some *S. aureus* organisms that are clindamycin-susceptible and erythromycin-resistant based on in vitro testing, will behave as though they are clindamycin-resistant in the presence of erythromycin. In other words, erythromycin, induces clindamycin

* Macrolide resistance may be due to one of three mechanisms, but the best known mechanism has been target site modification caused by methylation of adenine nucleotides in the 23S subunit of the 50S ribosomal RNA⁴. Specifically, methylation reduces the ability of macrolides, lincosamides, and type-B streptogramins to bind to the ribosomal subunits, thereby allowing protein synthesis to continue. In staphylococci and streptococci, a methylating enzyme present can be repressed in sensitive bacteria, but in the presence of subinhibitory concentrations of macrolides, the gene that confers resistance becomes expressed and the enzyme is induced⁵. Cross-resistance between all macrolides, lincosamides (clindamycin and lincomycin), and streptogramins B (pristinamycin I, quinupristin, and virginiamycin S) defining the MLS_B phenotype, occurs because of overlapping binding sites of these antimicrobials. Although other mechanisms of resistance to macrolides have been reported, ribosomal methylation remains the most prevalent mechanism^{2,7}. Biochemical studies demonstrate that the erm (erythromycin resistance methylase) genes encode the methylases that cause ribosomal modification leading to resistance^{7,8}.

resistance in some of these organisms. Erythromycin is one of the most effective inducers of resistance, but lincosamides (clindamycin) have been known to induce resistance resulting in subsequent treatment failure in patient infections with these *S. aureus* isolates⁶. Thus, although the lab reports the organism as being clindamycin sensitive, the organism behaves as if it is clindamycin resistant. This phenomenon is known as MLS inducible resistance, since any MLS antibiotic can theoretically induce resistance. MLS resistance is well known in the infectious disease literature, but it is less well discussed in the primary care, emergency medicine and general hospital care literature. The purpose of this report is to determine the frequency of erythromycin-induced clindamycin resistance in a sample of *S. aureus* isolates in Honolulu.

Methods

One hundred erythromycin-resistant and clindamycin-sensitive *Staphylococcus aureus* isolates were prospectively obtained from Clinical Laboratories of Hawaii from February 2003 to August of 2003 (includes outpatient and inpatient, community and hospital acquired). All strains were classified by susceptibilities to clindamycin and erythromycin with the Vitek system (Vitek, Hazelwood, MO). Isolates were tested for inducible clindamycin-resistance using the disc method described by Weisblum and Demohn⁹. Absence of inducible resistance (true clindamycin sensitivity) shows a normal clear zone around the clindamycin disc, even in the presence of erythromycin (Figure 1). Erythromycin-induced resistance to clindamycin shows growth into the clindamycin inhibition zone adjacent to the erythromycin disc (Figure 2). In other words, next to the erythromycin disc, the clindamycin zone of inhibition is small, demonstrating that the presence of erythromycin induces resistance to clindamycin. In the absence of erythromycin, the clindamycin inhibition zone is large. This phenomenon is also called D-zone resistance, since the clindamycin inhibition zone is shaped like the letter D.

Results

Of the 100 *S. aureus* isolates, 64 were methicillin sensitive (MSSA) and 36 were methicillin resistant (MRSA). Of the 64 MSSA isolates, 22 (34%) had inducible resistance. Of the 36 MRSA isolates, 4 (11%) had inducible resistance. Overall, 26% of these "clindamycin sensitive" *S. aureus* isolates exhibited erythromycin-induced resistance to clindamycin. See Table 1.

Discussion

Conventional testing may be underestimating the clindamycin resistance rate. From our data, 26% of *S. aureus* isolates sensitive to clindamycin based on

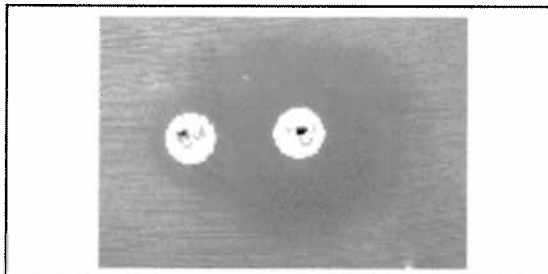


Figure 1. — Absence of MLS inducible resistance

The erythromycin disc is on the left and the clindamycin disc is on the right. This *S. aureus* isolate is erythromycin resistant (small zone of inhibition) and clindamycin sensitive (large zone of inhibition).

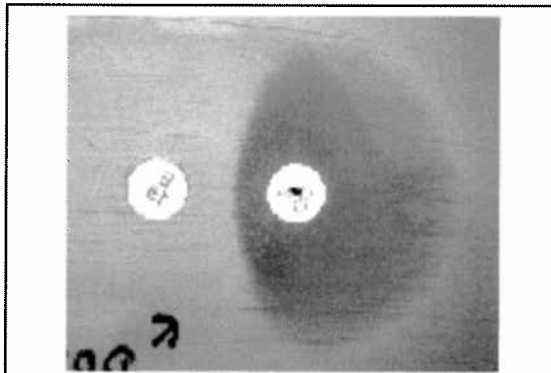


Figure 2. — Presence of MLS inducible resistance. D-zone resistance

Here, the erythromycin disc is on the left and the clindamycin disc is on the right. The clindamycin zone of inhibition is blunted on the left side of the clindamycin disc (resembling the letter "D"). This is an example of inducible clindamycin resistance^{6,7}, in which clindamycin resistance is induced by the presence of erythromycin.

Table 1.— MLS resistance rates among MSSA and MRSA isolates		
	MSSA	MRSA
D-zone Phenomenon (MLS resistance)	22	4
Total isolates	64	36
Percent inducible resistance	34%	11%

Table 2.— Clindamycin resistance rates among <i>S. aureus</i> isolates in Honolulu	
Year	Clindamycin-resistance rate
1999	2%
2000	4%
2001	5%
2002	8%
2003	15%

conventional testing, exhibited clindamycin resistance in the presence of erythromycin. Data comparisons between methicillin-sensitive (MSSA) and methicillin-resistant *S. aureus* (MRSA), suggest that MSSA isolates are three-times more likely to have inducible-resistance than MRSA.

There have been recent case reports of inducible-resistance of staphylococcal isolates during therapy while on clindamycin^{4,6}. Overall, organisms are becoming increasingly resistant to current antibiotics despite attempted changes in physician prescribing behavior. In Honolulu, clindamycin resistance rates for *S. aureus* have slowly risen. Data obtained from Clinical Laboratories of Hawaii show that clindamycin-resistance in *S. aureus* was 2% in 1999 (see Table 2). In 2003, clindamycin-resistant *S. aureus* isolates increased to 15%; a seven-fold increase over 5 years. The *in vivo* resistance rates are likely to be higher than this since inducible resistance is not detectable by conventional antibiotic sensitivity determinations.

We did not examine the clinical records of these patients. Nor did we stratify the *S. aureus* isolates by age group, specimen source or inpatient/outpatient. Furthermore, the isolates were not tested for the *erm* gene (see footnote*). Thus we were unable to definitively determine whether the inducible resistance was due to methylation or from one of the less common mechanisms^{2,7}.

MRSA comprises approximately 25% of *S. aureus* isolates in Honolulu, reducing the efficacy rate of anti-staphylococcal penicillins (e.g., methicillin, oxacillin, dicloxacillin) and cephalosporins. Clindamycin is an available oral alternative for *S. aureus* infections. Trimethoprim-sulfamethoxazole, doxycycline (not suitable for young children), rifampin and the very expensive drug, linezolid are other alternatives. Since the differential of causative microbial agents for soft tissue infections, often includes group A beta hemolytic streptococci (GABHS) and *S. aureus* together, clindamycin potentially covers these two well. The potential for inducible resistance to clindamycin reduces the efficacy certainty of clindamycin therapy. Additionally, inducible MLS inducible resistance is also exhibited by strains of GABHS¹⁰.

Increasing awareness of inducible resistance should be brought to the attention of primary care physicians, emergency physicians and hospital based physicians, treating potentially serious *S. aureus* infections such as cellulitis, septic arthritis, osteomyelitis, abscesses, staphylococcal pneumonia, bronchiectasis, bacterial endocarditis, bacterial pericarditis, etc. For serious and life-threatening infections with *S. aureus*, clindamycin's sensitivity rate is not good enough. The potential for inducible resistance further compromises the efficacy of clindamycin. Once the organism is identified, if clindamycin therapy is being considered, clindamycin sensitivity testing should ideally include testing for inducible resistance since conventional testing does not identify inducible resistance.

Additionally, there should be more judicious use (i.e., less use) of macrolides (e.g., azithromycin and clarithromycin) and clindamycin since both have been implicated as inducers of the resistance in *S. aureus*. However, an ideal practice parameter to determine appropriate use is difficult to develop.

Pediatric data suggests that community acquired MRSA can be treated with clindamycin¹, but this has the potential for the development of inducible resistance and possible treatment failure while on therapy⁶. In summary, inducible resistance to clindamycin may compromise the efficacy of clindamycin. The frequency of induc-

ible resistance in this series of "clindamycin sensitive" *S. aureus* isolates is 26%. It is likely that the true percentage of clindamycin resistance is being underestimated since testing for inducible MLS resistance is not routinely performed.

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