Inducible Clindamycin Resistance in Staphylococci: Should Clinicians and Microbiologists be Concerned?

James S. Lewis II¹ and James H. Jorgensen³
¹Pharmacy Service, University Health System, and Departments of ²Clinical Pharmacy and Pharmacology and ³Pathology, University of Texas Health Science Center, San Antonio, Texas

The increasing incidence of a variety of infections due to Staphylococcus aureus—and, especially, the expanding role of community-associated methicillin-resistant S. aureus (MRSA)—has led to emphasis on the need for safe and effective agents to treat both systemic and localized staphylococcal infections. Unlike most previously noted strains of health care–associated MRSA, community-acquired MRSA isolates are often susceptible to several non-β-lactam drug classes, although they are usually not susceptible to macrolides. Several newer antimicrobial agents and a few older agents are available for treatment of systemic staphylococcal infections, but use may be limited by the relatively high cost of these agents or the need for parenteral administration. Inexpensive oral agents for treatment of localized, community-acquired MRSA infection include clindamycin, trimethoprim-sulfamethoxazole, and newer tetracyclines. Clindamycin has been used successfully to treat pneumonia and soft-tissue and musculoskeletal infections due to MRSA in adults and children. However, concern over the possibility of emergence of clindamycin resistance during therapy has discouraged some clinicians from prescribing that agent. Simple laboratory testing (e.g., the erythromycin-clindamycin “D-zone” test) can separate strains that have the genetic potential (i.e., the presence of erm genes) to become resistant during therapy from strains that are fully susceptible to clindamycin.

Antimicrobial agent resistance in Staphylococcus aureus has become an ever-increasing problem among hospitalized patients, persons in long-term care facilities, and ambulatory outpatients. Between the mid-1970s and late-1990s, methicillin-resistant S. aureus (MRSA) was considered a health care system–associated pathogen among patients with well-recognized risk factors. Such strains often demonstrated resistance to multiple drug classes in addition to β-lactam resistance. It was uncommon to encounter MRSA infections in patients without recent contact with the health care system, who were not injection drug users, or who had not recently received antimicrobial chemotherapy. However, the rapid emergence of community-associated MRSA (CA-MRSA) in the past several years in patients without obvious risk factors has complicated the management of both severe and localized staphylococcal infections [1]. The traditional recommendations of various β-lactam antibiotics for first line therapy, including use of oral β-lactams for treatment of outpatients with staphylococcal infection, requires reassessment in the era of CA-MRSA. Because CA-MRSA strains often do not demonstrate the same degree of multidrug resistance, there has been a resurgence of interest in other, often older antimicrobial agent classes for the management of these infections. In contrast to health care–associated MRSA, CA-MRSA is often susceptible to trimethoprim-sulfamethoxazole, clindamycin, doxycycline or minocycline, and fluoroquinolones, although susceptibility to these agents may vary by geographic area [2, 3]. Given that the majority of reported CA-MRSA infections are skin and soft-tissue infections, clindamycin represents an attractive option for several reasons. First, clindamycin comes in both intravenous and oral formulations (with 90% oral bioavailability). Second, the drug distributes well into skin and skin structures, and unlike β-lactams, it is not impeded by a high bacterial burden at the infection site [4]. Clindamycin is also less costly than some of the newer agents that might be considered for these infections. Finally, clindamycin may be able to inhibit production of certain toxins and virulence factors in staphylococci [5].
One of the major concerns with regard to the use of clindamycin for CA-MRSA infection is the possible presence of inducible resistance to clindamycin [6, 7]. Inducible clindamycin resistance is not detected by standard broth microdilution testing, automated susceptibility testing devices, the standard disk diffusion test, or Etest (AB Biodisk) [8]. Uncertainty about the reliability of susceptibility reports for clindamycin, as well as confusion over the clinical importance of this inducible resistance, has led some clinicians to avoid use of clindamycin for staphylococcal infections whenever erythromycin resistance is noted. In this brief review, we will examine the mechanisms of clindamycin resistance in staphylococci, examine what is known regarding the clinical relevance of inducible clindamycin resistance, review the current NCCLS guidelines for susceptibility testing and reporting of results for clindamycin, and describe how clinicians can assess the reliability of susceptibility reports for clindamycin with staphylococci.

MECHANISMS OF RESISTANCE TO MACROLIDE, LINCOSAMIDE, AND GROUP B STREPTOGRAMIN (MLSB) ANTIBIOTICS IN STAPHYLOCOCCI

Two primary mechanisms result in resistance to macrolide antibiotics [9]. The first involves macrolide efflux and is relatively common in S. aureus in some geographic areas. A specific efflux pump is encoded by the gene msr(A) in staphylococci [10]. This energy-dependent pump effectively expels macrolides from the bacterial cell before they can bind to their target site on the ribosome. Notably, this mechanism of resistance does not create resistance to lincosamides (e.g., clindamycin and lincomycin), but only to macrolides, azalides (e.g., azithromycin), and group B streptogramins (e.g., quinupristin) [10]. The second mechanism of resistance to macrolides in staphylococci involves modification of the drug-binding site on the ribosome. This results in resistance to macrolides (and azalides), lincosamides, and group B streptogramins and is commonly referred to as “MLSB resistance” [11, 12]. An erm gene, usually erm(C) or erm(A), encodes methylation of the 23S rRNA–binding site that is shared by these 3 drug classes. Phenotypically, resistance can be expressed constitutively (the MLSBc phenotype) or only when induced into production (the MLSBi phenotype) [13].

When an erm gene is present, resistance to macrolides arises though binding of a macrolide to upstream translational attenuator sequences. This binding subsequently leads to alteration of the mRNA secondary structure, exposure of the ribosomal binding site, and translation of the erm methylase. For constitutive resistance (MLSBc) to be present, additional changes in these 5’ upstream sequences are required. These modifications can include deletions, duplications, or other mutations, and they result in constitutive expression of the methylase gene with obvious resistance to MLSB drugs [13, 14]. In contrast, although MLSBi strains are clearly resistant to 14-member macrolides (e.g., erythromycin, clarithromycin, and dirithromycin) and 15-member macrolides (e.g., azithromycin that may also be called an azalide), they appear to be susceptible in vitro to 16-member macrolides (e.g., josamycin and spiramycin), lincosamides, and group B streptogramins [9]. However, exposure to a suitable macrolide inducer (e.g., erythromycin) results in expression of lincosamide and streptogramin B resistance [9]. It is possible for mutations to occur spontaneously that will transform MLSBi strains to the MLSBc phenotype without the presence of a macrolide inducer. The concern is that this change in expression might be selected in the midst of therapy with a lincosamide (see Clinical Implications of MLSBi, below). Interestingly, the streptogramin B and A combination, quinupristin-dalfopristin, appears to retain its activity against MLSBc strains of staphylococci, although the presence of the MLSBc phenotype changes the agents activity from bactericidal to bacteriostatic with S. aureus [15].

CLINICAL IMPLICATIONS OF MLSBi

Emergence of clindamycin resistance in isolates with the MLSBi phenotype is readily accomplished by S. aureus in vitro [6, 7]. However, clinical data regarding the risk of emergence of clindamycin resistance through selection of resistant mutants during therapy of MLSBi S. aureus infections are limited primarily to a few case reports. Much of the recent data have been derived from pediatric patients, because CA-MRSA was recognized early among some pediatric groups. Although the data are not entirely conclusive, the trend has been that clindamycin treatment failures are more likely in MRSA infections due to MLSBi strains.

In 1969, McGehee et al. [6] reported 2 cases of erythromycin-resistant S. aureus infection that were treated with the chemical predecessor of clindamycin, lincomycin. Both of the isolates were susceptible to lincomycin before therapy was started but rapidly became resistant during therapy with lincomycin (table 1). The authors reported that neither patient responded to the lincomycin therapy and concluded that both lincomycin and clindamycin are ineffective when dealing with erythromycin-resistant isolates.

Rao [16] reported 3 cases of S. aureus infection with MLSBi in adults that were managed with clindamycin. Two of the cases were called clinical successes, although cultures for 1 of the patients continued to grow MRSA after the course of clindamycin had been completed (table 1). The case that was defined as a clinical success formation or any other sign of deep-seated infection. There was no mention of follow-up of the latter case. Many of the treatment failures described in the literature are recurrences of infection shortly after completion of therapy and
initial apparent resolution of infection. The third case resulted in failure but was clearly a more serious infection than the other 2 cases: the patient had bacteremia due to MLSBc MRSA, a pelvic abscess with no reported microbiology, and “extensive” cellulitis with a sinus track on the patient’s back. The patient responded well to clindamycin therapy initially; however, the infection relapsed 2 weeks later, with an MRSA isolate that demonstrated MLSBc resistance to clindamycin. These 3 cases illustrate the potential problem with managing staphylococcal infections that are initially MLSBc with clindamycin. The bacterial persistence in the first patient and the relapse with an MLSBc organism in the third patient call into question the efficacy of clindamycin. Further, the lack of reported follow-up for patients 1 and 2 does not rule out the possibility of relapse in those cases.

Drinkovic et al. [17] also described 3 patients with infections due to MLSBc S. aureus that were managed with clindamycin (table 1). Two of these patients were deemed to have had clinical successes. The first was an 87-year-old woman with pain and swelling in her right foot. Aspiration of pus from the infected site revealed MLSBi S. aureus. The patient was treated with clindamycin for 6 weeks, with no further sign of infection. The second case involved a 38-year-old man with a scalp wound infection. The infection failed to respond to outpatient erythromycin therapy, and the patient subsequently became tachycardic and hypotensive and required hospitalization. The wound, sputum, and blood cultures grew MLSBc MRSA, and the patient was treated with intravenous clindamycin for 2 weeks, followed by oral clindamycin for 2 weeks, with no evidence of persistence of infection. The final patient, an 84-year-old man, became septic secondary to an infected hip hemiarthroplasty. Wound cultures grew MLSBi MRSA. The patient received 1 day of vancomycin therapy, developed an urticarial rash, and had his therapy switched to intravenous clindamycin. Surgery was performed to wash out and debride the hip. The patient responded well to clindamycin, and therapy was switched to oral clindamycin (450 mg q8h). Five days later, the wound began to discharge, further surgery was performed, and intravenous clindamycin therapy was restarted. MLSBc MRSA was isolated from surgical specimens, and the patient developed sepsis syndrome and died.

In a recent review by Frank et al. [18], the use of clindamycin to treat S. aureus infections in pediatric patients was examined. The authors retrospectively identified 33 cases of erythromycin-resistant S. aureus with 31 confirmed MLSBc isolates by use of the D-zone test (see Implications for Susceptibility Reports and the Clinical Microbiology Laboratory, below). Only 10 of these cases were managed with clindamycin at some point during therapy, and in only 2 was it possible to evaluate the efficacy of clindamycin. In both of those cases, clindamycin therapy clearly failed to eradicate the MLSBi S. aureus infections and resulted in both patients having relapse (table 1). In one of the patients, on relapse, the organism had become MLSBc; the other maintained its MLSBc status, despite the exposure to clindamycin, further demonstrating that these organisms may not be effectively treated with clindamycin, even if constitutive resistance does not arise.

Finally, Siberry et al. [19] recently described in this journal a 5-year-old girl who was treated with clindamycin for an MLSBc MRSA infection in a surgical scalp wound. Importantly, there was no evidence of osteomyelitis when clindamycin therapy was initiated. The patient did not respond to the clindamycin therapy. The surgical wound infection continued to progress, with osteomyelitis developing under the wound site, requiring further debridement of the wound and the bone. Culture of the intraoperative samples grew MRSA that had become MLSBc (table 1). Prolonged therapy with vancomycin and rifampin was administered, and the infection resolved, with successful follow-up 1 year later.

**IMPLICATIONS FOR SUSCEPTIBILITY REPORTS AND THE CLINICAL MICROBIOLOGY LABORATORY**

The problem created by MLSBi resistance in staphylococci and hemolytic streptococci is one of not knowing whether the in vitro susceptibility results generated for clindamycin are trustworthy. As noted above, MLSBc strains are easily recognized as resistant to both macrolides and clindamycin. The problem is
that MLSBi resistance is not readily detected by standard in vitro susceptibility testing methods, unless they include measures that result in induction of clindamycin resistance. Such strains appear to be resistant to macrolides but susceptible to clindamycin under standard testing conditions [20]. A simple means to induce phenotypic resistance to lincosamides in MLSBi strains is to place an erythromycin susceptibility testing disk in close proximity to a clindamycin disk on an agar growth medium [20]. With MLSBi strains, this results in a blunting of the clindamycin zone of inhibition on the zone margin closest to the erythromycin disk resulting from enhanced expression of resistance among the bacterial cells in that area of the culture. The truncated or blunted clindamycin zone of inhibition may resemble the shape of the letter D (figure 1). Therefore, this type of disk induction testing is often referred to as a “D-zone test.”

The issue of detection and reporting of MLSBi in staphylococci has been addressed in the 2004 NCCLS susceptibility testing standards [21]. The NCCLS has described test methods that can routinely detect inducible clindamycin resistance. Two approaches are recommended according to a laboratory’s standard testing method for staphylococci. One method involves merely placing standard 15-μg erythromycin and 2-μg clindamycin disks in adjacent positions in the center of a standard Kirby-Bauer disk dispenser, which results in the disks being ∼26 mm apart from edge to edge [20]. For laboratories that normally test staphylococci using a broth-based method or an automated instrument, the NCCLS recommends placing erythromycin and clindamycin disks ∼15 mm apart on a standard blood agar plate that is used routinely to verify the purity of the bacterial inoculum [8]. Both of the approaches described above should be viewed as simple and inexpensive methods for clinical laboratories to provide routine detection of this form of resistance. Organisms that do not display a blunting of the clindamycin zone of inhibition on the edge closest to the erythromycin zone of inhibition (a negative D-zone test result) can be safely reported as susceptible to clindamycin. Isolates that demonstrate inducible clindamycin resistance (a D-zone test result positive for MLSBi) under these testing conditions should be reported as clindamycin resistant by the laboratory [21]. The NCCLS suggests possibly including the comment that “this isolate is presumed to be resistant based on detection of inducible clindamycin resistance. Clindamycin may still be effective in some patients” [21, p. 46]. The specific method of reporting is a decision best made individually by clinical laboratories. However, inclusion of this comment in susceptibility reports could serve to reassure clinicians that screening for the inducible resistance has been performed and that the reported clindamycin results are valid.

CONCLUSIONS

The emergence of CA-MRSA has led to a resurgence in interest in clindamycin therapy for S. aureus infection. Clindamycin represents a useful option for therapy for various CA-MRSA infections, including musculoskeletal infections, skin and soft-tissue infections, and even pneumonia with empyema [22]. At the present time, many CA-MRSA isolates are resistant to macrolides because of msrA-mediated efflux, and they are thus

Figure 1. Example of a positive D-zone test result for detection of inducible clindamycin resistance. The organism shown is Staphylococcus aureus ATCC BAA 977 that contains erm(C) and demonstrates the induced macrolide, lincosamide, and group B streptogramin resistance (MLSBi) phenotype.
susceptible to clindamycin [22]. However, the use of clindamycin for these infections has been somewhat hampered by concern over possible inducible resistance to clindamycin and its impact on clinical outcomes. The available clinical data are limited and somewhat conflicting, with some patients appearing to respond clinically to clindamycin therapy despite the presence of the MLSBi phenotype. However, the bulk of data from the available literature—both in vitro and in vivo data—appear to support the concerns that have been raised over the use of clindamycin in MLSBi infections, especially those that are deep seated or with large bacterial burden, such as endocarditis, abscesses, and osteomyelitis. There is also recent evidence that constitutive resistance to clindamycin in S. aureus prevents the inhibition of toxin production and fails to inhibit growth [5]. It is unclear whether inducible clindamycin resistance interferes with the inhibition of staphylococcal toxin production. The use of clindamycin for uncomplicated cellulitis due to MLSBi CA-MRSA also remains an unanswered question, because this represents the most widespread presentation associated with this organism, and clindamycin represents an attractive therapeutic option. In patients with non-MLSBi S. aureus infection, clindamycin can be used safely and effectively. If clindamycin is used for treatment of infections with MLSBi-producing isolates, close follow-up and monitoring for failure or relapse is needed. In more-severe infections, the presence of the MLSBi phenotype should preclude the use of clindamycin. Clinical microbiology laboratories, especially in areas where CA-MRSA has become problematic, should consider performing routine testing and reporting for inducible clindamycin resistance in staphylococcal isolates, as described in the 2004 NCCLS guidelines [21], to ensure that clinicians can rely on clindamycin susceptibility test results. It is also worth noting that the NCCLS has recommended that this testing be expanded to include routine testing of the hemolytic streptococci in 2005 [23]. Analogous mechanisms of inducible clindamycin resistance encoded by either erm(A/Tr) or erm(B) can be found in group A, B, and G β-hemolytic streptococci [24]. Although data suggesting that clinical failures are likely to occur in MLSBi streptococcal infections are lacking, by extension, the NCCLS has recommended performance of D-zone testing for detection of inducible clindamycin resistance in these hemolytic streptococci. Finally, more reporting of cases of CA-MRSA or hemolytic streptococcal infections managed with clindamycin are needed to better delineate the role of this compound in organisms with varying MLSB resistance phenotypes.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References


