Incidence of Constitutive and Inducible Clindamycin Resistance in 
Staphylococcus aureus and Coagulase-Negative Staphylococci in a
Community and a Tertiary Care Hospital

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The incidences of inducible clindamycin resistance at two hospitals (an inner-city hospital and a suburban
community hospital) were 7 and 12% for methicillin-resistant Staphylococcus aureus, 20 and 19% for methicillin-
susceptible S. aureus, and 14 and 35% for coagulase-negative staphylococci, respectively. Given the vari-
ability of inducible resistance to clindamycin found in our two hospitals, we conclude that susceptibility testing of
staphylococci should include the disk diffusion induction test (D-test).

Macrolide antibiotics are bacteriostatic agents that inhibit protein synthesis by binding reversibly to the 50S ribosomal
subunits of susceptible organisms. Target site modification is the most common mechanism of acquired resistance to mac-
rolides, lincosamides, and streptogramin B (MLS) antibiotics in staphylococci and confers cross-resistance to the MLS anti-
biotics (the so-called MLSB phenotype) (6). MLSB resistance can be either constitutive (MLS <sub>B</sub>E) or inducible (MLS <sub>B</sub>I).
When it is inducible, bacteria often test resistant to erythromycin (ER) but susceptible to clindamycin (CL). When the
disk diffusion test is used to determine susceptibility, a distorted “D-shaped” zone of inhibition is observed around CL if
an ER disk is placed nearby. Although isolates appear susceptible to CL in the absence of an inducing agent, there is wide-
spread reluctance to prescribe CL for treatment of patients with infections caused by such organisms because of concerns
that resistance to CL will develop during therapy. Beginning in 1990, one of our laboratories (University of Illinois Medical
Center [UIC]) began to see methicillin-resistant Staphylococcus aureus (MRSA) strains that exhibited resistance only to penicillin and oxacillin with implied cross-resistance to other β-lactam compounds but tested susceptible to most other drug
classes (4). Since most of these relatively susceptible MRSA strains originated from community-acquired infections (CA-
MRSA), there was interest on the part of our infectious disease clinicians in knowing the CL susceptibility of all staphylococcal
isolates. The CA-MRSA isolates were found by us to be more susceptible than hospital-acquired (or nosocomial) MRSA to
more antimicrobial classes, including ER and CL (4, 5). By the mid-1990s, CL-susceptible isolates accounted for most of the
MRSA isolates from children at our institution (4). CL is a frequent choice for treating some staphylococcal infections
because it can be given orally and is well tolerated. However, MLS <sub>I</sub> resistance is not recognized by standard susceptibility
test methods, including the Vitek system, which is the system in use in our two laboratories. We therefore decided to test all
staphylococci with the phenotype of intermediate ER resistance (ER-I) or ER resistance (ER-R) and CL susceptibility
(CL-S) to determine the percentages of strains with MLS <sub>I</sub> resistance in our two laboratories.

Four hundred fifty-two MRSA, 788 methicillin-susceptible S. aureus (MSSA), and 310 coagulase-negative staphylococci
(CNS) collected from consecutive clinical isolates were studied at our two hospitals. UIC is a 440-bed, inner-city, tertiary care hospital located on the near west side of Chicago and provides health care to a large, underserved population. Elmhurst Memorial
Hospital (EMH) is a 450-bed suburban community hospital located 16 miles from UIC and serves a largely sub-
urban, upper-middle-class population. Mueller-Hinton agar (MHA), CL disks (2 μg), and ER disks (15 μg) were purchased from Remel (Lenexa, Kans.). All staphylococcal isolates were tested for susceptibility to a battery of antibiotics with the Vitek 1 system (bioMérieux, St. Louis, Mo.). Isolates that were
CL-S but ER-R or ER-I were tested for inducible resistance by the D-test. A 0.5 McFarland equivalent organism suspension was inoculated onto an MHA plate as described in the NCCLS recommendations (8). CL (2 μg) and ER (15 μg) disks were placed 15 mm apart from center to center on MHA as described by Weisblum and Demohn (10). Plates were read after 18 h of incubation at 35°C. Quality control was performed with S. aureus ATCC 25923. Interpretation of the diameters of zones of inhibition was as follows: ER-S = ≥23 mm, ER-I = 14 to 22 mm, ER-R = ≤13 mm; CL-S = ≥21 mm, CL-I = 15 to 20 mm, CL-R = ≤14 mm. If the ER zone is ≤13 mm and the CL zone is ≥21 mm and both have a circular shape, the organism is negative for inducible resistance (D-test negative). If the zone is ≤13 mm and the CL zone is ≥21 mm with a D-shaped zone around the CL, the organism is positive for inducible resistance (D-test positive) (10).

The percentages of MLS <sub>I</sub> resistance in MRSA in our two hospitals were similar but low (7% at UIC, 12% at EMH). The percentages of MLS <sub>I</sub> resistance in MSSA in our two hospitals were similar and double the rate seen in MRSA (20% at UIC, 19% at EMH). The percentages of MLS <sub>I</sub> resistance in CNS in our two hospitals differed considerably (14% at UIC, 35% at
TABLE 1. Incidence of MLSBi and MLSBc among MRSA, MSSA, and CNS isolates in two hospitals

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>No. (%) of MRSA isolates</th>
<th>No. (%) of MSSA isolates</th>
<th>No. (%) of CNS isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UIC</td>
<td>EMH</td>
<td>UIC</td>
</tr>
<tr>
<td>ER-R CL-R</td>
<td>170 (84)</td>
<td>205 (82)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>ER-S CL-S</td>
<td>16 (8)</td>
<td>8 (3)</td>
<td>227 (76)</td>
</tr>
<tr>
<td>ER-R/CL-S D+</td>
<td>14 (7)</td>
<td>30 (12)</td>
<td>59 (20)</td>
</tr>
<tr>
<td>ER-R/CL-S D−</td>
<td>3 (1)</td>
<td>6 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>249</td>
<td>299</td>
</tr>
</tbody>
</table>

TABLE 2. Susceptibility to CL among all staphylococci

<table>
<thead>
<tr>
<th>Organism-hospital (no. of isolates)</th>
<th>No (%) with inducible resistance</th>
<th>No (%) with constitutive resistance</th>
<th>No (%) susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA-UIC (203)</td>
<td>14 (7)</td>
<td>170 (84)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>MRSA-EMH (249)</td>
<td>30 (12)</td>
<td>205 (83)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>MSSA-UIC (299)</td>
<td>59 (20)</td>
<td>10 (3)</td>
<td>230 (77)</td>
</tr>
<tr>
<td>MSSA-EMH (489)</td>
<td>94 (19)</td>
<td>88 (18)</td>
<td>307 (63)</td>
</tr>
<tr>
<td>CNS-UIC (155)</td>
<td>21 (14)</td>
<td>58 (37)</td>
<td>76 (49)</td>
</tr>
<tr>
<td>CNS-EMH (155)</td>
<td>55 (35)</td>
<td>40 (26)</td>
<td>60 (39)</td>
</tr>
</tbody>
</table>

EMH) (Table 1). Overall, 17% of MRSA, 8% of MSSA, and 50% of CNS isolates that exhibited the ER-R CL-S phenotype did not demonstrate MLSBi resistance and therefore can be reported as susceptible to CL. Overall CL susceptibility was highest for MSSA and lowest for MRSA (Table 2).

In our study, we performed the disk approximation test as described by Weisblum and Demohn (10). Fiebelkorn et al. (2) have recently shown that the D-test can be performed by a routine disk diffusion procedure by placing the CL and ER disks at adjacent positions in the disk dispenser. These same authors have also shown that the D-test can be performed by placing ER and CL disks 15 mm from edge to edge in the heavy-inoculum area of standard blood agar plates used for purity checks with automated susceptibility test systems (J. H. Jorgensen, S. A. Crawford, L. M. McElmeel, and K. R. Fiebelkorn, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. D-241, 2003).

Accurate susceptibility data are important for appropriate therapy decisions; however, little is known about the prevalence of inducible CL resistance in CA-MRSA isolates. In one study conducted in Minnesota, 58 (84%) of 69 isolates that tested ER-R CL-S were found to be inducibly resistant by the D-test (K. Como-Sabetti, A. Glennen, J. Bartkus, S. Vetter, K. LeDell, D. Boxrud, R. Danila, and R. Lynfield, Abstr. 40th Annu. Meet. Infect. Dis. Soc. Am., abstr. 92, 2002). In contrast, a study conducted at the University of Iowa demonstrated that 65 (62%) of 105 Staphylococcus sp. isolates with the ER-R CL-S phenotype showed the MLSBi resistance phenotype (9).

In a study conducted at the University of São Paulo, São Paulo, Brazil, 11.3% of S. aureus and 13.7% of CNS isolates were found to have the MLSBi resistance phenotype (I. M. Van der Heijden, S. Sinto, C. Oplustil, and C. Mendes, Abstr. 101st Gen. Meet. Am. Soc. Microbiol., abstr. C-074, 2003). In a study conducted at the University of Texas Health Science Center, 34% of 114 ER-R S. aureus isolates demonstrated constitutive resistance to CL and 29% showed inducible resistance, while 70% of CNS isolates demonstrated constitutive CL resistance and 30% demonstrated inducible resistance (2). These data suggest that the occurrence of the MLSBi resistance phenotype varies widely by hospital and geographic region. Failure to identify inducible CL resistance when the ER-R CL-S phenotype is detected may lead to clinical failure of CL therapy (1). Conversely, labeling all ER-R staphylococci as CL-R or not reporting CL resistance when ER resistance is present will likely prevent the use of CL in treating infections that would likely respond to CL therapy (3, 7).

Our data show that the MLSBi resistance phenotype is prevalent in clinical laboratories in the Chicago metropolitan area; however, the incidence differs from that reported in other U.S. cities and internationally. Furthermore, the incidence of inducible resistance to CL varied between the MRSA and CNS isolates tested in our two hospitals. The cost benefit of routinely performing the D-test must be evaluated in each laboratory setting after first determining the incidence of the MLSBi and MLSBc resistance phenotypes. For example, in both of our hospitals, the incidence of the ER-R/I CL-S phenotype in MRSA was low, 8% at UIC and 14% at EMH, and of these isolates, approximately 83% were D-test positive. On the other hand, a large percentage of CNS isolates exhibited the ER-R/I CL-S phenotype and only 42% (UIC) and 54% (EMH) were D-test positive. Given these data, one might consider a policy of performing the D-test only on CNS isolates and considering all MRSA isolates with the ER-R/I CL-S phenotype to be D-test positive because the number of MRSA isolates with the MLSBc phenotype in our two hospitals was very small. Decisions about routine testing of staphylococci with the ER-R/I CL-S phenotype should be made on an institution-by-institution basis after obtaining local prevalence data.

REFERENCES
