Clindamycin Resistance in Staphylococcus aureus: Brief overview

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Abstract

Inducible clindamycin resistance in Staphylococcus aureus presents a significant clinical challenge, potentially leading to treatment failure in infections where clindamycin is a preferred therapeutic option. This resistance phenotype is primarily mediated by erm (erythromycin ribosomal methylase) genes, which modify the bacterial ribosome, conferring cross-resistance to both macrolides (like erythromycin) and lincosamides (like clindamycin). Unlike constitutive resistance, where erm genes are continuously expressed, inducible resistance is triggered by exposure to a macrolide inducer, most commonly erythromycin. This mechanism involves a translational attenuation system where a leader peptide regulates erm gene expression. In the absence of an inducer, the leader peptide maintains the mRNA in a conformation that inhibits erm expression. However, upon exposure to a macrolide, the antibiotic interacts with the ribosome stalled on the leader peptide, causing a conformational change in the mRNA that permits erm gene translation and subsequent methylase production. The D-zone test, a phenotypic assay recommended by the Clinical and Laboratory Standards Institute (CLSI), is the standard method for detecting inducible clindamycin resistance. A flattened or "D-shaped" zone of inhibition around the clindamycin disk adjacent to an erythromycin disk indicates a positive result. Molecular methods, such as PCR amplification of erm genes, offer greater sensitivity and specificity. The clinical implications of undetected inducible resistance are serious, especially in severe infections where clindamycin's excellent tissue penetration is advantageous. Treatment failure and the potential selection for constitutive resistance during therapy underscore the importance of accurate detection. Strategies to combat this resistance include routine D-zone testing, judicious antibiotic stewardship, robust infection control measures, development of novel antibiotics, and exploration of alternative therapies. Understanding the molecular basis, detection methods, and clinical implications of inducible clindamycin resistance is crucial for effective management of staphylococcal infections.

Keywords: Clindamycin Resistance, Staphylococcus aureus

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Introduction

Staphylococcus aureus is a versatile Gram-positive bacterium, a prominent member of the human microbiota, and a frequent opportunistic pathogen. Its ability to cause a wide range of infections, from superficial skin lesions to life-threatening systemic diseases, makes it a significant public health concern (1). The rise of antibiotic resistance, particularly methicillin resistance (MRSA), has dramatically complicated the treatment of staphylococcal infections, necessitating the exploration and preservation of alternative therapeutic options (2). Clindamycin, a lincosamide antibiotic, has emerged as a valuable agent against staphylococcal infections, including MRSA, due to its excellent tissue penetration and efficacy against both community-acquired and hospital-acquired strains (3). However, the increasing prevalence of clindamycin resistance, both constitutive and inducible, threatens its continued clinical utility (4). This review provides an in-depth analysis of inducible clindamycin resistance in *S. aureus*, focusing on the role of *erm* genes, their molecular mechanisms, detection methods, clinical implications, epidemiology, and strategies for mitigating the spread and impact of this resistance phenomenon.

1. Mechanisms of Clindamycin Resistance in *S. aureus*

Resistance to clindamycin in *S. aureus* can arise through two principal mechanisms:

- **Target Site Modification (MLS_B Resistance):** This prevalent mechanism is mediated by *erm* (erythromycin ribosomal methylase) genes, which encode enzymes that methylate the 23S rRNA of the 50S ribosomal subunit, the binding site for both macrolides (e.g., erythromycin) and lincosamides (e.g., clindamycin) (5). This methylation prevents antibiotic binding, resulting in cross-resistance to both drug classes. MLS_B resistance can manifest as either constitutive, with continuous *erm* gene expression, or inducible, where expression is triggered by exposure to a macrolide inducer, typically erythromycin. This inducible phenotype is the focus of this review.
- **Active Efflux:** A less common mechanism involves efflux pumps, which actively transport clindamycin out of the bacterial cell, preventing it from reaching inhibitory concentrations (6). This mechanism typically confers resistance to clindamycin but not erythromycin, distinguishing it from MLS_B resistance. Several efflux pumps, including MsrA, have been implicated in clindamycin resistance in *S. aureus* (7).

2. *erm* Genes and the Molecular Basis of Inducible Clindamycin Resistance

Inducible clindamycin resistance poses a significant diagnostic and therapeutic challenge because it can be overlooked by standard susceptibility testing methods, leading to potential treatment failure if clindamycin is chosen empirically (8). The *erm* genes responsible for this phenotype are typically regulated by a complex translational attenuation mechanism.

In the absence of an inducing agent, a leader peptide, encoded upstream of the *erm* gene, is transcribed and translated. The ribosome stalls during translation of this leader peptide, maintaining the mRNA in a conformation that prevents ribosome access to the *erm* coding sequence (9). This effectively inhibits the production of the rRNA methylase.

Upon exposure to an inducing macrolide, such as erythromycin, the antibiotic binds to the ribosome stalled on the leader peptide. This binding event triggers a conformational shift in the

mRNA, disrupting the secondary structure that previously blocked ribosome access to the *erm* gene (10). The ribosome can then proceed to translate the *erm* gene, leading to the production of the methylase enzyme and subsequent modification of the 23S rRNA, conferring resistance to both the inducing macrolide and clindamycin.

The most prevalent *erm* genes in *S. aureus* are *ermA*, *ermB*, and *ermC* (11). While *ermA* and *ermC* are usually associated with constitutive MLS_B resistance, *ermB* is predominantly linked to the inducible phenotype (12). The genetic context of these genes, including their location on plasmids, transposons, or the chromosome, can influence their expression and dissemination (13).

3. Detection of Inducible Clindamycin Resistance: The D-zone Test and Beyond

Accurate and timely detection of inducible clindamycin resistance is paramount for effective treatment of staphylococcal infections. The gold standard phenotypic method recommended by the Clinical and Laboratory Standards Institute (CLSI) is the D-zone test (14). This simple yet powerful technique involves placing erythromycin and clindamycin disks 15-20 mm apart on a Mueller-Hinton agar plate inoculated with the *S. aureus* isolate.

A positive D-zone test is characterized by a flattened or "D-shaped" zone of inhibition around the clindamycin disk adjacent to the erythromycin disk. This indicates that erythromycin has induced clindamycin resistance. A negative D-zone test, showing a circular zone of inhibition around the clindamycin disk, suggests either clindamycin susceptibility or constitutive MLS_B resistance.

While the D-zone test is widely used, it has some limitations. False-positive results can occur due to factors like disk spacing and inoculum density (15). False-negative results can arise in strains with low-level inducible resistance or unusual *erm* gene regulation (16).

Molecular methods, such as PCR amplification and sequencing of *erm* genes, provide a more definitive approach to identifying inducible resistance mechanisms (17). These methods offer enhanced sensitivity and specificity compared to phenotypic tests, allowing for the identification of the specific *erm* gene present and providing valuable epidemiological information.

4. Clinical Implications and Therapeutic Challenges

The clinical consequences of failing to detect inducible clindamycin resistance can be significant. Treatment of serious staphylococcal infections with clindamycin in patients harbouring inducibly resistant strains can lead to therapeutic failure, potentially resulting in prolonged illness, increased morbidity, and even mortality (18). This is particularly concerning in severe infections like necrotizing fasciitis, osteomyelitis, and bacteremia, where clindamycin is often preferred due to its favorable pharmacokinetic properties and tissue penetration (19).

Furthermore, clindamycin use in patients with inducibly resistant strains can exert selective pressure, favoring the emergence of constitutive resistance during therapy. This further restricts treatment options and contributes to the overall problem of antibiotic resistance (20).

5. Epidemiology and Global Distribution

The prevalence of inducible clindamycin resistance varies geographically and across different *S. aureus* populations. Studies have reported varying rates of inducible resistance among both methicillin-susceptible *S. aureus* (MSSA) and MRSA isolates, ranging from a few percent to over 50% in some regions (21, 22). The spread of specific *erm* genes and clonal lineages contributes to these variations.

The emergence and dissemination of inducible resistance are linked to factors such as antibiotic usage patterns, infection control practices, and the movement of individuals and populations (23). Understanding the local epidemiology of inducible resistance is crucial for guiding empirical antibiotic therapy and implementing effective infection control strategies.

6. Strategies to Mitigate Inducible Clindamycin Resistance

Combating the growing threat of inducible clindamycin resistance requires a multi-faceted approach:

- **Enhanced Detection:** Routine implementation of the D-zone test in all clinical microbiology laboratories is essential. Consideration should also be given to incorporating molecular methods for *erm* gene detection, particularly in settings with high rates of inducible resistance.
- **Judicious Antibiotic Stewardship:** Implementing and enforcing antibiotic stewardship programs is critical. Restricting the use of both macrolides and lincosamides to only clinically indicated cases can help minimize selective pressure for the development and spread of resistance.
- **Reinforced Infection Control Measures:** Strict adherence to infection control protocols, including hand hygiene, proper disinfection of medical equipment, and isolation precautions for infected patients, can help prevent the transmission of resistant strains within healthcare settings.
- **Novel Therapeutic Development:** Research efforts are crucial for developing new antibiotics with activity against resistant *S. aureus*, including those with novel mechanisms of action that circumvent existing resistance mechanisms.
- **Alternative Therapies:** Exploring alternative treatment strategies, such as bacteriophage therapy, antimicrobial peptides, and immunotherapy, may offer promising avenues for combating resistant infections.

7. Conclusion

Inducible clindamycin resistance, mediated by *erm* genes, presents a significant challenge to the effective management of staphylococcal infections. The complexities of the underlying molecular mechanisms, the potential for diagnostic pitfalls, and the clinical implications of treatment failure underscore the importance of a comprehensive approach to addressing this resistance phenomenon. By strengthening diagnostic capabilities, promoting judicious antibiotic use, enhancing infection control efforts, and fostering innovative research, we can strive to preserve the clinical utility of clindamycin and other valuable antibiotics in the face of evolving resistance threats.

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