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The Role of Subinhibitory Concentrations of Daptomycin and Tigecycline in Modulating Virulence in *Staphylococcus aureus*

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Abstract: *Staphylococcus aureus* (*S. aureus*) infections are notoriously complicated by the ability of the organism to grow in biofilms and are difficult to eradicate with antimicrobial therapy. The purpose of the current study was to clarify the influence of sub-inhibitory concentrations (sub-MICs) of daptomycin and tigecycline antibiotics on biofilm adhesion factors and exoproteins expressions by *S. aureus* clinical isolates. Six clinical isolates representing positive biofilm *S. aureus* clones (3 methicillin-sensitive *S. aureus* (MSSA) and 3 methicillin-resistant *S. aureus* (MRSA)) were grown with sub-MICs (0.5 MIC) of two antibiotics (daptomycin and tigecycline) for 12 h of incubation. RNA extracted from culture pellets was used via relative quantitative real-time-PCR (qRT-PCR) to determine expression of specific adhesion (*fnbA*, *fnbB*, *clfA*, *clfB*, *fib*, *ebps*, *cna*, *eno*) and biofilm (*icaADBC*) genes. To examine the effect of sub-MIC of these antibiotics on the expression of extracellular proteins, samples from the culture supernatants of six isolates were collected after 12 h of treatment with or without tigecycline in order to profile protein production via 2D gel sodium dodecyl sulfate-polyacrylamide gel electrophoresis (2D gel-SDS-PAGE). Sub-MIC treatment of all clinical MRSA and MSSA strains with daptomycin or tigecycline dramatically induced or suppressed *fnbA*, *fnbB*, *clfA*, *clfB*, *fib*, *ebps*, *cna*, *eno*, and *icaADBC* gene expression. Furthermore, sub-MIC use of tigecycline significantly reduced the total number of separated protein spots across all the isolates, as well as decreasing production of certain individual proteins. Collectively, this study showed very different responses in terms of both gene expression and protein secretion across the various isolates. In addition, our results suggest that sub-MIC usage of daptomycin and tigecycline could signal virulence induction by *S. aureus* via the regulation of biofilm adhesion factor genes and exoproteins. If translating findings to the clinical treatment of *S. aureus*, the therapeutic regimen should be adapted depending on antibiotic, the virulence factor and strain type.

Keywords: *S.aureus*; adhesion genes; exoproteins; qRT-PCR; 2D gel SDS-PAGE

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1. Introduction

Staphylococcus aureus (*S. aureus*) is a major problem in many clinical situations, and antibiotic-resistant forms are classified as a "high priority" pathogen by the World Health