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Fitness Cost of Antibiotic Resistance in *Staphylococcus aureus*: A Systematic Review

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Background: Recent reports have shown the potential of *Staphylococcus aureus* for acquiring resistance to last-resort antibiotics. However, most antibiotic resistance mechanisms were associated with a fitness cost that was typically observed as a reduced bacterial growth rate. This systematic review aimed to address the fitness cost of antibiotic resistance in *S. aureus* that emerged by mutations.
Methods: A systematic review was conducted after searching in two databases (PubMed and Scopus) using specific keywords. We included peer-reviewed articles published only in English. All studies describing the fitness cost associated with antibiotic resistance in *S. aureus* were selected. For each article, the results of fitness testing, minimum inhibition concentrations of mutants, the position of mutation, and the appearance of compensatory mutations were recorded.
Results: At all, 35 articles were recorded in the final analysis examining the fitness cost associated with antibiotic resistance in *S. aureus* that conferred by mutations. Analysis of the data showed that 26 studies reported that the emergence of antibiotic resistance was frequently associated with a fitness cost.
Conclusion: This review summarized that the antibiotic resistance selection caused in the majority of cases a substantial fitness cost. Further *in vivo* experiments revealed that these mutations affected bacterial virulence and the ability to establish a successful infection.

Keywords: *Staphylococcus aureus*, antibiotic resistance, mutation, fitness cost, compensatory mutations

Introduction

Staphylococcus aureus remains a troublesome pathogen especially within the hospital setting, causing diseases such as endocarditis, abscesses, pneumonia, toxic shock syndrome, and sepsis.[1] Numerous novel antibiotic molecules used to be employed to treat staphylococcal infections, including those due to methicillin-resistant *S. aureus* (MRSA).[2] These include linezolid, daptomycin, tigecycline, quinupristin/dalfopristin, and ceftaroline. In addition to these newer agents, several older drugs also demonstrated activity against some MRSA strains, including trimethoprim/sulfamethoxazole, tetracycline, clindamycin, and rifampin.[3]

Within 50 years, the number of species and strains of pathogenic and commensal antibiotic-resistant bacteria, and the number of antibiotics they are resistant to, have increased worldwide.[4] Multidrug-resistant organisms have not only emerged in the hospital environment but were also identified in community settings.

Antibiotic resistance could arise by the acquisition of foreign DNA by horizontal gene transfer or from mutations in the chromosomal target genes.[5] This later is among the main contributing causes of evolution, giving the expected material work for natural selection.[6] Mutations conferring antibiotic resistance modify the antibiotic activity through one of the following pathways: (1) antibiotic target alterations, (2) a reduction in antibiotic absorption, (3) efflux activation mechanisms; or (4) broad modifications in essential metabolic paths through regulatory network modulation.[5]

In many cases, chromosomal mutations that confer antibiotic resistance typically alter essential targets like the ribosome, DNA gyrase, RNA polymerase, or cell wall synthesis. Usually, these target changes cause a fitness cost to cell homeostasis and have deleterious effects since they impair vital functions or confer metabolic burdens.[5,7] This results in decreased bacterial fitness, which may be expressed as decreased survival and reduced growth rate, or for pathogenic organisms, as reduced transmission rate and virulence.[7,8]

The ''Fitness'' could be considered as the replication rate within prevailing environmental factors and can be evaluated by competitive fitness assessments or by determining

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