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ORIGINAL ARTICLE

# Dexamethasone abrogates the antimicrobial and antibiofilm activities of different drugs against clinical isolates of *Staphylococcus aureus* and *Pseudomonas aeruginosa*

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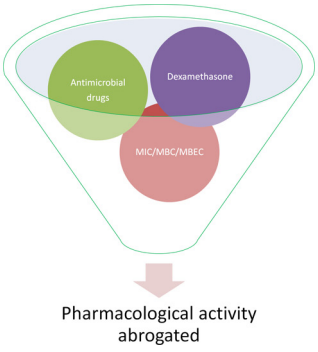
## GRAPHICAL ABSTRACT

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ABSTRACT

*Staphylococcus aureus* and *Pseudomonas aeruginosa* are part of the human microbiota and are also important bacterial pathogens, for which therapeutic options are lacking nowadays. The combined administration of corticosteroids and antimicrobials is commonly used in the treatment of infectious diseases to control inflammatory processes and to minimize potential toxicity of antimicrobials, avoiding sequelae. Although different pharmaceutical dosage forms of antimicrobials combined to corticosteroids are available, studies on the interference of corticosteroids on the pharmacological activity of antimicrobials are scarce and controversial. Here, we provide evidence of the interference of dexamethasone on the pharmacological activity of clinically important antimicrobial drugs against biofilms and planktonic cells of *S. aureus* and *P. aeruginosa*. Broth microdilution assays of minimal inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and minimum biofilm eradication concentration (MBEC) of gentamicin, chloramphenicol, oxacillin, ceftriaxone and meropenem were conducted with and without the addition of dexamethasone. The effect of all drugs was abrogated by dexamethasone in their MIC, MBC, and MBEC, except gentamicin and meropenem, for which the MBC was not affected in some strains. The present study opens doors for more investigations on *in vitro* and *in vivo* effects and safety of the combination of antimicrobials and glucocorticoids.


## Introduction

The treatment of bacterial infections presently faces major challenges due to the constant emergence of antimicrobial resistant strains. The rate of disease occurrence and mortality is increasing worldwide, as clinical treatments are steadily failing [1]. This microbial resistance picture has become a serious threat to public health, especially in developing countries, where health policies often do not include antimicrobial stewardship programs [2]. In addition, the number of new approved antimicrobial drugs has been decreasing since the 1950s. Because of the lack of novel antimicrobial drugs in the pharmaceutical market, scientists are worried on the possibility of the post-antibiotic era, in which scarce pharmacological options will be available for the treatment of even minor infectious diseases [1,2].

Several drug-resistant species have been detected in community and hospital outbreaks of infections. *Staphylococcus aureus* is a Gram-positive species which is part of the human microbiota, and is also an important opportunistic pathogen, which colonizes around 20% of the population [3]. Different diseases can be caused by *S. aureus* infections, including osteomyelitis, endocarditis, and otitis, and drug resistance among strains of this species is steadily growing worldwide [4,5]. *Pseudomonas aeruginosa* is an ubiquitous Gram-negative aerobic species, frequently isolated from aquatic and terrestrial environments and of the human microbiota [6,7]. Pathogenic strains of this species are commonly associated with chronic lung infections, and are capable of causing a wide range of opportunistic infections. High levels of phenotypic diversity of pathogenic strains have been described, and a clinically relevant consequence of this diversity is a poor antimicrobial susceptibility profile, making chronic *P. aeruginosa* infections very difficult to eradicate [1,8].

A common virulence factor involved in drug resistance by *S. aureus*, *P. aeruginosa* and several other microbial species are biofilms. Biofilms can be defined as microbial communities that grow attached to biological tissues or to abiotic surfaces, set in a matrix of extracellular polymeric substances (EPS) [9,10]. The EPS matrix is generally composed of polysaccharides, lipids, proteins and extracellular DNA, and has a protective and adhesive role in biofilm formation [11]. When planktonic bacteria start the transition to biofilms, varied biochemical-genetic regulatory pathways are activated to allow microbial attachment to surfaces, followed by microbial growth and EPS matrix production [12]. As microbial growth reaches a critical level for biofilm stability, the *quorum* sensing mechanism, an intracellular population-based communication system, is triggered, and micro-organisms are then detached from the biofilm [13]. The detached micro-organisms may attach to any near surfaces and form new biofilms, starting a new cycle of hard-to-treat infections [12].

Biofilm formation is associated with most of the known infectious diseases, and less than 0.1% of the known microorganisms live as planktonic (free) forms in the environment [10,13]. Biofilm-embedded strains have been described as more than 1000 times resistant to antimicrobial drugs than their planktonic counterparts due to the protective effect of the EPS, which may adsorb or react with antimicrobial drugs [14]. As a consequence, the entrance of active drugs into the biofilm is reduced, and it is possible that the adsorbed drugs, even at sub-inhibitory concentrations, can trigger transcription of genes associated with several resistance mechanisms [15].

In hospital settings, the treatment of infectious diseases in which a strong and extensive inflammatory process is noticed, the combined use of antimicrobials and corticosteroids is commonly adopted by prescribers [16,17]. Dexamethasone (1-dehydro-16α-methyl-9α-fluorohydrocortisone - DEXA) is a synthetic glucocorticoid widely used in such combinations on the treatment of infectious diseases, in order to modulate the immune responses triggered by microbial extracellular DNA, lipopolysaccharide and varied toxins [16,17]. Beyond its strong immunosuppressive properties, DEXA has the ability to penetrate the central nervous system, being used on the treatment