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PROCEEDINGS ABSTRACT

Pharmacodynamic study of several antibacterial–antifungal combinations against a *Staphylococcus aureus*–*Candida albicans* coinfection in an *in vitro* model: effects of albumin and platelets

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Optimizing antimicrobial treatment of bacterial–fungal coinfections remains a major clinical challenge due to the combined effects of the pathogen interaction and the host-related modifiers of drug activity. In particular, pharmacodynamic (PD) responses can be substantially altered by physiological factors such as protein binding and cellular components of the host environment, which are often not adequately captured in conventional *in vitro* models. This study was designed with the aim of quantitatively assessing how human albumin and platelets can influence the PD behaviour of combined antibacterial–antifungal therapies against *Staphylococcus aureus* and *Candida albicans*, using a dynamic *in vitro* pharmacokinetics / pharmacodynamics (PK/PD) model that simulates clinically relevant drug exposure. Such models have been shown to improve the translational prediction of antimicrobial efficacy [1]. Standard strains (*S. aureus* ATCC 25923 and *C. albicans* ATCC 90028), alone and in coinfection, were exposed to clinically relevant concentrations of antibacterial agents (vancomycin at 3 and 5 mg/L; clindamycin at 5 and 10 mg/L) administered as combination therapies with antifungal agents (caspofungin at 10 and 20 mg/L; amphotericin B at 2.5 and 5 mg/L). Experiments were conducted in the absence and presence of 2% human albumin and / or 2% platelet-rich plasma so as to mimic physiological conditions. Subsequently, the antimicrobial activity was assessed through relative optical density measurements and expressed in growth inhibition scales, with PD parameters estimated using a sigmoidal maximum effects (E_{max}) model and the area under the curve (AUC). The exposure–response relationships were defined using the $fAUC_{0–24}/C_{max}$ index, demonstrating an excellent model fitting (mean R^2 being ≈0.9) that is consistent with those of PK/PD analyses of antimicrobial combinations in previous studies [2]. Across all experimental conditions, combination therapies exhibited a concentration-dependent antimicrobial activity with characteristic sigmoidal E_{max} profiles. Notably, quantitative analyses revealed consistent and significantly augmented E_{max} values in the presence of host factors. Platelets markedly augmented the antimicrobial activity across all regimens, which may be attributed to the platelets essentially acting as key innate immune cells that upon activation by microorganisms or inflammatory mediators, release antimicrobial peptides from their granules in order to kill pathogens. This effect was further influenced by albumin, while the high-

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est E_{max} values were consistently observed in conditions combining an exposure to both albumin and platelets (p<0.001), thereby supporting previous findings on the host-mediated modulation of antimicrobial activity [3]. Among the tested regimens, vancomycin plus caspofungin demonstrated the highest intrinsic antimicrobial activity across mono- and coinfection models, achieving maximal E_{max} values. In contrast, vancomycin plus amphotericin B showed comparatively lower maximal activity, but maintained more stable PD responses across the assessed *in vitro* host conditions. On the other hand, the clindamycin-based combinations exhibited intermediate antimicrobial effects, but were significantly influenced by the host-related factors. Finally, in the coinfection models, all combinations exhibited reduced PD activity when compared to single-organism conditions, confirming the negative impact of polymicrobial interactions on treatment efficacy. Overall, this study suggests that while combination antimicrobial therapies can enhance the antimicrobial activity against bacterial–fungal coinfections, host-related factors (namely, protein binding and platelet interactions) can substantially influence the antimicrobial PD outcomes. These findings also underscore the importance of incorporating physiological conditions into the *in vitro* PK/PD models so as to improve the translational relevance of the generated data and to optimize therapeutic strategies for polymicrobial infections.

Keywords

albumin; antibacterial–antifungal synergy; pharmacodynamic model; platelets; polymicrobial infection

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Conflicts of interest statement

None to declare.

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