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# *In vitro* pharmacodynamic study of several antibiotic–antifungal combinations against a bacterial–fungal co-infection in the presence of albumin and / or platelets

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## ABSTRACT

*Background*: Managing bacterial–fungal co-infections remains clinically challenging due to complex pathogen interactions and host-related factors that can alter antimicrobial activity. *Aim*: This study aimed to evaluate the influence of albumin and platelets on the pharmacodynamic behavior of combined antibacterial–antifungal therapies against *Staphylococcus aureus and Candida albicans*. *Methodology*: Simulation of clinical drug exposures was performed using a dynamic *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model. Co-infection cultures were treated with combinations of an antibacterial (vancomycin or clindamycin) and an antifungal (caspofungin or amphotericin B) in the presence or absence of albumin, platelets, or both. Antimicrobial efficacy was determined by assessing microbial growth inhibition and calculating corresponding PD parameters. *Results*: Within this *in vitro* system, host factors significantly modulated antimicrobial efficacy. Platelets produced the greatest enhancement in growth inhibition, potentially via the release of antimicrobial peptides, while albumin appeared to modulate this platelet effect. Among the tested regimens, the vancomycin-caspofungin combination achieved the highest overall antimicrobial activity across the co-infection models, particularly when combined with platelets. Conversely, vancomycin plus amphotericin B demonstrated lower maximal efficacy. Clindamycin-based combinations showed intermediate activity and were highly sensitive to the presence of host factors. Generally, the co-infection environment reduced overall antimicrobial activity compared to baseline single-pathogen expectations. *Conclusion*: These *in vitro* findings suggest that host components, such as platelets and albumin, may play a meaningful role in shaping the PD outcomes of combination therapies. While these laboratory observations highlight the potential impact of the host microenvironment, cautious interpretation is warranted, and further *in vivo* research is required to validate whether these interactions translate to a clinical setting.

## KEYWORDS

polymicrobial co-infection, antibacterial–antifungal combination therapy, PK/PD modelling, host-related factors (albumin and platelets), $E_{max}$ and AUC analysis

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# 1. INTRODUCTION

Bacterial–fungal co-infections represent a complex therapeutic challenge, particularly when involving *Staphylococcus aureus* and *Candida albicans*, two opportunistic pathogens frequently co-isolated in bloodstream and device-associated infections. Their coexistence within the same host niche enables dynamic interspecies interactions that can alter microbial behavior, enhance virulence, and reduce susceptibility to antimicrobial agents, ultimately leading to poorer clinical outcomes and increased mortality rates [1,2]. These infections are increasingly observed among critically ill and immunocompromised patients, where disrupted host defenses and extensive antimicrobial exposure further complicate treatment strategies [3]. A major limitation in the management of such infections is the unpredictable impact of host-related factors on antimicrobial efficacy. Conventional susceptibility testing often fails to account for physiological conditions, particularly protein binding and host cellular components, which can significantly modify drug activity. The integration of host-derived components, such as human serum albumin and platelets, further enhances the physiological relevance of these models and allows a more accurate simulation of *in vivo* conditions. Albumin can significantly modify antimicrobial activity through drug protein binding, reducing the free and pharmacologically active fraction of agents, thereby prolonging their pharmacological effect [4,5]. Conversely, platelets contribute to host defense by releasing antimicrobial peptides and interacting directly with microorganisms. As active participants in innate immunity, they may alter microbial growth, biofilm formation, and susceptibility to antimicrobial agents, potentially enhancing or modulating antimicrobial responses [6]. Dynamic *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) modeling is a critical tool for mapping the relationship between drug exposure and antimicrobial efficacy in complex infections. By simulating clinical drug concentration profiles, these models replicate *in vivo* environments to accurately evaluate combination therapies [7,8]. In bacterial–fungal co-infections, combination therapy is vital to achieve adequate coverage and leverage synergistic drug effects. However, conventional testing falls short due to unpredictable interspecies dynamics and poorly defined host microenvironments. Consequently, controlled *in vitro* systems are necessary to reproducibly analyze microbial interactions and refine therapeutic strategies [9]. Additionally, dynamic *in vitro* PK/PD models offer a robust and cost-effective framework to evaluate exposure–response relationships. This allows researchers to identify the critical PD parameters required to guide precise dose optimization [10]. These advanced models are particularly invaluable for studying multidrug-resistant and polymicrobial infections where clinical data are scarce. They allow researchers to evaluate long-term antimicrobial effects and use high microbial inocula without the ethical constraints associated with *in vivo* animal testing [11,12]. Therefore, this study aimed to investigate the PD interactions and efficacies of combined antibacterial–antifungal therapies against S. aureus and C. albicans under co-infection conditions, using a dynamic *in vitro* PK/PD model system in the presence and absence of human albumin and platelets.

# 2. METHODOLOGY

## 2.1. Antimicrobial therapies

Vancomycin (Voxin; 1 g; Vianex S.A, Greece), Clindamycin phosphate (Clindafit; 600 mg/ampoule; Medizia Biotech, India), Caspofungin (Tecaspo; 50 mg/vial; Intelico, India) and Amphotericin B (Amfocare; 50mg/ vial; BPRL, India) were used. These agents were selected to represent commonly used antibacterial and antifungal therapies in clinical practice.

## 2.2. Microbial strains and media

Reference strains of *S. aureus ATCC 25923* and *C. albicans ATCC 90028* were used. Microorganisms were cultured in RPMI-1640 medium (Sigma-Aldrich, Germany) at 37°C under standard conditions. Inocula were prepared from 24-h cultures suspended in sterile normal saline and adjusted to a final concentration of $2 \times 10^4$ colony-forming units (CFU)/ mL using a counting chamber. The experimental medium consisted of RPMI-1640 supplemented with 2% human albumin (Kedrion Biopharma, Italy) and/or 2% platelet-rich plasma (PRP tube, China) (prepared by centrifuging fresh blood samples and used immediately in the experiment) to simulate physiological conditions. Simulated drug concentration–time profiles were generated in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines as (CLSI M26-A: Methods for Determining Bactericidal Activity of Antimicrobial Agents and CLSI M100/M27: Methods for Determining Fungicidal Activity).

## 2.3. PK/PD model setup

A dynamic *in vitro* PK/PD system driven by a peristaltic pump (Minipuls Evolution; Gilson Inc.,

France) was employed. The model consisted of a 500 mL beaker of external compartment (EC) with RPMI-1640 media containing 5 mL dialysis tubes representing the internal compartment (IC) containing the microorganisms. The dialysis membrane, composed of cellulose with a molecular weight cutoff of <50 kDa, allowed diffusion of antimicrobial agents while retaining microorganisms within IC. Antimicrobial agents were introduced into the system at clinically relevant concentrations, and drug elimination was simulated by continuous dilution with fresh medium at a rate corresponding to human plasma clearance, assuming a 24-h half-life. To simulate local host-pathogen interactions, human serum albumin and/or platelets were introduced directly into the 5 mL IC alongside the microbial inocula. This setup enabled dynamic, time-dependent changes in drug concentration, closely mimicking *in vivo* pharmacokinetics and providing a reliable platform for PD assessment. This was achieved by adding fresh broth to dilute its content at a rate equal to the clearance of antibiotic and antifungal drugs in the human plasma.

### 2.4. *In vitro* PD analysis

Microbial growth within the dialysis tubes was monitored over 24 h. At predetermined time points, 200 µL samples were collected and analyzed spectrophotometrically at 600 nm to determine the relative optical density (ROD). Growth inhibition (E) was calculated relative to baseline values. Growth inhibition at 24 h was used as the primary PD endpoint and analyzed using a sigmoidal dose–response model to characterize the relationship between drug exposure and the antimicrobial effect. The PK/PD index fAUC0–24/$C_{max}$ was calculated for each regimen to describe the exposure–response relationship.

### 2.5. Statistical analysis

Data were analyzed, and PD parameters were estimated using nonlinear regression analysis (GraphPad Prism 5.0 Software, San Diego, CA, USA) based on a sigmoidal $E_{max}$ model with a variable slope. $E_{max}$ values were determined for each antimicrobial combination under different experimental conditions (with and without albumin and/or platelets) and compared across treatment groups. The sigmoid $E_{max}$ model provided accurate and precise estimates when the $C_{max}$ was more than 85% of $EC_{50}$. Statistical significance between the baseline combinations and those supplemented with host factors was evaluated, with significance levels established at $p<0.05$, $p<0.01$, and $p<0.001$.

### 2.6. Ethical approval

This study is an *in vitro* laboratory evaluation using standard reference strains from the American Type Culture Collection (ATCC). No human participants, clinical specimens, or animal subjects were involved; therefore, formal institutional ethical approval was not required for this research protocol.

## 3. RESULTS

### 3.1. Pharmacodynamic activity ($E_{max}$) against *S. aureus* and *C. albicans* monocultures

PD activity ($E_{max}$) of all tested antimicrobial combinations against both single-pathogen models increased significantly upon the addition of human albumin, platelets, or both, with the magnitude of enhancement depending on the specific regimen (Table 1 and Table 2).

#### 3.1.1 *S. aureus* monoculture

Vancomycin–caspofungin combinations exhibited moderate baseline $E_{max}$ values (range: 5.834–6.054), which increased significantly in the presence of platelets (up to 13.710; $p<0.001$) and moderately with albumin alone ($p<0.01$). Clindamycin–caspofungin regimens showed intermediate baseline activity but experienced significant enhancement across all host-simulated conditions, particularly with platelets ($p<0.001$). Vancomycin–amphotericin B combinations demonstrated the lowest baseline $E_{max}$ values (range: 0.2695–0.3280) but still showed statistically significant improvements when exposed to albumin ($p<0.01$) and platelets ($p<0.001$).

#### 3.1.2. *C. albicans* monoculture

Vancomycin–caspofungin regimens achieved the highest baseline $E_{max}$ values (≈9.948–10.104), with further significant increases observed primarily in platelet-supplemented groups ($p<0.001$). Albumin alone produced a selective enhancement that reached significance predominantly at higher drug concentrations ($p<0.001$). Clindamycin–caspofungin combinations displayed lower baseline antifungal activity but were significantly enhanced by all host factors ($p<0.001$). Amphotericin B combinations maintained the lowest baseline activity ($E_{max}$ = 0.3280) but demonstrated consistent increases in platelet-supplemented environments ($p<0.001$).

**Table 1.** The $E_{max}$ (maximum of growth inhibition) in presence and absence of human albumin and/or platelets calculated for all antibacterial-antifungal combinations against *Staphylococcus aureus-ATCC-25923*.

| Antibacterial-Antifungal combinations | Mean $E_{max}$ without adding | Mean $E_{max}$ with albumin | Mean $E_{max}$ with platelets | Mean $E_{max}$ with albumin & platelets |
|---|---|---|---|---|
| Vancomycin 3mg/L+ Amphotericin B 2.5mg/L | 0.2695 | 0.565** | 0.8985*** | 0.5470** |
| Vancomycin 5mg/L+ Amphotericin B 5mg/L | 0.3280 | 0.6920** | 0.8885*** | 0.7370 |
| Clindamycin 5mg/L+ Caspofungin 10mg/L | 2.443 | 5.108** | 7.385*** | 3.984** |
| Clindamycin 10mg/L+ Caspofungin 20mg/L | 5.070 | 8.188** | 9.502** | 6.027* |
| Vancomycin 3mg/L+ Caspofungin10mg/L | 5.834 | 8.115** | 12.151*** | 9.114** |
| Vancomycin 5mg/L+ Caspofungin 20mg/L | 6.054 | 9.758** | 13.710*** | 10.310** |

Significant differences *versus* combination without addition (*: $p<0.05$; **: $p<0.01$, ***: $p<0.001$).

**Table 2.** The $E_{max}$ (maximum of growth inhibition) in presence and absence of human albumin and/or platelets calculated for all antibacterial-antifungal combinations against *Candida albicans ATCC-90028*.

| Antibacterial-Antifungal combinations | Mean $E_{max}$ without adding | Mean $E_{max}$ with albumin | Mean $E_{max}$ with platelets | Mean $E_{max}$ with albumin & platelets |
|---|---|---|---|---|
| Vancomycin 3mg/L+ Amphotericin B 2.5mg/L | 0.4165 | 0.5880* | 0.8385*** | 0.6560** |
| Vancomycin 5mg/L+ Amphotericin B 5mg/L | 0.3280 | 0.3655*** | 0.7455 | 0.5620* |
| Clindamycin 5mg/L+ Caspofungin 10mg/L | 1.243 | 4.518** | 8.815*** | 5.807*** |
| Clindamycin 10mg/L+ Caspofungin 20mg/L | 3.280 | 7.955*** | 10.51*** | 8.620*** |
| Vancomycin 3mg/L+ Caspofungin10mg/L | 5.987 | 9.948*** | 13.310*** | 11.720** |
| Vancomycin 5mg/L+ Caspofungin 20mg/L | 5.520 | 10.104*** | 14.023*** | 11.640* |

Significant differences *versus* combination without addition (*: $p<0.05$; **: $p<0.01$, ***: $p<0.001$).

## 3.2. PD activity ($E_{max}$) in polymicrobial co-infection

In the polymicrobial co-infection model, baseline $E_{max}$ values for all combinations were generally lower than those observed in single-pathogen environments. However, the addition of host factors consistently increased PD efficacy across all regimens (Table 3). Vancomycin–caspofungin combinations retained high baseline activity (range: 6.865–7.065), which was significantly augmented by platelets ($p<0.001$), while albumin alone had a minimal effect. Clindamycin–caspofungin regimens maintained intermediate baseline activity but exhibited significant increases under all host conditions, especially during combined albumin–platelet exposure. Amphotericin B combinations exhibited the lowest baseline values (range: 0.3445–0.3590) but showed consistent, statistically significant increases in the presence of both host components ($p< 0.05$ to $p<0.001$).

## 3.3. PK/PD modeling and exposure–response relationships

The *in vitro* PK/PD model successfully simulated human-like drug elimination kinetics. A strong, consistent relationship was observed between

drug exposure indexes ($fAUC_{0–24}$ and $C_{max}$) and overall antimicrobial activity across all evaluated regimens (mean $R^2 \approx 0.9$, Figure 1).

Under baseline drug-only conditions, increments in drug exposure correlated with enhanced PD responses.

**Table 3:** The $E_{max}$ (maximum of growth inhibition) in presence and absence of human albumin and/or platelets calculated for all antibacterial-antifungal combinations against Co-infection with both *Staphylococcus aureus-ATCC-25923* and *Candida albicans ATCC-90028*.

| Antibacterial-Antifungal combinations | Mean $E_{max}$ without adding | Mean $E_{max}$ with albumin | Mean $E_{max}$ with platelets | Mean $E_{max}$ with albumin & platelets |
|---|---|---|---|---|
| Vancomycin 3mg/L+ Amphotericin B 2.5mg/L | 0.3445 | 0.4875* | 1.093*** | 0.6025** |
| Vancomycin 5mg/L+ Amphotericin B 5mg/L | 0.3590 | 0.5200* | 0.6910** | 0.5850* |
| Clindamycin 5mg/L+ Caspofungin 10mg/L | 3.280 | 4.655* | 10.510*** | 7.620** |
| Clindamycin 10mg/L+ Caspofungin 20mg/L | 5.995 | 7.363* | 11.750*** | 8.461** |
| Vancomycin 3mg/L+ Caspofungin10mg/L | 7.065 | 9.211* | 13.817** | 10.981** |
| Vancomycin 5mg/L+ Caspofungin 20mg/L | 6.865 | 9.003* | 14.430** | 11.390** |

Significant differences *versus* combination without addition (*: $p<0.05$; **: $p<0.01$, ***: $p<0.001$).

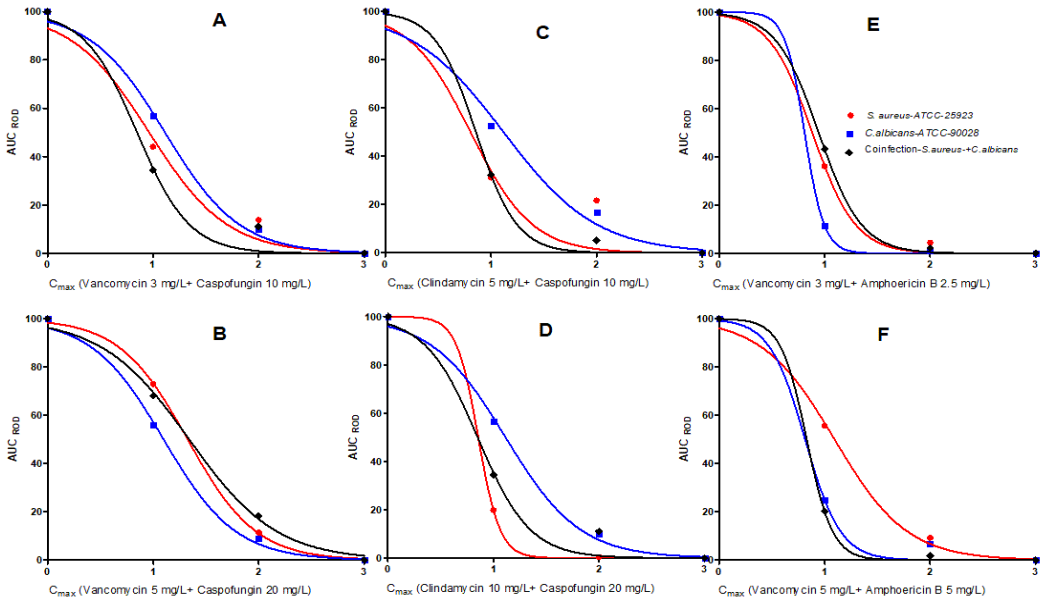


**Figure 1.** *In vitro* pharmacodynamic analysis of Non-linear regression modeling of normalized $AUC_{ROD}$ as the area under the concentration time curve ($fAUC_{0-24}$) (Y axis) *versus* $C_{max}$ for all six antibacterial-antifungal combinations (X-axis) (**0-** without addition; **1-** with 2% albumin only; **2-** with 2% albumin and 2% platelets and **3-** with 2% platelets only) against *S.aureus-ATCC-25923*, *C.albicans-ATCC-90028* and co-infection for both microorganisms. **(A)** $C_{max}$ (Vancomycin 3 mg/L+ Caspofungin 10 mg/L); **(B)** $C_{max}$ (Vancomycin 5 mg/L+ Caspofungin 20 mg/L); **(C)** $C_{max}$ (Clindamycin 5 mg/L+ Caspofungin 10 mg/L); **(D)** $C_{max}$ (Clindamycin 10 mg/L + Caspofungin 20 mg/L); **(E)** $C_{max}$ (Vancomycin 3 mg/L+ Amphotericin B 2.5 mg/L) and **(F)** $C_{max}$ (Vancomycin 5 mg/L+ Amphotericin B 5 mg/L).

The introduction of albumin and platelets caused a distinct upward shift in the exposure–response curves, as confirmed by normalized $AUC_{ROD}$ analysis. This profile shift indicates increased drug potency in host-supplemented media. This effect was most pronounced in setups containing platelets, whereas albumin alone exerted a moderate, regimen-dependent influence. Among the combinations, amphotericin B-containing regimens consistently yielded lower exposure–response profiles despite showing measurable growth inhibition. Conversely, the inclusion of caspofungin enhanced antifungal outcomes without compromising antibacterial efficacy.

## 4. DISCUSSION

This study evaluated the PD interaction between combination antimicrobial therapies and key host components using a dynamic *in vitro* PK/PD model. Our findings demonstrate that the addition of human albumin and platelets consistently enhances the growth-inhibitory activity ($E_{max}$) of both antibacterial and antifungal regimens. This effect was maintained across single-species cultures and polymicrobial *S. aureus–C. albicans* co-infections. The pronounced augmentation of antimicrobial activity mediated by platelets across most regimens may involve distinct biological mechanisms. Platelets are known components of the early innate immune response, capable of releasing an array of antimicrobial peptides (e.g., thrombocidins) and interacting directly with microbial cell walls [6,13]. These interactions may destabilize cell membranes, alter microbial growth rates, or interrupt early biofilm architecture, thereby rendering the pathogens more susceptible to conventional antibiotics and antifungals [14,15]. Albumin, by contrast, demonstrated a more modest and variable influence on drug activity. While albumin typically binds drugs and can restrict the free-fraction availability of highly protein-bound agents, it also serves as a physiological buffer and a modulator of platelet activation pathways. The observed synergy in combined albumin–platelet environments suggests that albumin may preserve or facilitate platelet-mediated microbial susceptibility, compensating for any potential reductions in free drug concentrations. The observed decline in baseline antimicrobial efficacy within the co-infection model underscores the complicating nature of interspecies dynamics. *S. aureus* and *C. albicans* are known to form dense, synergistic polymicrobial biofilms where the fungal extracellular matrix can physically shield bacterial cells from antibiotic penetration [1,3]. Strikingly, the addition of host factors particularly platelets mitigated some of this protection. This suggests that physiological components might alter interspecies biofilm dynamics or modify the expression of the surface receptors necessary for co-aggregation, thereby partially restoring drug efficacy. Among the specific therapeutics evaluated, the vancomycin–caspofungin combination emerged as the most robust regimen, maintaining superior $E_{max}$ values and favorable exposure–response profiles across both single and polymicrobial models [16] and a standardized 24-h elimination half-life was applied across all experimental runs. This uniform dilution rate represents an *in vitro* simplification necessary to systematically evaluate drug combinations with disparate human PK profiles under identical, controlled exposure kinetics [17]. This suggests a potential compatibility between these mechanisms of action that is preserved, and even enhanced, by host microenvironments. Conversely, amphotericin B-based combinations underperformed relative to caspofungin-based regimens, indicating that the baseline activity of the core antimicrobial pair remains a key determinant of overall efficacy, regardless of host-factor supplementation.

A primary limitation of this investigation is its reliance on an *in vitro* PK/PD model. While dynamic *in vitro* systems successfully simulate human drug concentration-time profiles, they cannot fully replicate the complex, shifting environment of an *in vivo* infection site. Furthermore, the model utilized a unified 24 h half-life for all evaluated agents to maintain technical reproducibility. In clinical settings, these drugs exhibit divergent elimination kinetics (e.g., clindamycin half-life ≈6 h vs. the prolonged clearance of amphotericin B (>24 h)). Additionally, static concentrations of albumin and platelets were utilized, which do not reflect the dynamic fluctuations in host cell counts and serum protein levels that occur during acute clinical sepsis. Consequently, while these findings suggest that integrating physiological factors into PK/PD modeling frameworks may refine the understanding of drug performance, these data must be interpreted with caution.

## 5. CONCLUSION

The findings from this *in vitro* model suggest that host factors, particularly platelets and albumin, have the potential to enhance the efficacy of antibacterial–antifungal combinations against polymicrobial infections, though cautious interpretation is required. Since conventional *in vitro* models often underestimate this potential, integrating physiological components is vital for more accurate assessments. Moreover, among the tested regimens, combinations involving caspofungin showed notable

improvements in growth inhibition. Adopting host-mimicking models ensures clinically relevant evaluations, aiding in the optimization of treatment strategies for complex co-infections.

## ADDITIONAL INFORMATION

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### CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

### ETHICAL STATEMENTS
This study is an *in vitro* laboratory evaluation using standard reference strains from the American Type Culture Collection (ATCC). No human participants, clinical specimens, or animal subjects were involved; therefore, formal institutional ethical approval was not required for this research protocol.

### ARTIFICIAL INTELLIGENCE (AI) USE
The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI. No AI tools were used in the preparation of this manuscript.

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