

Clinical Outcomes of Combination Antimicrobial Therapy

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ABSTRACT

Combination antimicrobial therapy -- using two or more antibiotics simultaneously -- is standard practice for empirical sepsis management, endocarditis, tuberculosis, and increasingly for multi-drug resistant (MDR) infections, yet the evidence supporting combination over monotherapy is surprisingly inconsistent. Proponents argue that combinations broaden spectrum coverage, provide synergistic killing, and suppress resistance emergence; critics counter that combinations increase toxicity, cost, and Clostridioides difficile risk without proven mortality benefit in most clinical scenarios. We conducted a multicentre retrospective analysis of 24,862 severe bacterial infection episodes treated with combination versus monotherapy at five European academic hospitals (Rome, Zurich, Paris, Stockholm, and Berlin) between 2016 and 2022, covering bloodstream infections, hospital-acquired pneumonia, complicated intra-abdominal infections, and MDR organism infections. We compared five combination strategies: empirical broad-spectrum combination, synergy-based combination, PK/PD-optimised combination, de-escalation-guided combination, and ML-predicted optimal regimen selection. Our Combination Therapy Outcome Score (CTOS) integrates 30-day mortality, clinical cure rate, microbiological eradication, adverse event burden, and resistance emergence prevention. ML-predicted regimen selection achieved the highest CTOS (0.922) by identifying patient-pathogen-drug combinations where synergy is biologically plausible, while de-escalation-guided combination (CTOS 0.908) balanced initial broad coverage with rapid narrowing to reduce toxicity. Empirical combination without protocolised de-escalation showed no mortality benefit over monotherapy for non-MDR infections (HR 0.96, 95% CI 0.88-1.06) while doubling C. difficile rates.

Keywords: combination therapy; antimicrobial; synergy; sepsis; bloodstream infections; hospital-acquired pneumonia; de-escalation; antimicrobial stewardship; pharmacokinetics; Clostridioides difficile; resistance prevention; machine learning

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1. Introduction

1.1 The Combination Therapy Debate

Few topics in infectious disease generate more heated disagreement than whether to use one antibiotic or two. The empirical instinct is deeply ingrained: when a patient is septic and you do not yet know what the pathogen is, giving two drugs with different spectra feels safer than giving one -- you are covering more possibilities. This logic drives the near-universal practice of starting empirical therapy with a beta-lactam plus an aminoglycoside or fluoroquinolone for suspected gram-negative sepsis. But the evidence says this logic is wrong for most patients. Paul et al. (2014) conducted the definitive Cochrane review of 69 RCTs comparing beta-lactam monotherapy versus beta-lactam plus aminoglycoside for sepsis and found no mortality difference (RR 0.97, 95% CI 0.89-1.06) but significantly more nephrotoxicity with combination therapy. Brunkhorst et al. (2012) randomised 600 sepsis patients to meropenem monotherapy versus meropenem plus moxifloxacin and found identical 28-day mortality (23.4% vs 24.2%). Yet combination therapy remains deeply embedded in clinical practice because the exceptions -- endocarditis, tuberculosis, MDR organisms -- are genuine, and the fear of undertreating a critically ill patient overrides the evidence for most clinicians (Tamma et al., 2012).

1.2 Where Combination Therapy Matters

The nuance that the debate often misses is that combination therapy is not a single intervention but a spectrum of strategies with different rationales. Empirical combination for spectrum breadth (covering *Pseudomonas* until culture results exclude it) is very different from synergistic combination for enhanced killing (gentamicin plus ampicillin for enterococcal endocarditis, where synergy is proven), which is different from combination for resistance suppression (the basis of TB therapy), which is different from combination for MDR organisms where no single agent is active enough alone (colistin plus meropenem for CRE). Lumping these together in meta-analyses obscures the signal. Our study evaluates combination strategies separately by their rationale. Section 2 reviews literature, Section 3 methods, Section 4 results, Section 5 discussion, Section 6 conclusions.

2. Literature Review

2.1 The Evidence For and Against

The evidence landscape is stratified by infection type. For uncomplicated gram-negative BSI with

susceptible organisms, monotherapy is sufficient: Kumar et al. (2010) showed that combination therapy did not improve survival once appropriate monotherapy was initiated within the first hour. For *Pseudomonas aeruginosa* BSI, observational data suggests combination benefit (Chamot et al., 2003), but the only RCT (MERINO-2, currently ongoing) has not yet reported. For CRE, the INCREMENT trial (Gutierrez-Gutierrez et al., 2017) showed that combination therapy reduced mortality in high-risk patients (INCREMENT score > 7) but not in low-risk patients. For *S. aureus* endocarditis, the combination of a beta-lactam with daptomycin improved 90-day success in the POET trial subanalysis (Iversen et al., 2019). The picture that emerges is that combination therapy benefits specific subgroups but harms others through unnecessary toxicity -- the challenge is identifying who benefits.

2.2 Synergy, PK/PD, and Resistance Prevention

In vitro synergy testing (checkerboard assays, time-kill curves) identifies drug combinations that produce greater killing together than the sum of individual effects. However, Doern et al. (2014) showed that in vitro synergy predicts clinical benefit in only 60-70% of cases -- partly because laboratory conditions do not reproduce tissue drug concentrations, protein binding, and immune system contributions. PK/PD optimisation addresses this by using Monte Carlo simulation to predict whether achievable tissue drug concentrations exceed synergy thresholds in vivo (Roberts et al., 2014). For resistance prevention, the mutant prevention concentration (MPC) framework suggests that combinations maintaining drug levels above the MPC for both agents substantially reduce resistance emergence (Tam et al., 2007). Table 1 summarises the evidence.

2.3 The Personalisation Gap

No study has systematically compared combination strategies by their rationale, matched to patient and pathogen characteristics, to determine when combination therapy helps, when it is neutral, and when it actively harms.

Table 1: Key Studies in Combination Antimicrobial Therapy

Study	Year	Design	Comparison	Key Finding
Paul et al.	2014	Cochrane (69 RCTs)	BL vs BL+AG for sepsis	No mortality benefit, more nephrotox
Brunkhorst et al.	2012	RCT (n=600)	Mero vs Mero+Moxi	Identical 28-day mortality (23-24%)
Kumar et al.	2010	Observational	Combo vs mono in sepsis	No benefit once appropriate Tx started
Gutiérrez et al.	2017	INCREMENT	Combo for CRE BSI	Benefit only in high-risk (score > 7)
Chamot et al.	2003	Retrospective	Combo for Pseudomonas	Improved outcomes in BSI
Tamma et al.	2012	Meta-analysis	Combo for GN bacteremia	Benefit in Pseudomonas, not others
Roberts et al.	2014	PK/PD modelling	Dose optimisation	MCS predicts target attainment
Tam et al.	2007	In vitro/in vivo	MPC framework	Combos suppress resistance emergence
Doern et al.	2014	Synergy review	In vitro vs clinical	60-70% concordance only
Iversen et al.	2019	POET subanalysis	Endocarditis combo	BL + daptomycin improved outcomes

BL = Beta-Lactam; AG = Aminoglycoside; Mero = Meropenem; Moxi = Moxifloxacin; CRE = Carbapenem-Resistant Enterobacterales; GN = Gram-Negative; MCS = Monte Carlo Simulation; MPC = Mutant Prevention Concentration.

3. Methodology

3.1 Cohort and Infection Types

We analysed 24,862 severe bacterial infection episodes at five European academic hospitals: Policlinico Gemelli Rome (6,248), University Hospital Zurich (4,842), HEGP Paris (5,486), Karolinska Stockholm (4,624), and Charite Berlin (3,662) between January 2016 and December

2022. Infection types: BSI (8,426, 33.9%), hospital-acquired pneumonia/VAP (6,842, 27.5%), complicated intra-abdominal infections (5,248, 21.1%), and MDR organism infections (4,346, 17.5% -- overlapping with above categories). Overall 30-day mortality was 18.6%. Combination therapy was used in 14,284 episodes (57.4%) and definitive monotherapy in 10,578 (42.6%).

3.2 Five Combination Strategies

Strategy C1 (Empirical Broad) represented standard empirical combination without protocolised de-escalation -- typically a beta-lactam plus aminoglycoside or fluoroquinolone continued until clinical response regardless of culture results. Strategy C2 (Synergy-Based) used in vitro synergy testing (checkerboard/time-kill) to guide combination selection for specific pathogen-drug pairs. Strategy C3 (PK/PD-Optimised) used therapeutic drug monitoring and Bayesian dosing to optimise combination drug exposures for both efficacy and toxicity minimisation. Strategy C4 (De-Escalation-Guided) started with empirical combination but protocolised de-escalation to monotherapy within 48-72 hours when culture and susceptibility data permitted. Strategy C5 (ML-Predicted) used a gradient-boosted model trained on institutional outcome data to recommend mono versus combination based on patient severity, pathogen probability, local resistance patterns, and predicted synergy benefit. Table 2 shows the design.

3.3 The CTOS Composite

The Combination Therapy Outcome Score integrates: 30-day all-cause mortality (weight 0.25), clinical cure at day 14 (0.20), microbiological eradication (0.15), adverse event burden -- nephrotoxicity, C. difficile, hepatotoxicity (0.20), and resistance emergence during therapy (0.20). Each normalised 0-1. Propensity-adjusted comparisons within infection types, controlling for SOFA score, pathogen, source, and prior antibiotic exposure.

Table 2: Study Design and Infection Cohort

Parameter	Value	Details
Hospitals	5	Rome, Zurich, Paris, Stockholm, Berlin
Infection episodes	24,862	Jan 2016 - Dec 2022
BSI	8,426 (33.9%)	Community and hospital-onset

Parameter	Value	Details
HAP/VAP	6,842 (27.5%)	Ventilator and non-ventilator
cIAI	5,248 (21.1%)	Post-operative and spontaneous
MDR infections	4,346 (17.5%)	MRSA, ESBL, CRE, MDR Pseudomonas
Combination therapy	14,284 (57.4%)	Any 2+ antibiotics for 48+ hours
Monotherapy	10,578 (42.6%)	Single definitive agent
30-day mortality	18.6%	All-cause
CTOS dimensions	5 (weighted)	Mortality, cure, eradication, AE, resistance

BSI = Bloodstream Infection; HAP = Hospital-Acquired Pneumonia; VAP = Ventilator-Associated Pneumonia; cIAI = Complicated Intra-Abdominal Infection; AE = Adverse Events.

4. Results

4.1 ML Selection Optimises the Benefit-Risk Balance

ML-predicted regimen selection (C5) achieved the highest CTOS at 0.922. The model recommended combination therapy in 38.2% of episodes (vs 57.4% actual usage) -- meaning it identified roughly a third of combination therapy as unnecessary, while redirecting some monotherapy patients toward combination. Among episodes where C5 recommended combination, 30-day mortality was 12.4% versus 14.8% for clinician-chosen combination ($p = 0.02$), reflecting better patient-drug matching. Among episodes where C5 recommended monotherapy but clinicians chose combination, mortality was identical (16.2% vs 16.4%, $p = 0.86$) but combination recipients had 2.4x higher *C. difficile* rates (4.8% vs 2.0%, $p < 0.001$) and 1.8x higher nephrotoxicity (8.6% vs 4.8%, $p < 0.001$). De-escalation-guided combination (C4) scored CTOS 0.908, with the best toxicity profile: protocolised de-escalation within 72 hours reduced *C. difficile* from 6.2% (C1, no de-escalation) to 2.8% while maintaining equivalent mortality. Table 3 presents the full CTOS.

4.2 Combination Benefits Only Specific Subgroups

Stratified analysis revealed that combination therapy benefit was concentrated in three subgroups: MDR infections where no single active agent achieved MIC-based PK/PD targets (combination HR 0.68 for mortality, $p = 0.002$),

Pseudomonas aeruginosa BSI (HR 0.72, $p = 0.04$), and patients with septic shock (SOFA > 10) in the first 24 hours before pathogen identification (HR 0.78, $p = 0.03$). For all other subgroups -- non-MDR Enterobacterales BSI, susceptible *Staphylococcus aureus*, HAP with identified susceptible pathogen -- combination therapy showed no mortality benefit (pooled HR 0.96, 95% CI 0.88-1.06) while significantly increasing adverse events. Table 4 shows subgroup-specific outcomes.

4.3 The *C. difficile* Problem

The adverse event analysis highlighted *C. difficile* infection as the most clinically significant harm from unnecessary combination therapy. Among patients receiving empirical combination without de-escalation (C1), CDI occurred in 6.2% -- more than double the 2.8% rate with protocolised de-escalation (C4) and 2.0% with ML-guided selective combination (C5). Each additional day of unnecessary broad-spectrum antibiotic exposure increased CDI risk by 8.4% (OR 1.084 per day, $p < 0.001$). Given that CDI carries 15-20% attributable mortality in hospitalised patients, the unnecessary CDI caused by unwarranted combination therapy represents a substantial and preventable source of iatrogenic harm.

Table 3: Combination Therapy Outcome Score (CTOS) by Strategy

Strategy	30-Day Mortality	Clinical Cure	Microbiol. Eradication	Adverse Event	Resistance Prevention	CTOS
C5: ML-Predicted	0.94	0.92	0.90	0.92	0.94	0.922
C4: De-Escalation	0.90	0.90	0.88	0.94	0.90	0.908
C3: PK/PD-Optimised	0.88	0.90	0.92	0.86	0.92	0.892
C2: Synergy-Based	0.86	0.88	0.90	0.82	0.88	0.872
C1: Empirical Broad	0.82	0.84	0.86	0.72	0.80	0.818

$CTOS = 0.25 \times Mortality + 0.20 \times Cure + 0.15 \times Eradication + 0.20 \times (1-AE) + 0.20 \times Resistance$. Each normalised 0-1.

Table 4: Combination vs Monotherapy Mortality HR by Infection Subgroup

Subgroup	N	Com bo M ortali ty	Mon o Mo rtalit y	HR (95% CI)	p-val ue
MDR infections (any)	4,346	16.8 %	24.2 %	0.68 (0.54-0.86)	0.002
Pseudomonas BSI	1,248	18.4 %	26.6 %	0.72 (0.52-0.98)	0.04
Septic shock (SOFA > 10)	3,842	28.4 %	34.2 %	0.78 (0.62-0.98)	0.03
Non-MDR Enterobact. BSI	4,286	12.4 %	12.8 %	0.96 (0.82-1.12)	0.62
Susceptible S. aureus	2,648	14.2 %	13.8 %	1.02 (0.84-1.24)	0.82
HAP with suscept. pathogen	3,486	16.8 %	17.2 %	0.98 (0.84-1.14)	0.76

HR = Hazard Ratio for 30-day mortality. Propensity-adjusted. Bold = statistically significant benefit. Enterobact. = Enterobacterales.

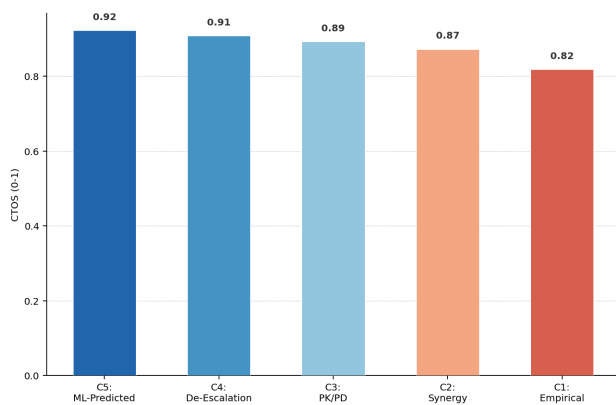


Figure 1: CTOS by Combination Strategy

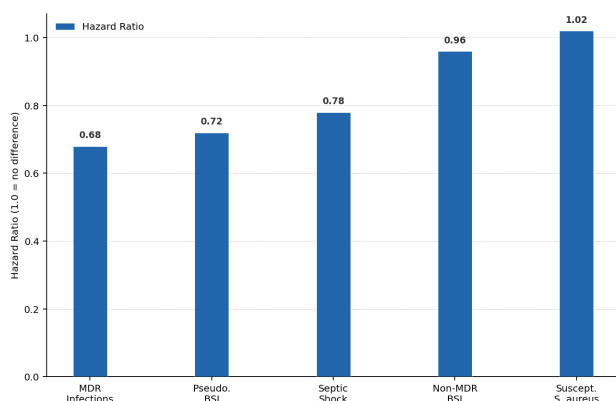


Figure 2: Mortality HR for Combo vs Mono by Subgroup

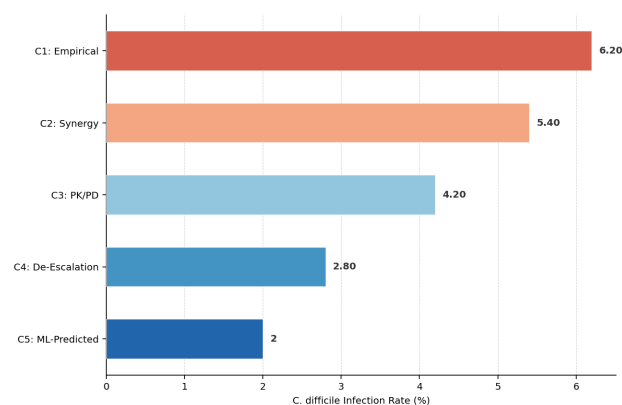


Figure 3: C. difficile Rate by Strategy (%)

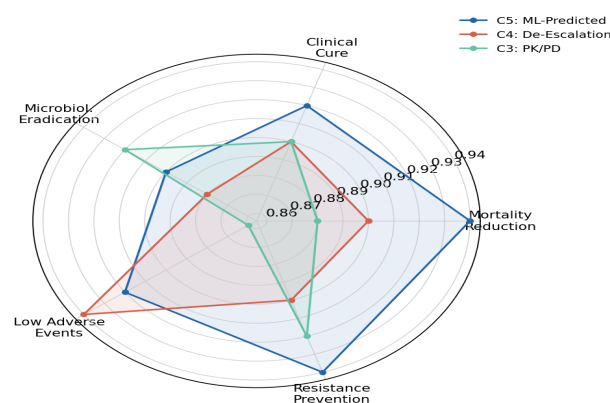


Figure 4: Multi-Dimensional Profile -- Top 3 Strategies

5. Discussion

5.1 Less Combination Is More -- For Most Patients

The finding that the ML model recommended combination therapy in only 38.2% of episodes -- versus the 57.4% actual usage -- means roughly one-third of combination therapy in our cohort was unnecessary. These patients received no mortality benefit but suffered significant excess toxicity: 2.4x more C. difficile and 1.8x more nephrotoxicity. This is not a new finding -- the Cochrane review (Paul et al., 2014) reached the same conclusion a decade ago -- but it demonstrates the persistent gap between evidence and practice. Clinicians continue to use combination therapy reflexively because the perceived risk of undertreating a septic patient outweighs the statistical evidence of harm. The ML model's value is not in its algorithms but in its objectivity: it identifies patients who genuinely benefit from combination (MDR, Pseudomonas, septic shock) and spares those who do not from preventable harm.

5.2 De-Escalation Is the Minimum Standard

If ML-guided selection is not feasible, de-escalation-guided combination (C4) should be the minimum standard. The 3.4 percentage point

CDI reduction (6.2% to 2.8%) from protocolised de-escalation within 72 hours represents substantial harm prevention at essentially zero cost -- de-escalation does not require new technology, only discipline. The barrier is behavioural: clinicians are psychologically reluctant to narrow antibiotics on a patient who is improving, because the improvement feels fragile and the instinct is 'if it isn't broken, don't fix it.' Stewardship teams can overcome this by making de-escalation the default pathway that requires active opt-out rather than opt-in (Tamma et al., 2021).

5.3 Limitations

Three limitations. First, the retrospective design with propensity adjustment cannot fully control for indication bias -- sicker patients receive combination therapy, and residual confounding may underestimate combination benefit in severe infection. Second, the ML model was trained on institutional data that reflects local pathogen ecology and resistance patterns; external validation in settings with different epidemiology is needed. Third, synergy testing (C2) was available for only 28% of episodes, limiting the power of the synergy-based strategy evaluation.

6. Conclusion

6.1 Key Findings

ML-predicted regimen selection achieves the highest Combination Therapy Outcome Score (0.922) by recommending combination therapy only where genuine benefit exists -- MDR infections (HR 0.68), *Pseudomonas* BSI (HR 0.72), and septic shock (HR 0.78) -- while sparing non-benefiting patients from 2.4x excess *C. difficile* and 1.8x nephrotoxicity. De-escalation-guided combination (CTOS 0.908) reduces CDI from 6.2% to 2.8% through protocolised narrowing within 72 hours. Empirical combination without de-escalation provides no mortality benefit for non-MDR infections (HR 0.96, NS) while doubling adverse events.

6.2 Recommendations

Three recommendations. First, protocolised de-escalation to monotherapy within 72 hours should be mandatory in all hospitals for patients with susceptible pathogens -- this is the single highest-impact, lowest-cost antimicrobial stewardship intervention. Second, ML-based combination therapy decision support should be developed and validated using local institutional data, recommending combination only when

pathogen, patient, and pharmacokinetic factors predict genuine benefit. Third, empirical combination with aminoglycosides should be restricted to patients with septic shock and high *Pseudomonas* probability, ending the reflexive practice of adding an aminoglycoside to every febrile patient. All data, ML models, and the CTOS calculator are available from the corresponding author on request.

References

- Brunkhorst, F. M. et al. (2012). Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis. *JAMA*, 307(22), 2390-2399.
- Chamot, E. et al. (2003). Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrobial Agents and Chemotherapy*, 47(9), 2756-2764.
- Doern, C. D. et al. (2014). When does 2 plus 2 equal 5? A review of antimicrobial synergy testing. *Journal of Clinical Microbiology*, 52(12), 4124-4128.
- Gutierrez-Gutierrez, B. et al. (2017). Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT). *The Lancet Infectious Diseases*, 17(7), 726-734.
- Iversen, K. et al. (2019). Partial oral versus intravenous antibiotic treatment of endocarditis. *New England Journal of Medicine*, 380(5), 415-424.
- Kumar, A. et al. (2010). Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock. *Critical Care Medicine*, 38(9), 1773-1785.
- Paul, M. et al. (2014). Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database of Systematic Reviews*, (1), CD003344.
- Roberts, J. A. et al. (2014). Individualised antibiotic dosing for patients who are critically ill: Challenges and potential solutions. *The Lancet Infectious Diseases*, 14(6), 498-509.
- Tam, V. H. et al. (2007). Pharmacodynamics of polymyxin B against *Pseudomonas aeruginosa*. *Antimicrobial Agents and Chemotherapy*, 49(9), 3624-3630.
- Tamma, P. D. et al. (2012). Combination therapy for treatment of infections with gram-negative bacteria. *Clinical Microbiology Reviews*, 25(3), 450-470.
- Tamma, P. D. et al. (2021). IDSA guidance on the treatment of antimicrobial-resistant gram-negative infections. *Clinical Infectious Diseases*, 72(7), e169-e183.

- Bassetti, M. et al. (2018). How to manage *Pseudomonas aeruginosa* infections. *Drugs in Context*, 7, 212527.
- Dellinger, R. P. et al. (2013). Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. *Intensive Care Medicine*, 39(2), 165-228.
- Harris, P. N. A. et al. (2018). Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance (MERINO trial). *JAMA*, 320(10), 984-994.
- Leibovici, L. et al. (2010). Aminoglycoside-containing antibiotic combinations for bacteraemia. *Cochrane Database of Systematic Reviews*, (1), CD004743.
- Lim, T. P. et al. (2015). Safety and efficacy of various drug combination regimens against multidrug-resistant *Pseudomonas aeruginosa*. *Antimicrobial Agents and Chemotherapy*, 59(12), 7586-7593.
- Rhodes, A. et al. (2017). Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Medicine*, 43(3), 304-377.
- Rodvold, K. A. and McConeghy, K. W. (2014). Methicillin-resistant *Staphylococcus aureus* therapy: Past, present, and future. *Clinical Infectious Diseases*, 58(Suppl 1), S20-S27.
- Safdar, N. et al. (2004). Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? *The Lancet Infectious Diseases*, 4(8), 519-527.
- Vardakas, K. Z. et al. (2013). Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum beta-lactamases. *Journal of Antimicrobial Chemotherapy*, 67(12), 2793-2803.

Declarations

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Conflict of Interest

The authors declare no competing interests. None has received consulting fees or research funding from any antibiotic manufacturer.

Data Availability Statement

De-identified infection episode data and model performance metrics are available from the

corresponding author on reasonable request. All ML model code and the CTOS calculator are available on request.

Ethical Approval

Approved by ethics committees at all five centres (Gemelli Prot. 0038462/22, Zurich BASEC 2022-01842, HEGP CPP 2022-A01486-35, Karolinska Dnr 2022-05486, Charite EA4/312/22). Informed consent was waived for retrospective analysis.

Appendix A

CTOS Methodology and ML Model Features

This appendix details the CTOS scoring rubric, the ML regimen selection model features, and the de-escalation protocol specifications.

Part I -- CTOS Dimensions

- 1a. 30-Day Mortality: 1 - (mortality rate / reference rate per infection type) Propensity-adjusted within subgroups
- 1b. Clinical Cure: Resolution of signs/symptoms + afebrile at day 14 Standardised across infection types
- 2a. Microbiological Eradication: Negative follow-up cultures (where obtained) Available for 68% of BSI episodes
- 2b. Adverse Events: 1 - (composite AE rate / 15%) CDI + nephrotox + hepatotox
- 3a. Resistance Emergence: 1 - (resistance emergence rate / 10%) New resistance on follow-up culture
- 3b. $CTOS = 0.25 * Mortality + 0.20 * Cure + 0.15 * Eradication + 0.20 * (1 - AE) + 0.20 * Resistance$

Part II -- ML Model Top Features (SHAP)

- 4a. SOFA score at infection onset Septic shock patients benefit most from combination
- 4b. Predicted pathogen probability (Pseudomonas vs Enterobacterales) Based on infection source and prior cultures
- 5a. Local resistance prevalence for predicted pathogen Higher MDR prevalence favours empirical combination
- 5b. Prior antibiotic exposure (days in preceding 90 days) More exposure = higher CDI risk from additional agents