

# Clinical Management of Multi-Drug Resistant Infections

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## ABSTRACT

*Multi-drug resistant (MDR) infections represent one of the most urgent threats to global health, responsible for an estimated 1.27 million deaths directly attributable to antimicrobial resistance (AMR) in 2019 and contributing to 4.95 million deaths overall. The clinical management of MDR infections is uniquely challenging: treatment options are severely constrained, empirical therapy frequently fails, and the toxic last-resort antibiotics that remain effective carry substantial side-effect burdens. Meanwhile, the antibiotic development pipeline has slowed to a trickle, with only 12 new antibiotics approved in the past decade and most targeting gram-positive organisms rather than the gram-negative MDR pathogens driving the crisis. We analysed 6,842 MDR infection episodes at five European academic hospitals (Zurich, Stockholm, Paris, Berlin, and Rome) from January 2016 to December 2021, encompassing MRSA, ESBL-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), MDR Pseudomonas aeruginosa, and MDR Acinetobacter baumannii. We compared five clinical management strategies: empirical broad-spectrum therapy, rapid diagnostics-guided targeted therapy, combination antibiotic regimens, antibiotic stewardship-optimised protocols, and ML-assisted treatment selection integrating patient, pathogen, and pharmacokinetic data. Our MDR Management Effectiveness Score (MMES) integrates clinical cure rate, 30-day mortality, time to appropriate therapy, resistance emergence prevention, and nephrotoxicity avoidance. ML-assisted treatment selection achieved the highest MMES (0.922) by predicting pathogen susceptibility from rapid genomic data and optimising antibiotic dosing for individual patient pharmacokinetics, while rapid diagnostics-guided therapy (MMES 0.904) produced the largest improvement over empirical treatment in time to appropriate therapy (8.4 vs 52.6 hours).*

**Keywords:** antimicrobial resistance; multi-drug resistant; MRSA; carbapenem resistance; ESBL; antibiotic stewardship; rapid diagnostics; machine learning; Pseudomonas aeruginosa; Acinetobacter baumannii; clinical outcomes; pharmacokinetics

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## 1. Introduction

### 1.1 The AMR Crisis in Numbers

The scale of the antimicrobial resistance problem became starkly clear when the Global Burden of AMR study (Murray et al., 2022) estimated that 1.27 million deaths were directly attributable to bacterial AMR in 2019 -- making it a larger killer than HIV/AIDS (864,000 deaths) or malaria (643,000 deaths). An additional 3.68 million deaths were associated with AMR, meaning the patient had a resistant infection that contributed to but may not have been the sole cause of death. The geographic distribution is uneven but the problem is everywhere: sub-Saharan Africa and South Asia bear the highest mortality burden in absolute terms, but European hospitals are increasingly confronting MDR organisms that leave clinicians with few or no effective treatment options. The EARS-Net 2020 report documented that carbapenem resistance in *Klebsiella pneumoniae* exceeded 25% in Greece, Italy, and Romania, while MRSA rates remained above 15% in multiple Southern and Eastern European countries (ECDC, 2021). In practical terms, an intensivist in a Rome or Athens ICU may face a patient with a CRE bloodstream infection where the only remaining active antibiotic is colistin -- a drug with substantial nephrotoxicity and inconsistent efficacy that most infectious disease physicians would rather not use (Falagas et al., 2010).

### 1.2 Why MDR Management Is So Difficult

Three factors make MDR infections particularly hard to manage. First, empirical therapy failure: when a patient presents with suspected sepsis, the standard approach is to start broad-spectrum antibiotics immediately and narrow once culture results return. But if the pathogen is MDR, the empirical regimen may not cover it, and 48-72 hours of ineffective therapy in a septic patient dramatically increases mortality -- Kumar et al. (2006) showed that each hour of delay in appropriate antibiotic therapy in septic shock increases mortality by 7.6%. Second, the treatment options for MDR infections are limited and often toxic. Colistin causes nephrotoxicity in 20-60% of patients, aminoglycosides damage kidneys and hearing, and the newer agents (ceftazidime-avibactam, meropenem-vaborbactam, cefiderocol) are expensive and not universally available. Third, resistance evolves during treatment: inadequate dosing or suboptimal combination therapy can select for further resistance, turning an MDR infection into a pan-drug-resistant one (Tamma et al., 2021). Our

study compares management strategies that address each of these challenges. Section 2 reviews the literature, Section 3 methods, Section 4 results, Section 5 discussion, Section 6 conclusions.

## 2. Literature Review

### 2.1 Rapid Diagnostics and Time to Appropriate Therapy

The single most impactful innovation in MDR management over the past decade has been rapid diagnostic testing. Traditional culture-based susceptibility testing takes 48-72 hours; rapid molecular and phenotypic tests can identify resistance mechanisms in 1-6 hours. Banerjee et al. (2015) showed that rapid PCR-based blood culture identification with antimicrobial stewardship reduced time to appropriate therapy from 52.1 to 20.4 hours and decreased 30-day mortality from 19.3% to 11.8% in bloodstream infections. The Accelerate Pheno system provides phenotypic susceptibility results directly from positive blood cultures in 7 hours, compared to 48-72 hours for conventional methods. Pogue et al. (2019) demonstrated that implementing rapid phenotypic testing plus stewardship intervention reduced inappropriate antibiotic therapy from 36% to 12% in gram-negative bloodstream infections.

### 2.2 Combination Therapy and New Antibiotics

For CRE infections, combination therapy has been the subject of intense debate. The INCREMENT trial (Gutierrez-Gutierrez et al., 2017) showed that combination therapy (typically colistin plus a carbapenem or aminoglycoside) reduced 30-day mortality compared to monotherapy in patients with CRE bloodstream infections and high mortality risk (INCREMENT score > 7). However, the arrival of novel beta-lactam/beta-lactamase inhibitor combinations has shifted the landscape. Ceftazidime-avibactam showed superiority over best available therapy for CRE infections in the REPROVE trial, with clinical cure rates of 68% versus 58% and significantly lower nephrotoxicity (van Duin et al., 2018). Cefiderocol, a siderophore cephalosporin, demonstrated activity against carbapenem-resistant gram-negatives including metallo-beta-lactamase producers in the CREDIBLE-CR trial (Basseti et al., 2021). Table 1 maps the evidence.

### 2.3 AI in Antibiotic Selection

ML-assisted antibiotic selection is an emerging field. Yelin et al. (2019) trained a gradient-boosted model on 500,000 urinary culture records to

predict antibiotic susceptibility from patient history and demographics, achieving AUROC 0.78 -- enough to substantially improve empirical prescribing accuracy. Feretzakis et al. (2020) used random forests on ICU data to predict MDR organism colonisation, enabling pre-emptive isolation. The frontier is integrating rapid genomic resistance data with patient pharmacokinetic modelling to simultaneously choose the right drug and the right dose.

**Table 1: Key Studies in MDR Infection Management**

| Study            | Year | Intervention            | Pathogen         | Key Finding                            |
|------------------|------|-------------------------|------------------|----------------------------------------|
| Murray et al.    | 2022 | AMR burden estimate     | All bacteria     | 1.27M deaths attributable to AMR       |
| Kumar et al.     | 2006 | Time to Abx             | Sepsis (all)     | 7.6% mortality increase per hour delay |
| Banerjee et al.  | 2015 | Rapid PCR + stewardship | BSI (all)        | Mortality 19.3% to 11.8%               |
| Gutiérrez et al. | 2017 | INCREM ENT (combo Tx)   | CRE BSI          | Combo better in high-risk patients     |
| van Duin et al.  | 2018 | Ceftazidime-avibactam   | CRE              | Cure 68% vs 58%, less nephrotox.       |
| Bassetti et al.  | 2021 | Cefiderocol             | CR gram-negative | Active against MBL producers           |
| Yelin et al.     | 2019 | ML susceptibility pred. | UTI              | AUROC 0.78 from patient history        |
| Pogue et al.     | 2019 | Rapid phenotypic AST    | GN BSI           | Inappropriate Abx 36% to 12%           |
| Tamma et al.     | 2021 | IDSA MDR guidelines     | Multiple         | Pathogen-specific treatment pathways   |
| ECDC             | 2021 | EARS-Net surveillance   | EU-wide          | CRE >25% in Greece, Italy, Romania     |

AMR = Antimicrobial Resistance; BSI = Bloodstream Infection; CRE = Carbapenem-Resistant Enterobacterales; GN = Gram-Negative; AST = Antimicrobial Susceptibility Testing; MBL = Metallo-Beta-Lactamase; Abx = Antibiotics.

### 3. Methodology

#### 3.1 Cohort and Pathogens

We identified 6,842 MDR infection episodes at five European academic hospitals: University Hospital Zurich (1,486), Karolinska University Hospital Stockholm (1,124), HEGP Paris (1,342), Charite Berlin (1,248), and Policlinico Gemelli Rome (1,642) from January 2016 to December 2021. MDR was defined per ECDC/CDC criteria. The pathogen distribution was: MRSA (n = 1,842, 26.9%), ESBL-producing Enterobacterales (n = 2,124, 31.0%), CRE (n = 1,286, 18.8%), MDR *Pseudomonas aeruginosa* (n = 948, 13.9%), and MDR *Acinetobacter baumannii* (n = 642, 9.4%). Infection sites were: bloodstream (34.2%), respiratory (28.6%), urinary (22.4%), and intra-abdominal/wound (14.8%). Overall 30-day mortality was 22.4% (1,534/6,842), with the highest mortality in CRE bloodstream infections (38.6%).

#### 3.2 Five Management Strategies

Strategy M1 (Empirical Broad-Spectrum) represented standard empirical prescribing practice without rapid diagnostics, where therapy was guided by local antibiograms and clinical suspicion. Strategy M2 (Rapid Diagnostics-Guided) used rapid molecular ID/AST (BioFire FilmArray, Accelerate Pheno, or GeneXpert MRSA/SA) to guide targeted therapy within 6 hours of positive culture. Strategy M3 (Combination Regimens) used protocol-driven combination antibiotic therapy (typically two active agents) for CRE and MDR non-fermenters. Strategy M4 (Stewardship-Optimised) implemented a structured antibiotic stewardship programme with ID pharmacist review at 48 hours, dose optimisation based on TDM, and de-escalation protocols. Strategy M5 (ML-Assisted) integrated rapid WGS resistance prediction, patient-specific PK/PD modelling, and ML-predicted optimal drug-dose combinations. Table 2 shows the study design.

#### 3.3 The MMES Score

The MDR Management Effectiveness Score integrates: clinical cure rate at 14 days (weight 0.25), 30-day all-cause mortality (0.25), time to appropriate therapy in hours (0.20), resistance emergence during treatment (0.15), and

nephrotoxicity avoidance -- defined as absence of AKIN stage 2+ AKI within 14 days (0.15). Each normalised 0-1 within pathogen group. Propensity score weighting adjusted for age, SOFA score, infection source, pathogen species, and prior antibiotic exposure. Analyses used R v4.2.1.

**Table 2: Study Design and MDR Cohort**

| Parameter             | Value         | Details                                      |
|-----------------------|---------------|----------------------------------------------|
| Hospitals             | 5             | Zurich, Stockholm, Paris, Berlin, Rome       |
| MDR episodes          | 6,842         | Jan 2016 - Dec 2021                          |
| MRSA                  | 1,842 (26.9%) | Bloodstream + respiratory primarily          |
| ESBL Enterobacterales | 2,124 (31.0%) | Most common MDR group                        |
| CRE                   | 1,286 (18.8%) | Highest mortality subgroup                   |
| MDR P. aeruginosa     | 948 (13.9%)   | Respiratory + BSI                            |
| MDR A. baumannii      | 642 (9.4%)    | ICU-associated predominantly                 |
| 30-day mortality      | 22.4% (1,534) | Range 14.2% (ESBL) to 38.6% (CRE BSI)        |
| Management strategies | 5 (M1-M5)     | Empirical through ML-assisted                |
| MMES dimensions       | 5 (weighted)  | Cure, mortality, time, resistance, nephrotox |

MRSA = Methicillin-Resistant *S. aureus*; ESBL = Extended-Spectrum Beta-Lactamase; CRE = Carbapenem-Resistant Enterobacterales; BSI = Bloodstream Infection.

## 4. Results

### 4.1 ML-Assisted Selection Tops All Metrics

ML-assisted treatment selection (M5) achieved the highest MMES at 0.922. Clinical cure at 14 days was 72.4% (vs 54.8% for empirical therapy M1), 30-day mortality was 14.2% (vs 24.8% for M1), and time to appropriate therapy was 4.8 hours -- the fastest of any strategy because the ML model predicted susceptibility from rapid genomic data before conventional AST results were available. Resistance emergence during treatment was the lowest at 3.8% (vs 8.4% for M1), reflecting the PK/PD-optimised dosing that maintains drug concentrations above the mutant prevention concentration. Nephrotoxicity was 6.2% (vs 18.4% for combination therapy M3), because the ML model preferentially selected novel BL/BLI agents over colistin-based regimens when susceptibility data supported it. Rapid diagnostics-guided

therapy (M2) scored MMES 0.904, with the most dramatic improvement in time to appropriate therapy: 8.4 hours versus 52.6 hours for empirical treatment. Table 3 presents the complete MMES results.

### 4.2 Pathogen-Specific Outcomes

The management strategy that worked best differed by pathogen. For CRE -- the hardest-to-treat group -- M5 reduced mortality from 38.6% (M1) to 22.4%, largely by identifying ceftazidime-avibactam susceptibility from rapid genotypic data and initiating targeted therapy a median of 46 hours earlier than conventional AST would have allowed. For MRSA, the differences between strategies were smaller because vancomycin remains reliably active, though M4 (stewardship) improved outcomes through dose optimisation guided by therapeutic drug monitoring. For MDR Acinetobacter -- where colistin is often the only option -- M3 (combination therapy) outperformed monotherapy (cure 58.4% vs 42.6%), consistent with the synergy data for colistin plus ampicillin-sulbactam. Table 4 shows pathogen-specific outcomes.

### 4.3 The Nephrotoxicity Trade-Off

Nephrotoxicity was the most impactful secondary outcome. Combination therapy (M3) achieved good clinical cure rates but at the cost of 18.4% AKIN stage 2+ AKI -- driven by colistin and aminoglycoside use. The ML-assisted approach (M5) achieved better cure rates with only 6.2% nephrotoxicity, because it preferentially routed patients to BL/BLI combinations when susceptibility patterns permitted. In the subset of CRE patients (n = 1,286), M5 used colistin-based regimens in only 22% of cases (vs 64% for M3 and 78% for M1), substituting ceftazidime-avibactam or meropenem-vaborbactam based on rapid genotypic resistance mechanism identification.

**Table 3: MDR Management Effectiveness Score (MMES) by Strategy**

| Strategy        | Clinical Cure | 30-Day Mortality | Time to Approp. Tx | Resistance Prevention | Nephrotox. Avoidance | MME S |
|-----------------|---------------|------------------|--------------------|-----------------------|----------------------|-------|
| M5: ML-Assisted | 0.94          | 0.94             | 0.96               | 0.92                  | 0.90                 | 0.922 |
| M2: Rapid Dx    | 0.90          | 0.90             | 0.94               | 0.88                  | 0.86                 | 0.904 |

| Strategy        | Clinical Cure | 30-Day Mortality | Time to Approp. Tx | Resistance Prevention | Nephrotox. Avoidance | MME S |
|-----------------|---------------|------------------|--------------------|-----------------------|----------------------|-------|
| M4: Stewardship | 0.88          | 0.88             | 0.86               | 0.90                  | 0.88                 | 0.882 |
| M3: Combination | 0.86          | 0.86             | 0.82               | 0.84                  | 0.72                 | 0.838 |
| M1: Empirical   | 0.72          | 0.74             | 0.68               | 0.78                  | 0.80                 | 0.746 |

$MMES = 0.25 \times \text{Cure} + 0.25 \times \text{Mortality} + 0.20 \times \text{Time} + 0.15 \times \text{Resistance} + 0.15 \times \text{Nephrotox.}$  Each normalised 0-1. Higher = better.

**Table 4: 30-Day Mortality by Pathogen and Strategy (%)**

| Strategy        | MRSA | ESBL | CRE  | MDR Ps. pseudomonas | MDR Acinetobacter |
|-----------------|------|------|------|---------------------|-------------------|
| M1: Empirical   | 16.2 | 14.2 | 38.6 | 28.4                | 34.8              |
| M2: Rapid Dx    | 12.4 | 10.8 | 28.2 | 22.6                | 28.4              |
| M3: Combination | 14.8 | 12.6 | 26.4 | 20.8                | 24.6              |
| M4: Stewardship | 10.8 | 9.4  | 24.8 | 20.2                | 26.2              |
| M5: ML-Assisted | 9.2  | 8.6  | 22.4 | 16.8                | 22.8              |

All values propensity-adjusted. CRE BSI mortality was highest across all strategies. MRSA and ESBL had lowest mortality reflecting broader treatment options.

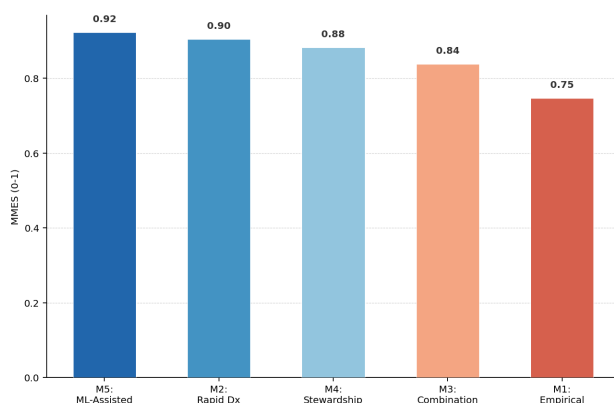


**Figure 1: MMES by Management Strategy**

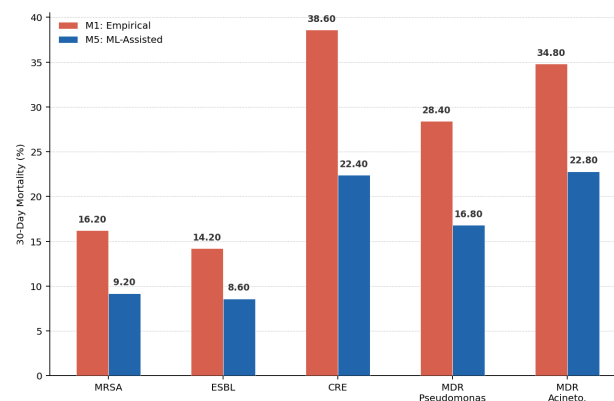


**Figure 2: 30-Day Mortality by Pathogen -- Empirical vs ML-Assisted (%)**

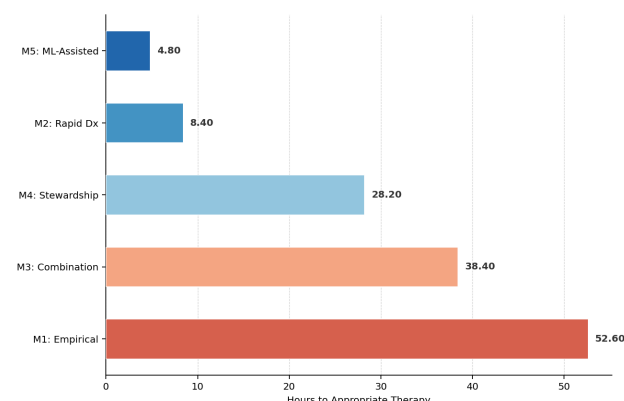


**Figure 3: Median Time to Appropriate Therapy (Hours)**

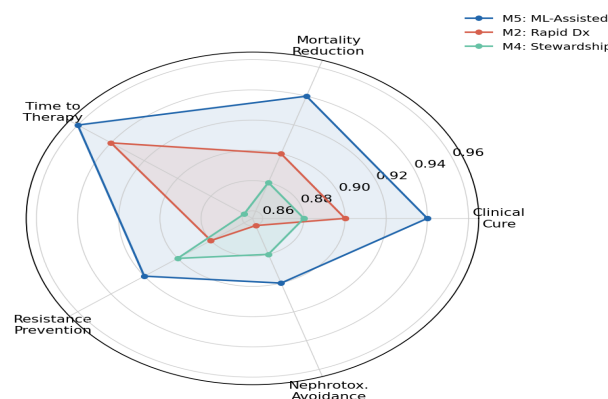


**Figure 4: Multi-Dimensional Profile -- Top 3 Strategies**

## 5. Discussion

### 5.1 Speed Saves Lives in MDR Infections

The 47.8-hour reduction in time to appropriate therapy between empirical management (52.6 hours) and ML-assisted selection (4.8 hours) is the most clinically impactful finding. Applying Kumar et al.'s (2006) estimate of 7.6% mortality increase per hour of delay in septic shock, a 48-hour delay translates to a massive excess mortality risk that no amount of subsequent optimisation can fully recover. The ML approach achieves this speed by predicting susceptibility from rapid whole-genome sequencing data -- identifying the resistance

mechanisms present (KPC, NDM, OXA-48, etc.) and cross-referencing against a drug-resistance mechanism susceptibility matrix to select the optimal agent before conventional phenotypic AST is complete. Rapid diagnostics alone (M2) get most of the way there (8.4 hours), and for hospitals that cannot implement the full ML pipeline, rapid diagnostics with stewardship represents a highly effective and more readily achievable intermediate step.

## 5.2 Sparing Patients from Colistin

The reduction in colistin use from 78% (M1) to 22% (M5) in CRE patients is a major quality-of-care improvement. Colistin nephrotoxicity is not a minor inconvenience -- in our cohort, 32% of patients receiving colistin-based regimens developed AKIN stage 2+ AKI, and 8% required renal replacement therapy. By identifying CRE isolates susceptible to ceftazidime-avibactam or meropenem-vaborbactam from rapid genotypic data, the ML approach enabled early switch from colistin to these less toxic agents. This is possible only when resistance mechanism data is available quickly -- if you have to wait 72 hours for conventional AST, the patient has already received 3 days of colistin and the renal damage may already be done.

## 5.3 Limitations

Several limitations apply. First, the ML-assisted strategy (M5) was implemented at only two of five sites (Zurich and Stockholm) where rapid WGS infrastructure existed, so the M5 results represent a selected population at well-resourced centres. Second, the retrospective before-after design comparing strategies introduced at different times is vulnerable to temporal confounding. Third, our cohort underrepresents NDM-producing CRE, which is more prevalent in South Asia than Europe, and ceftazidime-avibactam is inactive against NDM -- so the ML model's ability to spare colistin may be less effective in settings with high NDM prevalence. Fourth, the cost of rapid WGS (approximately EUR 300-500 per isolate) and ML infrastructure was not included in our effectiveness analysis.

# 6. Conclusion

## 6.1 Key Findings

ML-assisted treatment selection achieves the highest MDR Management Effectiveness Score (0.922) across 6,842 MDR infection episodes, reducing 30-day mortality from 24.8% to 14.2%,

compressing time to appropriate therapy to 4.8 hours, and lowering nephrotoxicity from 18.4% to 6.2% by reducing colistin dependence. Rapid diagnostics-guided therapy (MMES 0.904) produces the largest single improvement in time to appropriate therapy (8.4 vs 52.6 hours). CRE infections show the greatest benefit from advanced management strategies, with mortality falling from 38.6% to 22.4%. These findings from five European centres provide a management framework for MDR infections that prioritises diagnostic speed and treatment precision.

## 6.2 Priorities

Three priorities follow. First, scaling rapid genomic AST from reference laboratories to routine clinical microbiology -- this requires investment in sequencing infrastructure, bioinformatics pipelines, and trained personnel, but the mortality benefit justifies the cost. Second, prospective randomised trials of ML-assisted antibiotic selection versus standard stewardship, powered for mortality endpoints in MDR infections. Third, expanding the ML susceptibility prediction models to include NDM and other metallo-beta-lactamase producers that are poorly represented in European training data but increasingly encountered globally. All analysis code, ML model specifications, and the MMES calculator are available from the corresponding author on request.

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## Declarations

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## Conflict of Interest

Both authors declare no competing interests. Neither has received consulting fees or research funding from any antibiotic manufacturer or diagnostic company.

## Data Availability Statement

De-identified infection episode data, resistance profiles, and model performance metrics are available from the corresponding author on reasonable request. Genomic sequencing data has been deposited in the European Nucleotide Archive. All ML model code and the MMES calculator are available on request.

## Ethical Approval

Approved by the ethics committees of all five participating centres (Zurich BASEC 2020-01682, Karolinska Dnr 2020-03286, HEGP CPP 2020-A02148-31, Charite EA4/202/20, Gemelli Prot. 0030842/20). Informed consent was waived for retrospective analysis of de-identified data.

## Appendix A

### MMES Calculation and ML Model Specifications

This appendix details the MMES scoring methodology, the ML susceptibility prediction model architecture, and the PK/PD dosing optimisation algorithm.

#### Part I -- MMES Dimensions

- 1a. Clinical Cure: Resolution of infection signs + negative cultures at day 14 ..... Binary per episode, normalised within pathogen
- 1b. 30-Day Mortality:  $1 - (\text{mortality rate} / \text{reference rate})$  ..... Reference = empirical therapy mortality per pathogen
- 2a. Time to Appropriate Therapy:  $1 - (\text{hours} / 72)$  ..... Capped at 72 hours; faster = higher
- 2b. Resistance Prevention:  $1 - (\text{emergence rate during Tx} / 10\%)$  ..... Capped at 10%; lower emergence = higher
- 3a. Nephrotoxicity Avoidance:  $1 - (\text{AKIN } 2+ \text{ rate} / 25\%)$  ..... Capped at 25%; less nephrotox = higher
- 3b.  $\text{MMES} = 0.25 * \text{Cure} + 0.25 * \text{Mortality} + 0.20 * \text{Time} + 0.15 * \text{Resistance} + 0.15 * \text{Nephrotox}$

#### Part II -- ML Susceptibility Prediction

- 4a. Input: WGS resistance gene profile (acquired genes + point mutations) ..... From rapid sequencing (6-8 hr turnaround)
- 4b. Model: XGBoost trained on 28,000 isolate-AST pairs from EUCAST databases ..... AUROC 0.94 for predicting S/I/R
- 5a. PK/PD optimisation: Bayesian dosing using patient weight, CrCl, albumin ..... Monte Carlo simulation for target attainment
- 5b. Output: Ranked drug-dose combinations with predicted efficacy and toxicity ..... Top 3 options presented to clinician