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Short Communication

Which patients benefit from model-informed precision dosing of beta-lactam antibiotics and ciprofloxacin at the ICU?

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ABSTRACT

Objectives: Antibiotic dosing is not optimal in the ICU. Our recent trial investigated the effect of model-informed precision dosing (MIPD) of beta-lactam antibiotics and ciprofloxacin and showed no significant differences in clinical outcomes in all patients. This study aimed to identify subgroups of patients in which the MIPD of these antibiotics could be beneficial for clinical outcomes.

Methods: We analysed data from the DOLPHIN randomized controlled trial, which compared MIPD to standard dosing of beta-lactam antibiotics and ciprofloxacin in 388 ICU patients. We divided patients into subgroups based on baseline characteristics and assessed the effect of MIPD on 28-day mortality, 6-month mortality, change in sequential organ failure assessment (delta-SOFA), and ICU length of stay (LOS).

Results: We found a lower 28-day mortality in patients with a SOFA below 8 randomized to MIPD (OR 0.40; 95% CI 0.17–0.88). However, patients with a higher SOFA show an increased 28-day mortality (OR 1.94; 95% CI 1.07–3.59) in the MIPD group. ICU LOS was increased in patients receiving MIPD with a SOFA below 8 (IRR 1.36; 95% CI 1.01–1.83) and those receiving MIPD for ceftriaxone (IRR 1.76; 95% CI 1.24–2.51). Patients receiving a dose recommendation within 24 hours show a trend towards decreased ICU LOS (IRR 0.77; 95% CI 0.52–1.16) and higher delta-SOFA (estimate -1.19; 95% CI -2.98–0.60).

Conclusions: ICU patients with a SOFA below 8 using MIPD had an increased ICU LOS but a lower 28-day mortality. Fast dose recommendations using MIPD of beta-lactam antibiotics and ciprofloxacin needs to be investigated in ICU patients.

1. Introduction

Beta-lactam antibiotics and fluoroquinolones are frequently prescribed in intensive care units (ICUs). Because of the pathophysiological changes in critically ill patients, the pharmacokinetics (PK) of these antibiotics is severely changed. These changes result in frequent pharmacodynamic target (PDT) nonattainment of beta-lactam antibiotics and ciprofloxacin [1,2]. PDT nonattainment is linked to poorer chances of clinical cure, bacteriological eradication, and an increased chance of antimicrobial resistance development [3,4].

One approach to optimize antibiotic exposure in the individual patient is therapeutic drug monitoring (TDM), which involves assessing serum drug levels to guide dosing regimens. Model-informed precision dosing (MIPD) combined with TDM is an approach that uses population PK models to assess the probability of target attainment for different dosing regimens by using Bayesian forecasting [5].

Recently, the first results of the DOLPHIN trial, a study comparing the outcome in patients with or without MIPD, were published [6]. No significant differences in clinical outcomes or improvement in target attainment were found to be due to MIPD in the whole study population. Other studies have indicated that male sex, high

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creatinine clearance, and younger age are risk factors associated with PDT nonattainment [7]. Furthermore, some patients will have more variation of PK changes over time, such as the use of extracorporeal therapy and changes in organ failure, disease severity, or hemodynamic state. It has not been investigated whether subgroups of patients at risk for not attaining the PDT may benefit from MIPD.

This study aimed to investigate potential subgroups of patients in which MIPD of beta-lactam antibiotics and ciprofloxacin is potentially beneficial for clinical outcomes compared to standard dosing.

2. Materials and methods

2.1. Study design and participants

Data from the previously published DOLPHIN multicentre, open-label, randomized controlled trial (RCT) were used in our analyses (EudraCT 2017-004677-14) [8]. This trial evaluated the effect of MIPD on clinical outcomes in critically ill patients. Medical ethical board approval was obtained at the Erasmus University Medical Center (Erasmus MC; MEC-2017-568). The trial was conducted in eight hospitals in the Netherlands. After the initial antibiotic dose, patients were included and randomized within 36 h to the MIPD or standard dosing group. Patients were eligible for inclusion if they were older than 18 years, admitted to the ICU, and expected to receive at least one of the target antibiotics using intermittent infusion for at least 2 days. Patients who met any of the following criteria were excluded: being pregnant, stopping antibiotics before the first blood sample was taken, participating in another intervention trial, being admitted for burn injuries, receiving study antibiotics only as part of selective decontamination of the digestive tract prophylaxis (SDD), or having a primary diagnosis of COVID-19 upon admission.

Initial dosing for patients in both groups was based on standard clinical practice. The intervention consisted of MIPD after measuring the concentrations at 48-hour intervals. The first intervention was 36 h after the initial antibiotic dose (T1), and then continued at day 3 (T3) and day 5 (T5). The epidemiological cutoff values as defined by EUCAST (MIC_{ECOFF}) were used as a measure of antibacterial potency [9]. The defined target for beta-lactam antibiotics was a free concentration for 100% time above MIC_{ECOFF} as a function of the dosing interval ($fT > MIC_{ECOFF}$) and for ciprofloxacin the ratio of the area under the drug serum concentration–time curve over 24 h to the MIC_{ECOFF} ($AUC_{0-24\ h}$ /MIC_{ECOFF}) above 125. Above target was defined as a steady-state trough concentration ($C_{trough,ss}$) of more than 10 times the MIC_{ECOFF} in the case of beta-lactam antibiotics and an AUC_{0-24h}/ MIC_{ECOFF} ratio of more than 500 for ciprofloxacin.

2.2. Subgroup selection

The following subgroups were deemed to be of interest: obese patients (BMI $\geq$30 kg/m^2), male patients, patients with high renal clearance, younger patients [2], the use of renal replacement therapy (RRT) [2,10], low Sequential Organ Failure Assessment (SOFA) score [11], lack of positive microbiology [11], and patients with sepsis (defined using the Sepsis III criteria). SOFA is a daily score that is used to grade organ failure of six organ systems. With increased score, there is more severe organ failure. Patients who received a dose recommendation within 24 h after initiation of the study antibiotic and those who received ceftriaxone were also analysed as separate subgroups, as ceftriaxone was the most used beta-lactam within the trial. Groups that were based on continuous variables were divided based on the median value.

2.3. Study outcomes

The outcomes were 28-day mortality; 6-month mortality; delta-SOFA score; ICU length of stay (LOS); target attainment at T1 and T3; and above target attainment at T1 and T3. The delta-SOFA score measures the change in SOFA scores over time in critically ill patients. It provides information on organ dysfunction progression and treatment response. The delta-SOFA score was the difference between SOFA score at T0 and T5 in which a decrease was an improvement. Patients who did not have a SOFA score at T5 were not included for this analysis. The ICU LOS was calculated as the days between ICU admission and ICU discharge, ICU transfer, or death. The SOFA score was set to 0 for patients dismissed to a hospital ward. ICU-free days alive were the number of days that a patient was not admitted to the ICU within 28 days after T0. For patients who died within 28 days, the ICU-free days were set to zero.

2.4. Statistical analyses

We analysed the data in three steps. First, descriptive statistics of the population were presented. For continuous variables, the median (interquartile range) was presented. Differences between the two groups were tested using a Mann-Whitney *U* test. Categorical variables are presented as numbers (percentages). For these variables, differences between the two groups were tested using a Fisher's exact test or χ^2 test when appropriate.

Second, for 28-day mortality, 6-month mortality, target attainment, and above target attainment, a binary logistic regression was used. The odds ratio (OR) and 95% confidence interval (95% CI) were reported. For the delta-SOFA score between day 0 and day 5, a linear regression was used. The effects were reported as an estimate with 95% CI. For ICU LOS, the associations between MIPD vs. standard dosing treatment using a negative binomial regression was examined. Estimates are expressed as the incidence risk ratio (IRR) with the associated 95% confidence intervals (95% CI). Finally, for ICU-free days alive, a Mann-Whitney *U* test was performed. Statistical analyses were performed using R (version 4.2.2). *P*-values below 5% were considered statistically significant.

3. Results

3.1. Baseline characteristics

In total, 450 patients were randomized in the DOLPHIN trial. Sixty-two patients were excluded from analyses because they met exclusion criteria between randomization and the first study intervention. This leaves 388 patients in total, of which 189 patients are in the MIPD group and 199 patients in the standard dosing group. The subgroups and their respective cohort sizes are shown in Figure 1. There were no major differences in baseline characteristics in the total population between the MIPD and standard dosing groups (Table 1).

3.2. Clinical outcomes

Patients with a SOFA score below 8 at T0 had a decreased 28-day mortality when randomized to the MIPD group (11% MIPD vs. 24% standard dosing; OR 0.40; 95% CI 0.17–0.88) (Figure 2, Supplementary Table S1). In contrast, patients with a SOFA score above or equal to 8 show increased 28-day mortality (39% MIPD vs. 25% standard dosing; OR 1.94; 95% CI 1.07–3.59) and 6-month mortality (52% MIPD vs. 35% standard dosing; OR 2.04; 95% CI 1.16–3.62) (Supplementary Table S2).

Applying MIPD only for ceftriaxone showed a decreased delta-SOFA score (-3 MIPD vs. -3 standard dosing; estimate 1.85; 95% CI 0.02–3.67). However, dose recommendations within 24 h resulted

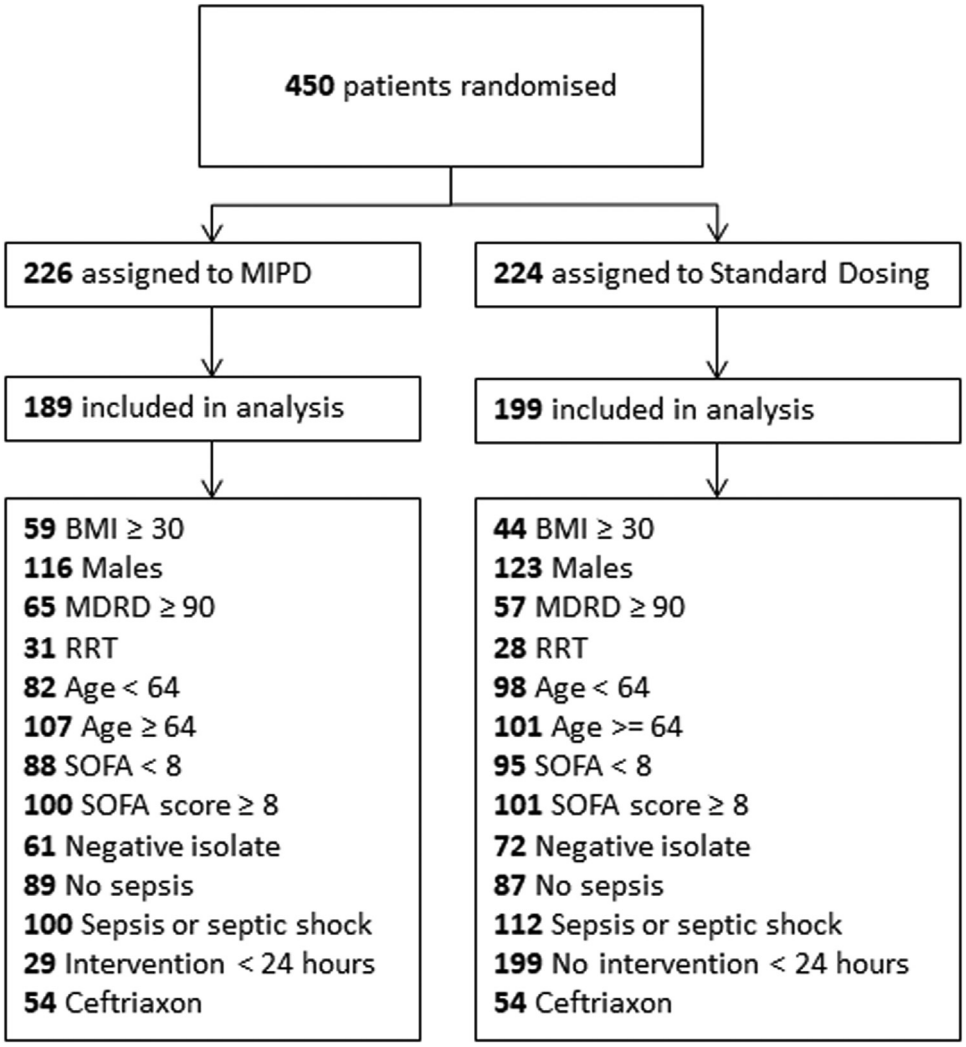

Figure 1. Patient flow and subgroup sizes. Abbreviations: RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

in a trend towards increased delta-SOFA score for all antibiotics (-4 MIPD vs. -2 standard dosing; estimate -1.19; 95% CI -2.98 to 0.60) (Supplementary Table S3).

For both beta-lactams and ciprofloxacin, patients with a SOFA score below 8 at T0 had an increased ICU LOS when randomized to the MIPD group (12 MIPD vs. 6 standard dosing; IRR 1.36; 95% CI 1.01–1.83) (Supplementary Table S4). Early dose recommendations within 24 h showed a trend towards a decreased ICU LOS in MIPD (5 MIPD vs. 8 standard dosing; IRR 0.77; 95% CI 0.52–1.16). Using MIPD for only ceftriaxone resulted in an increased ICU LOS (7 MIPD vs. 4 standard dosing; IRR 1.76; 95% CI 1.24–2.51). All other subgroups showed no major differences.

Patients with lower age and those receiving ceftriaxone had significantly fewer ICU-free days alive when randomized to the MIPD group (Supplementary Table S5).

3.3. PK/PD outcomes

Patients receiving MIPD for ceftriaxone had a higher chance of attaining the target at T1 (94% MIPD vs. 85% standard dosing; OR 3.02; 95% CI 0.82–14.43) and T3 (92% MIPD vs. 77% standard dosing; OR 3.35; 95% CI 0.84–16.82) and were more often above target at T1 and T3 (Supplementary Tables S6 and S7). Patients with a SOFA score below 8 were at equal risk for target attainment at T1 and T3 in the MIPD and standard dosing group. Those with a SOFA score equal or above 8 were at a slightly higher odds to reach the target at T3 (83% MIPD vs. 77% standard dosing; OR 1.46; 95% CI 0.67–3.22). Early intervention resulted in an increased chance of target attainment at T3 (92% MIPD vs. 68% standard dosing; OR 5.59; 95% CI 1.04–103.87) and to be above target at T3 (38% MIPD vs. 7% standard dosing; OR 7.73; 95% CI 1.97–29.50).

4. Discussion

This secondary analysis of the DOLPHIN RCT data is the first study to examine various subgroups in which MIPD could be beneficial. Patients with a SOFA score below 8 who received MIPD showed better mortality outcomes and therefore remained longer in the ICU. Those with a SOFA score above or equal to 8 who received MIPD showed worse 28-day and 6-month mortality outcomes. In addition, patients who received MIPD for ceftriaxone remained longer on the ICU and had a worse delta-SOFA. Finally, patients who received an early dose recommendation had a decreased ICU stay and an improved delta-SOFA.

Previous analyses of the DOLPHIN trial indicated that MIPD of beta-lactams and ciprofloxacin did not provide any benefit when all ICU patients were included. However, the heterogeneity of treatment effect analyses was not analysed since there were no predefined post hoc analyses. The TARGET trial investigated patients with sepsis [12]. They observed an increase in target attain-

Table 1
Baseline characteristics of all patients

Characteristic	Control N = 199[a]	MIPD N = 189[a]
Male sex	123 (62%)	116 (61%)
Age (years)	64 (53–71)	65 (57–71)
Body mass index (kg/m^2)	26.0 (23.0–29.2)	26.3 (23.4–31.2)
Charlson Comorbidity Index	3 (2–4)	3 (2–4)
Sepsis (III criteria)		
Sepsis	60 (30%)	61 (32%)
Septic shock	52 (26%)	39 (21%)
APACHE IV score	70 (50–91)	71 (53–89)
SOFA score	8 (5–10)	8 (5–11)
Mechanical ventilation at start of antibiotics	146 (73%)	136 (72%)
ECMO or RRT at start of antibiotics	29 (15%)	29 (15%)
MDRD (mL/min/1.73 m^2)	60 (33–98)	65 (32–110)
Albumin (g/L)	27.0 (23.0–33.0)	27.0 (23.0–32.0)
Unknown	21	17
C-reactive protein (mg/L)	185 (64–294)	173 (72–291)
Unknown	4	5
Procalcitonin (mg/L)	2.34 (0.58–10.34)	1.58 (0.42–17.00)
Unknown	20	26

[a] Median (IQR) or *n* (%) for continuous and categorical variables, respectively.

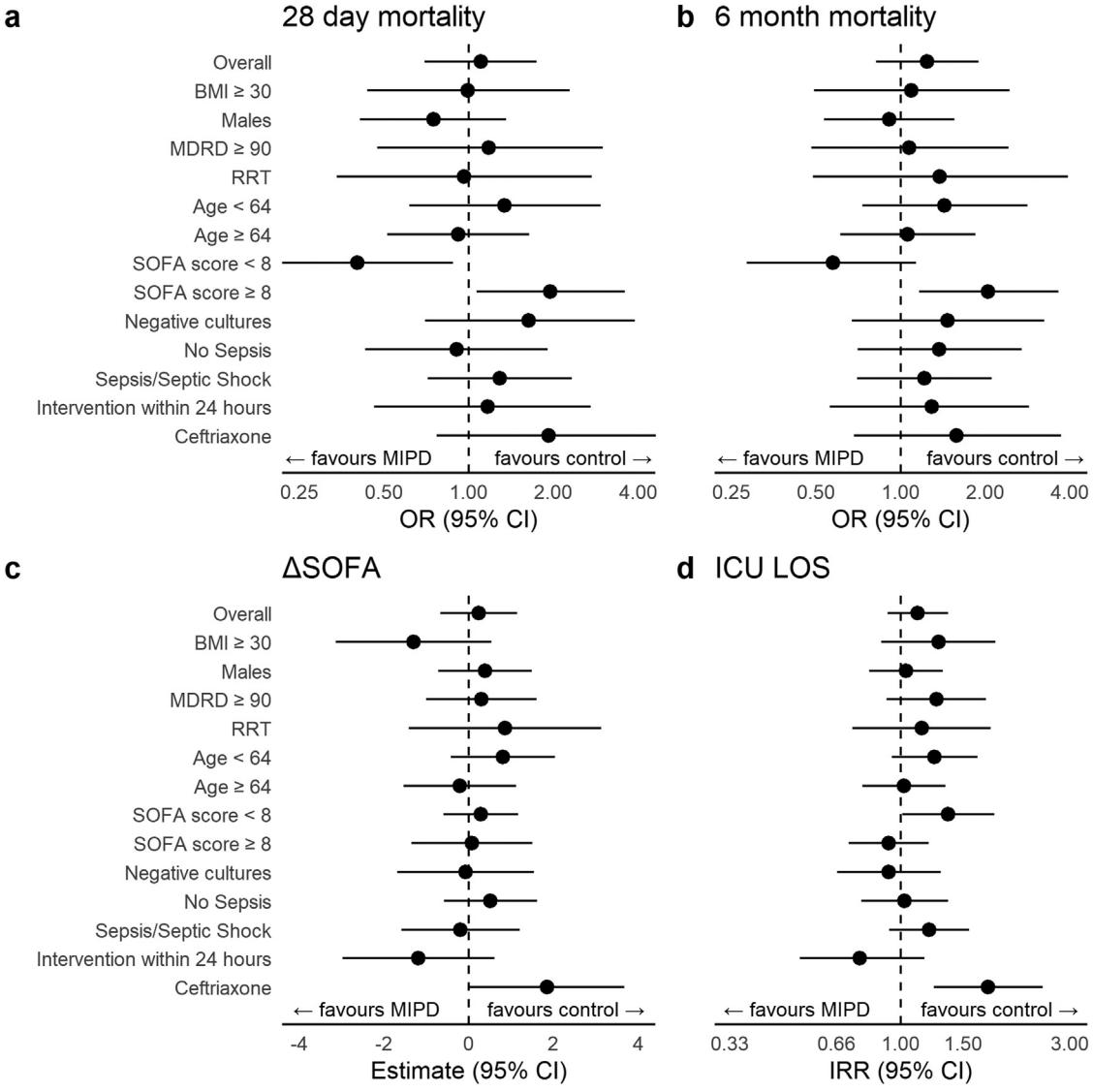

Figure 2. Effect sizes in subgroup analyses. Data represented as (a, b) odds ratio (OR), (c) estimate, or (d) incidence risk ratio (IRR) with 95% confidence intervals. Abbreviations: RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

ment with MIPD, but also no significant changes in clinical outcomes. Fournier et al. showed that TDM in critically ill burn patients resulted in better target attainment, but no improvement in clinical outcomes was found [13]. There were no analyses of TDM in specific ICU subgroups published in other trials.

In our study, we found heterogeneity in the clinical effect of MIPD based on the SOFA score of patients at the start of antibiotic treatment. We divided the groups based on a SOFA score of 8, since this was the median of our total population. In general, a SOFA score below 8 is associated with decreased overall mortality, whereas a SOFA above 8 shows a strong linear correlation with mortality [14]. We found that patients with a SOFA below 8 had a decreased 28-day mortality at the cost of a longer ICU LOS when randomized to the MIPD group. This can be explained since patients who die have a shorter stay in the ICU. This hypothesis is supported by the observation that ICU-free days alive is also similar in both study groups. Patients with a SOFA above 8 showed increased mortality when randomized to the MIPD group. We did observe only a small increase in target attainment for patients randomized to the MIPD group with a SOFA score below 8, and we observed a greater increase in patients with more organ failure receiving MIPD. The true explanation for this phenomenon is unclear. A possible explanation might be that the relative effect of our intervention has more effect on clinical outcomes in patients with a lower SOFA score. Severe illness, other interventions, or complications might have more effect on those with more severe organ failure. Another explanation could be that concentrations of antibiotics in patients with more severe organ failure are higher at some sites due to physiological changes such as increased blood–brain barrier, leakage of drugs, and renal failure, which might result in toxicity [2,15].

Another group that might benefit from MIPD are patients who receive early dose recommendations. This group showed a trend towards a shorter ICU LOS and better delta-SOFA. This change in SOFA score over time is a strong predictor for mortality and leads to increased statistical power in smaller groups using this continuous variable instead of a dichotomous variable [16]. Furthermore, the odds of achieving target were increased at T3 compared to T1. Early antibiotic treatment is associated with reduced mortality in trials with critically ill patients [17]. Therefore, earlier dose optimization might be more beneficial in the early stages of infection. There are some challenges to implementing fast interventions: a fast assay for determining the antibiotic concentrations needs to be implemented, as many hospitals currently have no means of determining antibiotic concentrations within several hours on a daily base [18].

Ceftriaxone MIPD resulted in worse clinical outcomes than in other antibiotics, which was an unexpected result. We did not find any renal or hepatic toxicity in our dataset. Neurotoxicity is difficult to detect in the ICU setting and could occur without a proper diagnosis [19]. More patients were at target and above target at T1 and T3 when receiving MIPD for ceftriaxone. The current cutoff value for dose decrease is not yet based on conclusive evidence and should perhaps be adjusted [20]. A comprehensive analysis towards finding the correct target cutoff value will need to be performed and will need to investigate possible toxicity thresholds. Prospective validation of these findings is dose-optimizing strategies in certain patient subgroups can be implemented.

The present results are from an analysis using data from one of the first major RCT investigating MIPD, although there are some limitations we would like to discuss. First, we studied the clinical outcomes in subgroups that were relevant but were not defined in our protocol and should be regarded as explorative. Furthermore, the sample sizes of these subgroups were relatively small. Also, we could not analyse the attributable risk differences, such as infection-related mortality, as they were not registered during the trial. Nevertheless, our results may inform researchers to improve future RCT designs.

5. Conclusions

ICU patients with a SOFA below 8 using MIPD had an increased ICU LOS but a lower 28-day mortality. Fast dose recommendations using MIPD of beta-lactam antibiotics and ciprofloxacin needs to be investigated in ICU patients.

Competing interests: All authors reported no possible competing interests.

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Ethical approval: MEC-2017-568, Medical ethical board approval at the Erasmus Medical Center ethics committee.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106931.

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