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Factors associated with meropenem pharmacokinetic/ pharmacodynamic target attainment in septic critically ill patients treated with extended intermittent infusion or continuous infusion

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Keywords:

Meropenem Continuous infusion Extended intermittent infusion Pharmacokinetic ICU

Abbreviations:

AKI, acute kidney injury; BMI, body mass index; CI, continuous infusion; C_{min}, trough concentration; C_{ss}, steady-state concentration; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; eGFR, estimated glomerular filtration rate; EII, extended intermittent infusion; EUCAST, European Committee on Antimicrobial Susceptibility Testing; ICU, intensive care unit; IHD, intermittent haemodialysis; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; SAPS, Simplified Acute Physiology Score; SLED, sustained low-efficiency dialysis; SOFA, Sequential Organ Failure Assessment; TDM, therapeutic drug monitoring; 100% *f*T > MIC , 100% of the dosing interval with a free drug concentration above the MIC of the treated microorganism; 50% *f*T > MIC , 50% of the dosing interval with a free drug concentration above the MIC of the treated microorganism; 95%CI, 95% confidence interval.

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a b s t r a c t

Objectives:

The use of extended intermittent infusion (EII) or continuous infusion (CI) of meropenem is recommended in intensive care unit (ICU) patients, but few data comparing these two options are available. This retrospective cohort study was conducted between 1 January 2019 and 31 March 2020 in a teaching hospital ICU. It aimed to determine the meropenem plasma **concentrations achieved with CI and EII.**

Methods:

The study included septic patients treated with meropenem who had one or more meropenem plasma trough (C_{min}) or steady-state concentration (C_{ss}) measurement(s), as appropriate. It then assessed the factors independently associated with attainment of the target concentration (C_{min} or C_{ss} \geq 10 mg/L) and the toxicity threshold (C_{min} or C_{ss} \geq 50 mg/L) using logistic regression models.

Results:

Among the 70 patients analysed, the characteristics of those treated with EII ($n = 33$) and CI ($n = 37$) were balanced with the exception of estimates glomerular filtration rate (eGFR): median 30 mL/min/m² (IQR 30, 84) vs. 79 mL/min/m² (IQR 30, 124). Of the patients treated with EII, 21 (64%) achieved the target concentration, whereas 31 (97%) of those treated with CI achieved it ($P < 0.001$). Factors associated with target attainment were: CI (OR 16.28, 95% CI 2.05–407.5), daily dose \geq 40 mg/kg (OR 12.23, 95% CI 1.76–197.0; $P = 0.03$) and eGFR (OR 0.98, 95% CI 0.97–0.99; $P = 0.02$). Attainment of toxicity threshold was associated with daily dose > 70 mg/kg (OR 35.5, 95% CI 5.61–410.3; $P < 0.001$).

Conclusion:

The results suggest the use of meropenem CI at 40–70 mg/kg/day, particularly in septic ICU patients with normal or augmented renal clearance.

1. Introduction

Antimicrobial resistance and carbapenem consumption are increasing worldwide [1]. Among the carbapenems, meropenem is one of the most commonly used in the treatment of severe healthcare-associated infections and, to a lesser extent, community-acquired infections [2]. Meropenem mainly displays time-dependent killing [3]; therefore, in intensive care units (ICUs), either extended intermittent infusion (EII) or continuous infusion (CI) of meropenem are recommended to optimise the time during which the plasma concentration of meropenem is maintained above the minimum inhibitory concentration (MIC) of the treated microorganism(s) [4].

Optimal management of patients with sepsis and septic shock requires the earliest initiation of broad-spectrum antibiotic therapy in a regimen that achieves effective therapeutic concentrations [4, 5]. In this setting, the choice of the best administration modality may influence patient outcomes [4, 5]. Population PK analysis with Monte Carlo simulations suggested that CI outperforms EII in achieving the pharmacokinetic/pharmacodynamic (PK/PD) target in ICU patients [6, 7]; however, data comparing both regimens are scarce in routine practice.

This study aimed to determine the meropenem plasma concentrations achieved in critically ill septic patients treated with CI and EII of meropenem, and to assess the factors independently associated with attainment of the PK/PD target and toxicity threshold.

2. Material and Methods

2.1. Study Design and Settings

A single-centre, retrospective, observational study was conducted in the 20-bed medical ICU of the Montpellier University Hospital, France. All consecutive patients admitted to the ICU between 1 January 2019 and 31 March 2020 and who had at least one meropenem therapeutic drug monitoring (TDM) were screened using the Pharmacology and Toxicology Department database; each patient's medical chart was then reviewed (by ST and RL). The study included adult patients treated with meropenem for severe infections [5], and when a patient had more than one meropenem plasma concentration measurement, only the first meropenem concentration was considered. The study excluded patients aged < 18 years, who were pregnant or who did not fulfil the criteria of the TDM sampling protocol (see below).

2.2. Meropenem Dosage Regimens

The meropenem (Meropenem Arrow®, Arrow Laboratories, Lyon, France) dosage regimen was selected by the treating physician. During the study period, meropenem was administered by either: (i) EII, 2 g over 5 h, three times/day, or (ii) CI, 1g over 4 h, six times/day. Patients treated with CI received an initial loading dose of 2 g over 30 min. All patients were treated with one of these two dosage regimens for at least 24 h, then the treating physician could make dosage adjustments based on the estimated glomerular filtration rate (eGFR) as recommended [8]. Glomerular filtration rates were estimated by creatinine clearance measured by 24-h UV/P creatinine at the time of TDM [9]. Augmented renal clearance was defined as an eGFR > 130 mL/min/1.73 m² with a normal serum creatinine [9].

2.3. Meropenem Therapeutic Drug Monitoring Sampling Protocol

Blood samples were taken 15–30 min before the start of the next infusion (i.e. at trough or C_{min}) in patients treated with EII, and at least 24 h after the start of CI (i.e. at steady-state or C_{ss}, actually reached in 5 h) in patients treated with CI. Sampling was performed within 2 days of treatment initiation or a change in dosage regimen. The Pharmacology and Toxicology Department measured meropenem plasma concentrations using an ultra-high performance liquid chromatography method adapted

from Legrand et al. [10] . Total plasma concentrations of meropenem were considered equivalent to free concentrations [4 , 11].

2.4. Meropenem Pharmacokinetic/Pharmacodynamic Target

The recommended PK/PD target of meropenem plasma concentration in critically ill patients is 50–100% of the dosing interval with a free drug concentration above the MIC of the treated microorganism (50% $fT > MIC$ to 100% $fT > MIC$) [4] . However, most evidence suggests an optimal PK/PD target at a free concentration above four-fold or even five-fold the MIC throughout the whole dosing interval (100% $fT > 4xMIC$ to 100% $fT > 5xMIC$) [4] .

As no exact MIC values were available, the critical MIC break- point for susceptibility of Enterobacterales and *Pseudomonas aeruginosa* to meropenem of 2 mg/L was used to calculate PK/PD target according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [12]. Hence, PK/PD target attainment was defined as C_{min} or $C_{ss} \geq 10$ mg/L corresponding to 100% $fT > 5xMIC$. As recommended, this study determined a toxicity threshold as C_{min} or $C_{ss} > 50$ mg/L [4] .

2.5. Data Collection

Demographic, clinical, pharmacological and laboratory data were collected from patient's medical charts. Patient conditions were evaluated using the Charlson Comorbidity Index and disease severity by calculation of the Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) score, 24 hours after ICU admission. Acute kidney injury (AKI) was defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

2.6. Statistical Analysis

Quantitative data were described as median and interquartile range (IQR) and qualitative data as number and percentage. The study population was divided according to the attainment (C_{min} or $C_{ss} \geq 10$ mg/L) or non-attainment (C_{min} or $C_{ss} < 10$ mg/L) of meropenem PK/PD target concentrations. Categorical variables were compared using χ^2 tests and continuous variables were compared using the Wilcoxon test or the Fisher's exact test, as appropriate.

Factors independently associated with the attainment of meropenem PK/PD target concentrations were assessed using a logistic regression model. A conditional stepwise regression was performed to select the most informative variables (with $P \leq 0.2$ in the univariate analysis for entry into the model). Finally, given the small number of events, the three most clinically relevant and statistically significant variables in the univariate analysis were selected for inclusion in the multivariate analysis. Interactions and correlations between explanatory variables were carefully checked for. The same analyses were performed to determine the factors associated with the attainment of the toxicity threshold (C_{min} or $C_{ss} > 50$ mg/L).

All tests were two-sided and P -values < 0.05 were considered statistically significant. Analyses were performed using R software version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Characteristics of the study population.

Characteristics	Overall, n = 70 ¹	EII, n = 33 ¹	CI, n = 37 ¹
Age, years	69 (60, 74)	71 (62, 77)	68 (57, 72)
Male	48 (69%)	23 (70%)	25 (68%)
BMI, kg/m²	24 (22, 29)	26 (23, 30)	23 (21, 28)
Charlson index	4 (3, 7)	5 (3, 7)	4 (3, 6)
SAPS II	54 (41, 67)	59 (43, 69)	53 (40, 63)
SOFA score	8 (6, 10)	9 (6, 11)	7 (4, 10)
Diagnosis			
Sepsis	26 (37%)	13 (39%)	13 (35%)
Septic shock	39 (56%)	16 (48%)	23 (62%)
Febrile neutropenia	5 (7%)	4 (12%)	1 (2.7%)
Infection sources			
Pneumonia	37 (53%)	16 (48%)	21 (57%)
Urinary tract	13 (19%)	5 (15%)	8 (22%)
Intra-abdominal	9 (13%)	5 (15%)	4 (11%)
Catheter	3 (4%)	1 (3%)	2 (5%)
Skin and soft tissue	3 (4%)	3 (9%)	0 (0%)
Unknown	5 (7%)	3 (9%)	2 (5%)
Bloodstream infection	7 (10%)	5 (15%)	2 (5%)
Fluid balance, mL	878 (37, 2236)	1200 (232, 2545)	700 (-193, 2025)
Positive fluid balance	43 (61%)	23 (70%)	20 (54%)
Albumin, g/L	27 (24, 30)	26 (24, 30)	27 (24, 30)
Creatinine, µmol/L	103 (56, 208)	192 (73, 266)	91 (48, 115)
eGFR, mL/min/m²	55 (30, 120)	30 (30, 84)	79 (30, 124)
Augmented renal clearance	12 (17%)	6 (18%)	6 (16%)
Acute kidney injury	35 (50%)	20 (61%)	15 (41%)
KDIGO Stage 1	6 (9%)	2 (6%)	4 (11%)
KDIGO Stage 2	7 (10%)	5 (15%)	2 (5%)
KDIGO Stage 3	22 (31%)	13 (39%)	9 (24%)
Renal replacement therapy	13 (19%)	11 (33%)	2 (5%)
SLED/IHD	5 (7%)	5 (15%)	0 (0%)
CVVHD/CVVHDF	8 (11%)	6 (18%)	2 (5%)

¹ N (%) or median (IQR). Abbreviations: IQR, interquartile range; EII, extended intermittent infusion; CI, continuous infusion; BMI, body mass index; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; eGFR, estimated glomerular filtration rate, calculated using the 24-h LV/P formula; KDIGO, Kidney Disease Improving Global Outcomes; SLED, sustained low-efficiency dialysis; CVVHDF, continuous veno-venous haemodiafiltration; CVVHD, continuous veno-venous haemodialysis; IHD, intermittent haemodialysis.

3. Results

3.1. Patients

Among 1125 patients admitted during the study period, 110 patients had at least one meropenem TDM representing 238 blood samples. Of these, 70 patients were included in the analysis (Supplementary Figure). The characteristics of the study population are presented in Table 1.

Most of the patients (69%) included in the study were men and the median age and body mass index of the population was 69 years (IQR 60–74) and 24 kg/m² (IQR 22–29), respectively. At ICU admission, the median Charlson index, SOFA score and SAPS II were 4 (IQR 3–7), 6 (IQR 5–10) and 54 (IQR 41–67), respectively.

Sepsis and septic shock ($n = 65$; 93%) were the main reasons for ICU admission, and pneumonia ($n = 37$; 53%) and urinary tract infection ($n = 13$; 19%) were the main sources of infection. Thirty-five of the patients (50%) had AKI, including 13 who required renal replacement therapy, whereas 13 (19%) had augmented renal clearance.

Characteristics of patients treated with EII and CI were balanced, except for eGFR: 30 mL/min/m² (IQR 30–84) vs. 79 mL/min/m² (IQR 30–124), and renal replacement therapy requirement: 11 patients (33%) vs. 2 (5%), respectively.

3.2. Pharmacokinetic/Pharmacodynamic Target Attainment

Characteristics of meropenem TDM are summarised in Table 2. Meropenem was administered by CI at a median dose of 6 g over 24 h (IQR 6–6) in 37 patients, and by EII at a median daily dose of 3 g (IQR 2–4), divided into three doses/day (IQR 2–3) administered over 5 hours (IQR 5–5) in 33 patients. Among the patients treated with EII, 21 (64%) achieved the target concentration, whereas 31 (97%) of those treated with CI achieved it ($P < 0.001$). The median plasma concentration of meropenem was $C_{min} = 16$ mg/L (IQR 8, 23) in the EII group and $C_{ss} = 34$ mg/L (IQR 27, 49) in the CI group ($P < 0.001$).

In detail, among the 13 patients (19%) who were below the meropenem concentration target of 10 mg/L, 12 received EII ($P < 0.001$) and 10 had a daily dose of meropenem < 40 mg/kg, including eight patients who had an eGFR < 50 mL/min. Of the remaining five patients who did not reach the meropenem concentration target, all had an eGFR > 120 mL/min, including one patient treated with CI of meropenem.

On the contrary, nine of 11 patients with meropenem concentration above the toxicity threshold were in the CI group ($P = 0.036$). However, three patients were reported with neurological adverse effects attributable to meropenem: two in the EII group and one in the CI group ($P = 0.6$) with meropenem concentrations at 9 mg/L, 21 mg/L and 53 mg/L, respectively. Four patients treated with EII and 10 treated with CI died ($P = 0.12$), bringing the ICU mortality rate to 20.0% (14 patients).

Table 2
Characteristics of meropenem therapeutic drug monitoring.

Characteristics	Overall, n = 70 ¹	EII, n = 33 ¹	CI, n = 37 ¹	P-value ²
Meropenem regimen				
Daily dose, g	4 (3, 6)	3 (2, 4)	6 (6, 6)	
Daily dose, mg/kg of TBW	57 (35, 81)	35 (27, 55)	74 (60, 90)	
Dose/day	–	3 (2, 3)	–	
Infusion time, h	–	5 (5, 5)	–	
Meropenem concentration				
Median (IQR)	25 (14, 39)	16 (8, 23)	34 (27, 49)	< 0.001
> 2 mg/L	67 (96%)	30 (91%)	37 (100%)	0.10
> 10 mg/L	57 (81%)	21 (64%)	36 (97%)	< 0.001
> 50 mg/L	11 (16%)	2 (6%)	9 (24%)	0.036
10–50 mg/L	46 (66%)	19 (58%)	27 (73%)	0.2
Outcomes				
Neurological adverse events	3 (4%)	2 (6%)	1 (3%)	0.6
Late awakening	1 (1%)	1 (3%)	0 (0%)	
Delirium	1 (1%)	0 (0%)	1 (3%)	
Seizures	1 (1%)	1 (3%)	0 (0%)	
ICU mortality	14 (20%)	4 (12%)	10 (27%)	0.12
ICU length of stay, d	12 (7, 21)	15 (8, 19)	11 (7, 22)	0.8

¹ N (%) or median (IQR).

² Wilcoxon rank sum test; Fisher's exact test; Pearson's χ^2 test, as appropriate. Abbreviations: IQR, interquartile range; EII, extended intermittent infusion; CI, continuous infusion; ICU, intensive care unit; TBW, total body weight.

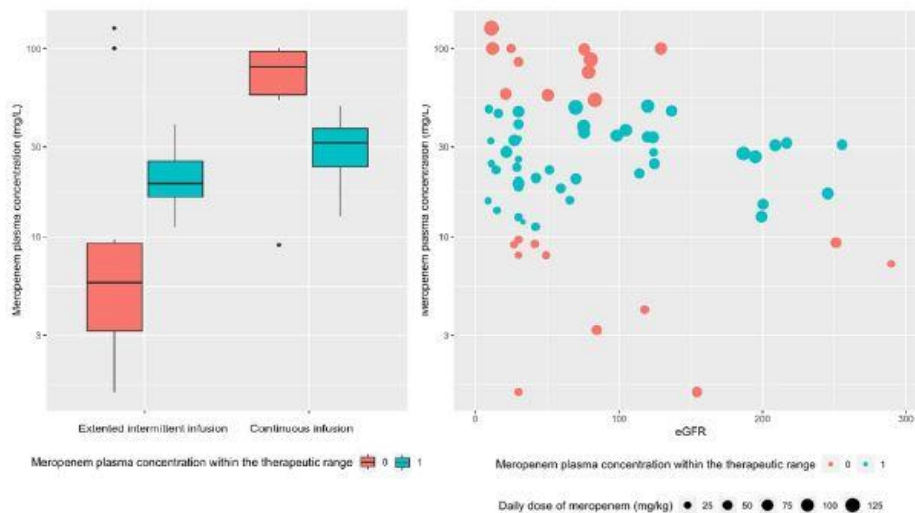


Figure 1. Meropenem plasma concentration in (green) or out of (red) the pharmacokinetic/pharmacodynamic target after continuous infusion and prolonged intermittent infusion, and among septic intensive care unit patients with different estimated glomerular filtration rates (eGFR).

As illustrated in Figure 1, those treated with CI were at greater risk of overdose, whereas those treated with EII were at risk of meropenem underdosing. The meropenem plasma concentrations were also modified by the eGFR and the dose/kg of total body weight. Finally, 27 patients treated with CI (73%) and 19 treated with EII (58%) were within the therapeutic range (10–50 mg/L) of meropenem plasma concentrations ($P = 0.2$).

3.3. Factors Associated With Attainment of Meropenem Pharmacokinetic/Pharmacodynamic Target Concentrations and Attainment of Meropenem Concentrations Above the Toxicity Threshold

The results of univariate and multivariable analyses are presented in Supplementary Tables 1 and 2. A meropenem dose > 40 mg/kg of total body weight (OR 12.23, 95% CI 1.76–197.0; $P = 0.03$) and administration by continuous infusion (OR 16.28, 95% CI 2.05–407.5) were independent factors associated with attainment of meropenem PK/PD target concentrations, whereas higher eGFR was associated with non-attainment of 10 mg/L (OR 0.98, 95% CI 0.97–0.99; $P = 0.02$). The only factor independently associated with the attainment of meropenem concentrations above the toxicity threshold was daily dose of meropenem > 70 mg/kg of total body weight (OR 35.5, 95% CI 5.61–410.3; $P < 0.001$).

4. Discussion

This study reported the results of a single-centre retrospective cohort study including 70 septic ICU patients. It found that meropenem CI more frequently achieved the therapeutic target than EII. Furthermore, it found that meropenem CI was independently associated with achievement of the PK/PD target. Other factors associated with achieving the PK/PD target were lower eGFR and daily meropenem dose ≥ 40 mg/kg, whereas daily dose > 70 mg/kg was independently associated with plasma concentrations above the toxicity threshold.

Some have pointed out that ca. one-third of the ICU patients treated with intermittent bolus infusion of meropenem failed to achieve the lowest PK/PD targets 100% $fT > 2$ mg/L [13]. Thus, CI and EII have been proposed to limit the risk of underdosing [4 , 6 , 7 , 13]. The current study found that CI outperforms EII in real-world situations, as it has been suggested in population PK analysis with Monte Carlo simulations [6 , 7], confirming that CI is the best dosing strategy to increase the likelihood of achieving the most optimised PK/PD targets, especially in ICU patients [13] . The current study also reported plasma meropenem concentrations ranging 8–100 mg/L after CI, whereas concentrations ranged from < 2 mg/L to > 100 mg/L after EII. This finding is consistent with data [9] showing that CI provides more predictable antibiotic PK profiles by limiting the impact of changes in volume of distribution and/or renal clearance.

Another interesting result was the high median meropenem concentration at 34 mg/L (IQR 27, 49) achieved in CI-treated patients that enabled optimising the treatment of bacteria classified ‘susceptible, increased exposure’ to meropenem or even treating bacteria classified ‘resistant’ according to the EUCAST breakpoint [12] . Using CI, a PK/PD target of 100% $fT > 4xMIC$ [4] was achievable for the treatment of bacteria with MICs up to 8 mg/L or even MICs up to 16 or 32 mg/L [7] for PK/PD targets ranging from 50% $fT > MIC$ to 100% $fT > MIC$ [4] . Clinicians might then reconsider the use of meropenem to treat infections due to *Enterococcus faecalis* (MIC range 2–16 mg/L) and anaerobic bacteria [12], whereas imipenem was considered superior in these indications [2]. Similarly, meropenem CI may be an attractive dosing strategy for treating carbapenemase-producing Enterobacterales [7].

As with the mode of administration, the total daily dose matters and the current results suggest that a meropenem dose range of 40–70 mg/kg/day (maximum 6 g/day) may limit the risk of underdosing and overdosing. Clinicians should be careful with obese patients [14] ; however, a lower antibiotic daily dose may be appropriate with CI [15] or in those with lower eGFR [13 , 16]. In agreement with these results, Scharf et al. [13] reported that patients with

eGFR < 70 mL/min did not benefit most from CI administration of meropenem and did not require a dose > 3 g/day.

The use of meropenem CI has some drawbacks. Some authors have reported that meropenem also exhibited a concentration- dependent killing and suggested that optimisation of both $T > MIC$ and peak concentration/MIC ratio should be considered [2]. The risk of physicochemical incompatibility is increased with CI, which therefore requires a dedicated intravenous line [15]. Meropenem is not stable upon prolonged exposure to room temperature [15]. Based on previous studies [17, 18], the CI of meropenem over 24 h was performed by dividing the total daily dose in four to six syringes of 60 mL infused over 4–6 h, four to six times/day. Finally, regarding the risk of meropenem-related toxicity, some authors [19, 20] have reported that neurotoxicity may be more related to high peak concentrations than to high trough concentrations. These results are in agreement with the current results and those of other authors [16] who have shown that meropenem CI was safe, although it increased the risk of overdose.

This study had several limitations. First, it was limited by its retrospective, single-centre design, small cohort size, and heterogeneity of the study population that included different meropenem dosing regimens and patient renal function due to its observational nature, which may have limited the generalisability of the results. However, it reported real-life data, observed in a case-mix of septic ICU patients, consistent with PK studies using Monte-Carlo simulations [6, 7]. In addition, to limit bias in data collection, both electronic and paper charts were reviewed to include data collected prospectively at the bedside by nurses. Second, the study was not randomised and the choice between EII and CI was left to the discretion of the physicians. Most of them were trained in PK/PD and had chosen EII in patients with AKI, which may have limited comparability of the groups. Third, the study did not report any association between CI and microbiological or clinical outcomes. Nonetheless, several studies have reported that EII or CI of β -lactams improved outcomes [4]. Finally, due to confounding actors the estimation of meropenem neurotoxicity may have been skewed and it did not investigate meropenem-associated renal toxicity [4, 19].

5. Conclusions

In this cohort of meropenem-treated septic ICU patients, those treated with CI achieved higher median plasma meropenem concentration (C_{min} or C_{ss}) than those treated with EII. Continuous administration of meropenem was a better dosing strategy to achieve the optimal PK/PD target (100% $fT \geq 10$ mg/L), especially in patients with the higher eGFR. These results also highlighted the importance of a daily meropenem dose between 40–70 mg/kg to achieve an optimal PK/PD target. Further studies are needed to confirm these results and to assess the impact of continuous administration on ICU patient outcomes, particularly in case of infections caused by difficult-to-treat resistance bacteria such as non-fermenters or carbapenemase-producing Enterobacterales.

Declarations

Funding:

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Competing Interests:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval:

This study was conducted according to the guidelines of the Declaration of Helsinki. The Institutional Review Board of Montpellier University Hospital approved the study (No. 2019_IRB-MTP_03-01) and waived the need for signed consent to participate.

Sequence Information:

Not applicable.

Author contributions:

RL conceived and designed the study; ST, NB, VB, DD, LP and PC collected the data; ST, KK and RL analysed and interpreted the data; ST and RL wrote the first draft of the article; OM, MV, KK and RL revised it critically for important intellectual content; all authors approved the final version of the submitted manuscript.

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