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Real-time TDM-based optimization of continuous-infusion meropenem for improving treatment outcome of febrile neutropenia in oncohaematological patients: results from a prospective, monocentric, interventional study

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Objectives: To assess the role that real-time therapeutic drug monitoring (TDM)-guided optimization of continuous-infusion (CI) meropenem may have in maximizing empirical treatment and in preventing breakthrough infection and/or colonization with carbapenem-resistant Enterobacteriaceae (CRE) among oncohaematological patients with febrile neutropenia (FN).

Methods: A monocentric, interventional, prospective study was conducted. The pharmacodynamic (PD) target was a steady-state meropenem concentration-to-MIC ratio (C_{ss}/MIC) of 4–8. The primary endpoint was 14 day all-cause mortality. The secondary endpoint was the prevalence of CRE colonization in rectal swabs of patients rehospitalized within 3 months.

Results: Among the 75 patients enrolled, most (56%) had AML, almost half (37/75, 49.3%) underwent HSCT and one-third (32%) received meropenem as monotherapy. Meropenem dosages were adjusted in 30.1% of TDM reassessments. Gram-negative infections were microbiologically documented in 20.0% of patients. All of the 12 patients having infections caused by *in vitro* meropenem-susceptible pathogens attained the desired PD target and were cured. Three patients had infections caused by *in vitro* meropenem-resistant pathogens. Two of these achieved a C_{ss}/MIC target of 1 and were cured; the other one achieved a suboptimal PD target (0.59) and died. The 14 day all-cause mortality (10.7%) was significantly associated, at multivariate regression, with HSCT (OR 0.086, 95% CI 0.008–0.936, $P = 0.044$) and with augmented renal clearance (OR 10.846, 95% CI 1.534–76.672, $P = 0.017$). None of the patients who had hospital readmissions in the 3 month follow-up (63/75) had CRE colonization in rectal swabs.

Conclusions: Real-time TDM-guided CI meropenem may be a useful approach for attaining adequate exposure and preventing CRE emergence in FN oncohaematological patients.

Introduction

Patients treated for oncohaematological malignancies may suffer from febrile neutropenia (FN) and severe bacterial infections, which may be complicated by sepsis and/or septic shock.[1] The prevalence of bloodstream infections (BSIs) in this patient population may range between 21% and 35%,[2,3] with mortality rates up to 32%.[3] Gram-negative bacteria may account for approximately 50% of BSI episodes.[3,4] The most common aetiological agents of bacterial infections are the Enterobacteriaceae that may translocate from the damaged gastrointestinal tract.[4] However, about half of cases have unknown aetiology.

Empirical antimicrobial treatment of FN is guided by a risk-adapted strategy based on the patient's clinical status and on the presence of well-recognized risk factors for MDR pathogens.[5]

Current guidelines recommend the use of an antipseudomonal β-lactam as first-line empirical treatment of high-risk FN oncohaematological patients.[6] Knowledge of the local epidemiology and resistance patterns is fundamental for choosing the appropriate therapy. Monotherapy with piperacillin/tazobactam, ceftazidime or cefepime should be preferred in clinically stable FN patients not having had previous infections and/or colonization caused by MDR Gram-negative bacteria. The addition of an aminoglycoside should be considered in patients with haemodynamic instability and/or with sepsis.[7] In the absence of a clinical response within 48–72 h, therapy may be escalated to meropenem or imipenem.[5]

Optimizing the exposure to meropenem may be especially relevant in FN patients. On the one hand, the pathophysiological changes occurring in FN may significantly affect the pharmacokinetic behaviour of meropenem.[8–10] Augmented renal clearance (ARC) is a quite prevalent condition in this special population[11] and may accelerate drug elimination. Consistently, the administration of standard meropenem doses by intermittent infusion (II) may result in very low plasma trough levels (C_{min}). The recent use of meropenem may represent a major risk factor of colonization or of infection with carbapenem-resistant Enterobacteriaceae (CRE).[12,13] Accordingly, it may be worthwhile adopting dosing strategies that may minimize either subtherapeutic levels of meropenem or CRE emergence.

The pharmacodynamic determinant of meropenem efficacy is the duration of time that the plasma concentration exceeds the MIC ($T_{>MIC}$).[14] The minimum target is 40% $T_{>MIC}$,[15] but more aggressive thresholds have been proposed for severely ill patients.[16] It is generally agreed that targeting the C_{min} at 4–6 times the MIC ($T_{>4-6\times MIC}$) may either maximize bacterial killing[17] or prevent resistance development.[18,19]

Administration of meropenem by continuous infusion (CI) with optimization of drug exposure by means of real-time therapeutic drug monitoring (TDM) may represent a step forward in achieving both of these goals in FN patients.

The aim of this prospective study was to assess the role that real-time TDM-guided optimization of CI meropenem may have in maximizing empirical treatment and in preventing breakthrough infection and/or colonization with CRE among FN oncohaematological patients.

Materials and methods

Study design

This was a prospective, monocentric, interventional study carried out between February 2017 and December 2018 at the Azienda Sanitaria Universitaria Integrata of Udine, Italy. Enrolled patients were adults (≥18 years old) with oncohaematological disease who were admitted to the Clinic of Haematology and received empirical escalation therapy with meropenem for the treatment of an episode of FN.

The treatment algorithm was as follows. Oncohaematological patients having an absolute neutrophil count (ANC) of $<1.0\times10^9$/L received antimicrobial prophylaxis with levofloxacin and itraconazole until recovery. If suffering from FN (defined as ANC $<0.5\times10^9$/L or ANC $<1.0\times10^9$/L predicted to decline to ANC $<0.5\times10^9$/L coupled with an oral temperature of >38°C on two consecutive measurements), first-line empirical antipseudomonal treatment was started. In clinically stable patients, monotherapy with piperacillin/tazobactam was used. In patients with haemodynamic instability and/or with sepsis, combination therapy with piperacillin/tazobactam and amikacin was used. In the presence of documented Gram-positive infection and/or signs of central venous catheter-related infections, an anti-Gram-positive agent (vancomycin, daptomycin or linezolid) was added.

In the absence of clinical response within 48–72 h, therapy was escalated to meropenem [1 g loading dose (LD) over 30 min followed by CI maintenance dose (MD) of 1 g q8h over 8 h if estimated creatinine clearance (eCR_{CL})[20] was ≥60 mL/min/1.73 m^2 or 0.5 g q6h over 6 h if eCR_{CL} was <60 mL/min/1.73 m^2]. Considering the time-dependent instability of meropenem in aqueous solution, CI was granted by reconstitution of the solution every 6–8 h with infusion over 6–8 h.[21] In non-responders without a documented bacterial infection and with a high risk of invasive fungal infections (IFIs), antifungal therapy (liposomal amphotericin B, voriconazole or caspofungin) was added. High risk of IFI was defined as having at least one of the following factors: previous IFI in the last 2 years; >7 days of aplasia; a human leucocyte antigen (HLA)-matched unrelated donor (MUD) HSCT; or an haploidentical HSCT with graft-versus-host disease (GVHD).

Per protocol, patients were enrolled at the time of treatment escalation to meropenem. All patients underwent a proactive real-time TDM programme of optimization of meropenem exposure. The desired meropenem steady-state plasma concentration (C_{ss}) was 8–16 mg/L. This approach was aimed at attaining a C_{ss} of 4–8 times the EUCAST clinical breakpoint of meropenem against the Enterobacteriaceae and *Pseudomonas aeruginosa* (2 mg/L).[22,23] This approach was deemed to be the best strategy for maximizing meropenem efficacy during empirical treatment of FN patients. The rationale was of both maximizing meropenem efficacy and preventing bacterial regrowth potentially leading to CRE breakthrough infections and/or colonization.[16,18] A recent review assessed the relationship between antibiotic exposures and emergence of resistance in Gram-negative bacteria and showed that C_{ss}/MIC ≥ 4 for β-lactams may suppress the emergence of antibiotic resistance.[19] In the presence of documented Gram-negative infections, no dosage reduction was applied whenever clinical isolates were fully susceptible to meropenem (MIC ≤2 mg/L) and meropenem C_{ss} was within the desired target range, irrespective of the precise MIC value. Conversely, in the presence of *in vitro* meropenem-resistant pathogens with an MIC up to 32 mg/L, if the attending clinician still considered meropenem as the backbone of treatment, a TDM-based high-dose CI approach was pursued, as previously described.[24] In these cases, C_{ss}/MIC was targeted at 1–3 and a meropenem C_{ss} safety threshold was placed at 100 mg/L to prevent neurotoxicity risk.[24]

TDM was assessed first on Day 2–3 and then repeated every 48–72 h until the end of treatment. The TDM dose adjustments were provided by the clinical pharmacologists and were based on personal interpretation of the levels. Clinical pharmacological advice was provided to clinicians via the intranet system within 12 h from TDM assessment and meropenem dosage adjustments, when needed, were applied by the end of the same day.

On the TDM assessment day, peripheral venous blood samples (4 mL) were drawn and sent immediately to the Institute of Clinical Pharmacology. After centrifugation at 3500 rpm for 5 min, plasma was separated and meropenem concentrations were analysed by means of a validated HPLC method,[25] with some modifications as previously described.[23,26] Precision and accuracy were assessed by replicate analyses of quality control samples against calibration standards. Intra- and inter-assay coefficients of variation were always <10%. The lowest limit of detection was 0.5 mg/L.

Demographic and clinical data were anonymized and recorded. Information obtained included age, weight, gender, underlying haematological disease, type and date of HSCT, type and site of infection, serum creatinine (SCr), eCR_{CL}, C-reactive protein (C-RP) and ANC, bacterial clinical isolate (if identified) and MIC of meropenem (determined by broth microdilution). At each TDM instance, SCr, eCR_{CL} and C-RP were reassessed. Patients with eCR_{CL} >130 mL/min/1.73 m^2 were defined as having ARC.[11] Antimicrobial therapy was updated daily up to the end of treatment. Clinical outcome and duration of treatment were recorded. Patients were followed up for 3 months and, in the case of hospital readmission, rectal swabs were collected and tested for eventual CRE colonization.

Assessment of outcomes

Only patients who became definitely neutropenic (ANC < 0.5×10^9/L) were included in the final analysis. The primary endpoint was 14 day all-cause mortality, defined as death from any cause occurring within 14 days following the end of treatment with meropenem. Clinical cure was considered if all of the following criteria were met at the end of treatment: disappearance of fever for >48 h, microbiological eradication with negative cultures in at least two subsequent assessments (for microbiologically documented infections), radiological resolution of signs of infection (if present), no change of antimicrobial therapy or step-down to oral treatment. The secondary endpoint was the prevalence of CRE colonization in rectal swabs from patients rehospitalized within the 3 month follow-up.

Ethics

This study was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Ethics Committee of the Friuli Venezia Giulia Region (protocol number: 20496/CEUR). Written informed consent was obtained from each patient before enrolment.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess normal or non-normal distribution of data. Accordingly, mean ± SD or median and IQR were used for the descriptive statistics. Logistic regression analysis was performed to assess the association of 14 day all-cause mortality with the patients' clinical variables. Covariates with a P value of $\leq$0.20 at the univariate analysis were included in the multivariate analysis. All statistical analyses were performed using Systat software version 13 (Systat Software GmbH, Schimmelbuschstrasse 25, D-40699, Erkrath, Germany).

Results

Patient enrolment and characteristics

A total of 100 oncohaematological patients were prospectively enrolled (Figure 1). Twenty-five of them were excluded from the final analysis because they did not become definitely neutropenic (ANC < 0.5×10^9/L).

Demographic and clinical characteristics of the 75 definitely FN patients are summarized in Table 1. Median age was 58 years (IQR 51–66 years) and the majority of patients were male (62.6%). Most of the patients (56.0%) had AML, almost half (37/75, 49.3%) underwent HSCT and one-third (24/75; 32%) received meropenem as monotherapy. The remaining 68% received meropenem combined with amikacin (12/75; 16%), an anti-Gram-positive agent (31/75; 41.3%) or with both amikacin and an anti-Gram-positive agent (8/75; 10.7%). Seven patients (9.3%) received co-treatment with antifungals [caspofungin (5.3%), liposomal amphotericin B (2.7%) or voriconazole (1.3%)]. Median dose of CI meropenem was 1 g q8h over 8 h. Median duration of meropenem therapy was 10 days (IQR 7–12 days). Total number of TDM instances was 228 (median 3 per patient). Meropenem dosage was adjusted in 30.1% of TDM reassessments (46/153) [increased in 15.7% (24/153) of cases and decreased in the other 14.4% (22/153)]. No major meropenem-related adverse events were observed. Forty-one out of 75 patients (54.8%) had clinically documented infections; BSI (26.7%) and pneumonia (18.7%) accounted for most of them. Infections were microbiologically documented in 26.7% of patients (20/75). Among these, 15/20 (75%) were caused by Gram-negative bacteria and 5/20 (25%) by MDR Gram-positive bacteria (Table 2). The 14 day all-cause mortality was 10.7% (8/75) and the overall clinical cure rate was 89.3% (67/75).

Analysis of clinical and microbiological outcomes

Figure 2 shows the flow chart history of antimicrobial therapy, microbiological outcome and clinical outcome among the 75 FN patients.

Patients with microbiologically documented MDR Gram-positive infections had therapy with meropenem withdrawn at the time of microbiological documentation. Likewise, those having documented Gram-negative infections had anti-Gram-positive agents withdrawn. Overall, among the 70 patients who had definitive empirical or targeted treatment with meropenem, clinical cure rate was 90% (63/70) and 14 day all-cause mortality rate was

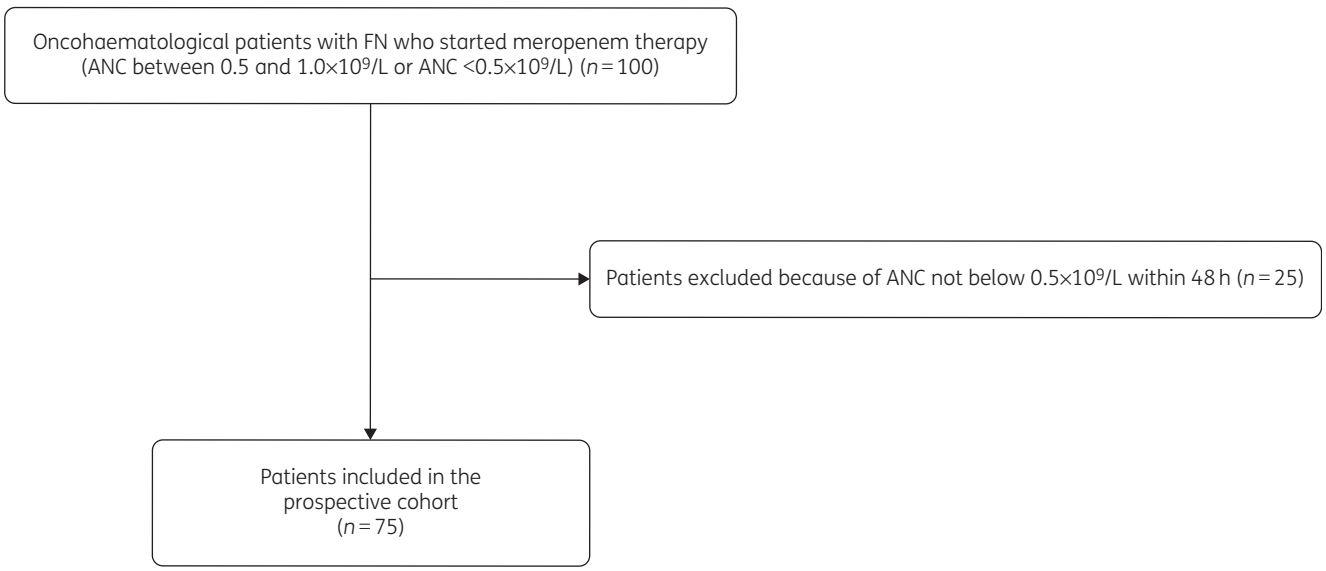

Figure 1. Flow chart of patient inclusion and exclusion criteria.

Table 1. Patient characteristics

Patient demographic	
total number of patients	75
age (years), median (IQR)	58 (51–66)
gender (male/female), *n*/*n*	47/28
body weight (kg), median (IQR)	77 (62–85.5)
eCR_{CL} at baseline (mL/min/1.73 m^2), median (IQR)	113.3 (85.7–144.3)
patients with ARC, *n* (%)	27 (36.0)
ANC at baseline ($\times 10^9$/L), median (IQR)	0.001 (0–0.042)
Underlying haematological disease, *n* (%)	
AML	42 (56.0)
NHL/CLD	18 (24.0)
ALL	9 (12.0)
MDS/MPN	4 (5.4)
MM	2 (2.6)
HSCT, *n* (%)	
allogeneic	32 (42.7)
autologous	5 (6.7)
Meropenem treatment	
median CI dose (g), median (IQR)	1 g q8h over 8 h (0.5 g q6h over 6 h–1 g q8h over 8 h)
length of therapy (days), median (IQR)	10 (7–12)
number of TDM assessments, median (IQR)	3 (2–4)
meropenem C_{ss} (mg/L), median (IQR)	12.7 (9.7–17.6)
patients with amikacin, *n* (%)	12 (16.0)
patients with anti-Gram-positive agents, *n* (%)	31 (41.3)
patients with amikacin plus anti-Gram-positive agents, *n* (%)	8 (10.7)
patients with antifungal agents, *n* (%)	7 (9.4)
Patients with clinically documented infections, *n* (%)	
BSIs	20 (26.7)
pneumonia	14 (18.7)
intra-abdominal infections	5 (6.7)
skin and soft tissue infections	2 (2.7)
Patients with microbiological clinical isolates, *n* (%)	
Gram-negative bacteria	15 (20.0)
Gram-positive bacteria	5 (6.7)
Clinical outcome, *n* (%)	
cured	67 (89.3)
14 day all-cause mortality	8 (10.7)
death due to AML progression	6 (8.0)
death due to therapy failure	2 (2.7)
patients with CRE colonization at 3 month follow-up, *n*	0/63

ARC defined as eCR_{CL} >130 mL/min/1.73 m^2);[20] CLD, chronic lymphoproliferative disorder; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma.
Data are presented as median (IQR) for continuous variables and as *n* (%) for dichotomous variables.

Table 2. Bacterial clinical isolates (*n* = 20) from the 75 FN oncohaematological patients

Pathogen	No. of isolates	MIC or MIC range (mg/L) of meropenem
Gram-negative bacteria		
Escherichia coli	9	≤0.125
P. aeruginosa	4	≤0.125–32
KPC-Kp	1	16
Citrobacter freundii	1	≤0.125
Gram-positive bacteria		
MRSA	2	—
MRSE	2	—
Enterococcus faecium	1	—

MRSE, methicillin-resistant *Staphylococcus epidermidis*.

10% (7/70). At multivariate logistic regression analysis (*n* = 70, Table 3), 14 day all-cause mortality of patients who had definitive empirical or targeted treatment with meropenem was significantly associated with HSCT (OR 0.086, 95% CI 0.008–0.936, *P* = 0.044) and ARC (OR 10.846, 95% CI 1.534–76.672, *P* = 0.017).

Pharmacokinetic/pharmacodynamic analysis of CI meropenem in patients with documented Gram-negative infections

Fifteen out of 75 patients (20%) had definitive targeted therapy with CI meropenem because of documented Gram-negative infections (13 BSI and 2 pneumonia; Table 4). All of the 12 patients having infections caused by *in vitro* meropenem-susceptible pathogens attained the desired pharmacodynamic target of efficacy (C_{ss}/MIC = 4–8) and were cured. Conversely, none of the three patients having infections caused by *in vitro* meropenem-resistant pathogens achieved this threshold. Two of them achieved a minimum C_{ss}/MIC target of 1 and were cured; the other one achieved only a suboptimal pharmacodynamic target (0.59 against an MDR *P. aeruginosa* strain with an MIC of 32 mg/L) and died.

Analysis of CRE colonization in the 3 month follow-up period

Sixty-three out of 75 patients (84%) had hospital readmissions during the 3 month follow-up period for continuing the treatment programme of the haematological underlying diseases (median 2 follow-up visits; IQR 1–2). Notably, none of them had CRE colonization in the rectal swabs at any time (Table 1).

Discussion

To our knowledge, this is the first study that prospectively assessed the role that a real-time TDM-based approach for CI meropenem may have in both maximizing the efficacy and preventing the emergence of CRE colonization among FN oncohaematological patients.

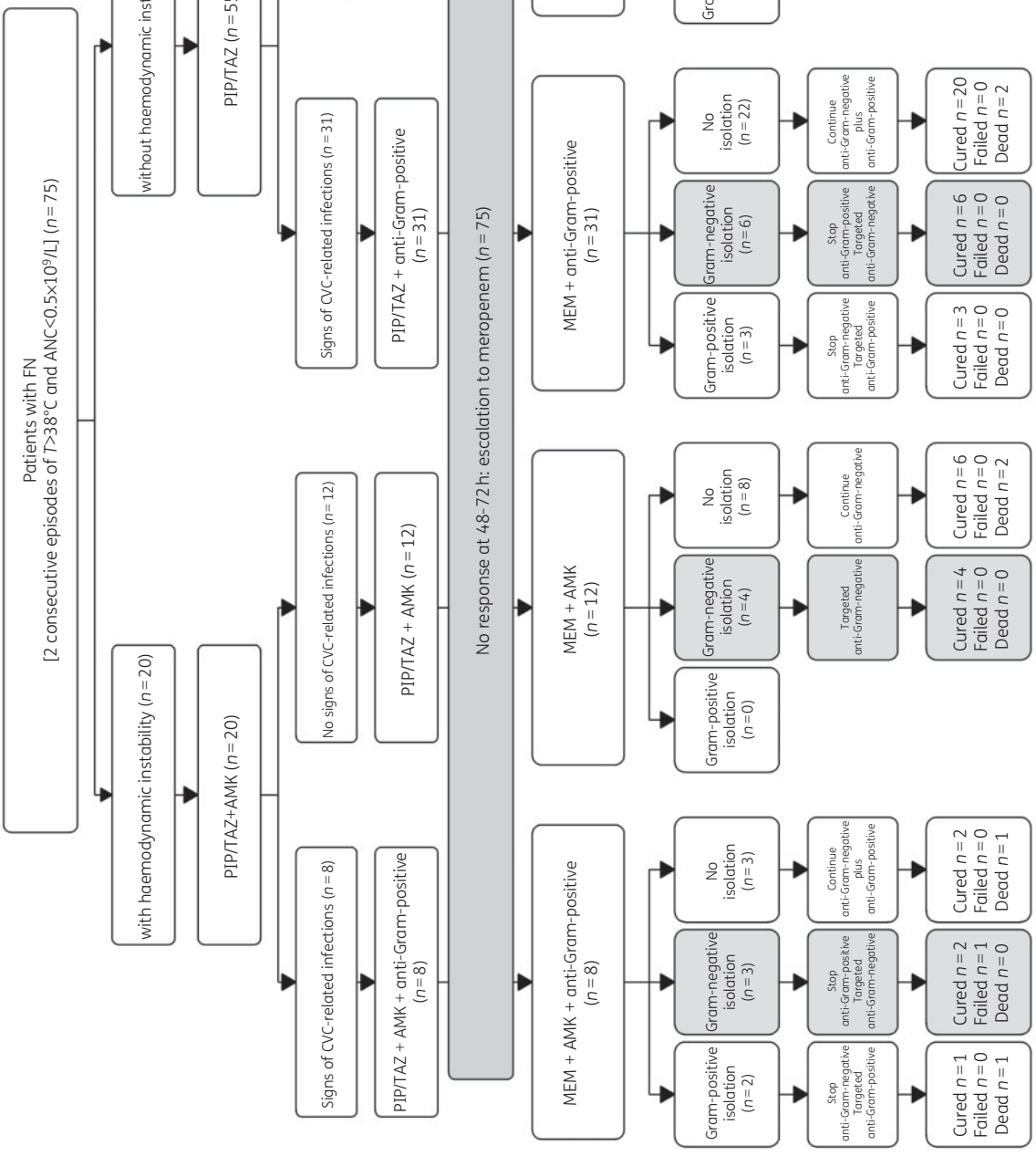

Figure 2. Flow chart of antibacterial treatment, microbiological isolation and clinical outcome in the study cohort ($n = 75$). PIP/TAZ, piperacillin/tazobactam; AMK, amikacin; MEM, meropenem.

Table 3. Univariate and multivariate logistic regression analysis for 14 day all-cause mortality in the 70 patients who had definitive therapy with meropenem

	Univariate model			Multivariate model		
Factor	OR	95% CI	*P* value	OR	95% CI	*P* value
Age >75 years	2.400	0.482–11.950	0.285			
Female gender	0.569	0.102–3.162	0.520			
Length of meropenem therapy >7 days	1.080	0.192–6.064	0.931			
History of HSCT	**0.152**	**0.017–1.332**	**0.089**	**0.086**	**0.008–0.936**	**0.044**
ANC < 0.1×10^9/L at baseline	0.472	0.080–2.779	0.406			
BSI	0.842	0.156–4.546	0.842			
ARC (CR_{CL} > 130 mL/min/1.73 m^2)	**5.000**	**0.894–27.963**	**0.067**	**10.846**	**1.534–76.672**	**0.017**
Meropenem C_{ss}* < 8 mg/L	2.457	0.422–14.324	0.317			
Combination with amikacin (and/or clinical instability)	4.667	0.932–23.358	0.061	3.319	0.534–20.630	0.198
Combination with anti-Gram-positive agent	2.625	0.524–13.139	0.240			
Combination with antifungal agent	1.453	0.152–13.875	0.746			

ARC defined as eCR_{CL} > 130 mL/min/1.73 m^2); C_{ss}*, steady-state concentration at first TDM assessment.
Bold highlights the factors significantly associated with 14 day all-cause mortality at multivariate analysis.

Table 4. Pharmacokinetic/pharmacodynamic analysis of patients having targeted treatment with CI meropenem for documented Gram-negative infections (n = 15)

Patient ID	Age (years)	Gender	Site of infection	Bacterial isolate	MIC (mg/L)	$C_{ss\text{-}avg}$ (mg/L)	$C_{ss\text{-}avg}$/MIC	Other antimicrobials	Antifungal agents	Treatment duration (days)	Outcome
1	51	F	BSI	*E. coli*	≤0.125	12.58	≥100.64	vancomycin[a]	—	28	cured
2	56	M	BSI	*E. coli*	≤0.125	33.32	≥266.56	amikacin	caspofungin	12	cured
3	62	M	BSI	*E. coli*	≤0.125	14.60	≥116.83	amikacin	caspofungin	12	cured
4	53	M	BSI	*E. coli*	≤0.125	9.46	≥75.71	linezolid[a]	—	11	cured
5	62	F	BSI	*E. coli*	≤0.125	14.69	≥117.49	—	—	7	cured
6	43	F	BSI	*E. coli*	≤0.125	15.48	≥123.84	amikacin, daptomycin[a]	—	18	cured
7	23	F	BSI	*E. coli*	≤0.125	16.12	≥128.94	vancomycin[a]	—	11	cured
8	43	F	BSI	*E. coli*	≤0.125	13.95	≥111.57	amikacin	—	9	cured
9	39	F	BSI	*C. freundii*	≤0.125	16.93	≥135.42	vancomycin[a]	—	11	cured
10	58	F	BSI	*E. coli*	0.125	17.84	142.72	linezolid[a]	—	7	cured
11	49	M	pneumonia	*P. aeruginosa*	0.5	18.70	74.78	amikacin, vancomycin[a]	—	10	cured
12	52	M	BSI	*P. aeruginosa*	1	16.73	16.73	daptomycin[a]	—	6	cured
13	28	M	pneumonia	*P. aeruginosa*	16	19.29	1.21	—	—	9	cured
14	71	F	BSI	*K. pneumoniae*	16	21.07	1.32	amikacin	—	14	cured
15	68	M	BSI	*P. aeruginosa*	32	18.88	0.59	amikacin, linezolid[a]	—	10	failed

$C_{ss\text{-}avg}$, average C_{ss}; F, female; M, male.
[a]Stopped at time of microbiological identification.

Overall, in our cohort around one-quarter of infections were microbiologically documented (26.7%), with a large prevalence of Gram-negative bacteria (75%). This is consistent with the findings of other previous studies that reported similar rates for both of these indices in the same setting (26%–29.6% of microbiologically documented infections with prevalence for Gram-negative bacteria of 52.8%–63.6%).[4,27,28]

Likewise, the 14 day all-cause mortality (10.7%) and the mortality rate attributable to failure of antibiotic therapy (2.7%) were similar to previous findings. The overall mortality rates among FN oncohaematological patients ranged between 6.7% and 14.3%, both in retrospective[29] and in prospective[28,30] clinical studies, and 2.4% were attributable to failure of meropenem therapy.[31]

Our findings suggest that CI administration coupled with real-time TDM-guided optimization of drug exposure may represent a step forward in maximizing the effectiveness of meropenem treatment among FN patients. Data on the effect of the mode of administration of meropenem on clinical outcome are currently lacking in the setting of FN oncohaematological patients. The only available data concern the effect of extended infusion (EI). Among 164 patients with HSCT or AML, administration of meropenem by 4 h EI led to better clinical outcome than conventional II and was independently associated with clinical success at Day 5 (OR 3.13), fewer additional antibiotics, faster defervescence and more rapid decrease of inflammatory markers.[31]

The role that CI meropenem administration may have in improving the clinical outcome of infections was documented in other studies carried out among critically ill patients. In an early retrospective study carried out among 89 ventilator-associated pneumonia patients receiving meropenem, CI was associated with a higher survival rate compared with II (90.5% versus 59.6%, $P < 0.001$).[32] More recently, a meta-analysis of three randomized clinical trials of β-lactam use showed that among 632 patients with severe sepsis or with septic shock, administration of β-lactams by CI was associated with a lower 30 day in-hospital mortality rate compared with administration by II (19.6% versus 26.3%, $P = 0.045$).[33]

Real-time TDM-guided targeting of meropenem C_{ss} at 8–16 mg/L (i.e. 100% T at >4–8 times the EUCAST clinical breakpoint) may represent a valuable approach for coupling maximization of effectiveness against Gram-negative bacteria during empirical treatment with prevention of emergence of CRE colonization.

Interestingly, among the 20% of patients who had targeted CI meropenem for the treatment of documented Gram-negative infections, cure was achieved in all of those with meropenem C_{ss}/MIC >4 (80%). Favourable clinical outcome was documented even in the two patients who had infections caused by meropenem-resistant pathogens (with an MIC of 16 mg/L) and achieved a meropenem C_{ss}/MIC of >1. Conversely, clinical failure was observed in the only patient who had an infection caused by an MDR *P. aeruginosa* strain with an MIC of 32 mg/L and attained a suboptimal pharmacodynamic target (C_{ss}/MIC = 0.59). These findings are in line with our previous findings in a retrospective cohort of 30 patients who received high-dose CI meropenem in combination therapy (mainly with tigecycline and colistin) for the treatment of KPC-producing *Klebsiella pneumoniae* (KPC-Kp) infections.[24] Successful clinical outcome against KPC-Kp with an MIC of meropenem up to 32 mg/L was significantly associated at univariate analysis with a meropenem C_{ss}/MIC either ≥ 1 (OR = 10.556, 95% CI 1.612–69.122, $P = 0.014$) or ≥ 4 (OR = 12.250, 95% CI 1.268–118.361, $P = 0.030$).[24]

Multivariate logistic regression analysis showed that HSCT was associated with decreased early 14 day all-cause mortality (OR 0.086, 95% CI 0.008–0.936, $P = 0.044$). This is in line with a recent study showing that very early treatment-related mortality was very low among 114 491 patients with HSCT (83.7% allogeneic) for leukaemia and significantly decreased in recent years.[34]

Conversely, ARC was significantly associated with an increased risk of 14 day all-cause mortality (OR 10.846, 95% CI 1.534–76.672, $P = 0.017$). ARC is a rather frequent condition among FN patients and may cause an increase in the renal clearance of hydrophilic antimicrobials like meropenem.[11] ARC was present in 16.4% of 292 FN patients included in a Japanese observational study.[35] In that study, FN was significantly associated with ARC occurrence (OR 2.76) and treatment with a hydrophilic antibiotic (vancomycin) was associated with a 2-fold higher probability of causing subtherapeutic levels in ARC patients compared with non-ARC ones (68.8% versus 32.8%).[35] This supports the helpful role that real-time TDM optimization of hydrophilic antibiotics, like meropenem, may have in individualizing antimicrobial therapy in FN patients, as already advocated by various authors.[10,36–38]

Treatment with a carbapenem in the previous 3 months is a rather frequent occurrence among oncohaematological patients who have CRE infections.[39] It is generally agreed that the amount of antibiotic exposure required to suppress the emergence of resistance must exceed that associated with clinical efficacy.[19] For β-lactams, the threshold to suppress the emergence of antibiotic resistance was C_{min}/MIC ≥ 4.[18,19] This threshold was achieved in the vast majority of our FN patients and may explain the total absence of emergence of CRE colonization in rectal swabs in all of those (84%) who had rehospitalization during the 3 month follow-up period. This is different from what was previously observed in a prospective cohort of 185 adult patients hospitalized for HSCT over a period of 8 months. The prevalence of CRE colonization in rectal swabs was as high as 11.4%.[40] In another study, antipseudomonal antibiotic exposure within the previous 3 months was associated, at multivariable analysis, with a significant risk for colonization or infection with CRE (OR 5.20, 95% CI 1.71–15.9, $P = 0.004$).[13] Our findings suggest that administering meropenem by CI and targeting C_{ss}/MIC at >4–8 may play an important role in preventing the emergence of CRE.

We are aware of some limitations in this study. The absence of a control arm of patients receiving meropenem by II did not allow us to address the issue of superiority of CI on clinical outcome. Most patients did not have a microbiologically documented diagnosis and were co-treated with other antimicrobials that might represent confounding factors. The inclusion in the regression analysis of all patients having definitive empirical therapy with meropenem and not only of those having targeted therapy could be a potential bias. Conversely, the prospective study design, the pharmacokinetic/pharmacodynamic analysis of meropenem in patients with documented Gram-negative infections and the absence of occurrence of CRE colonization at 3 month follow-up are valuable strengths.

In conclusion, real-time TDM-guided CI meropenem may be a useful approach for attaining adequate exposure and preventing CRE emergence in FN oncohaematological patients. Prospective randomized studies comparing CI versus II are warranted for confirming the clinical benefits that prolongation of meropenem infusion time may have in this patient population.

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Transparency declarations

A.C. has received honoraria from and has been a speaker for Pfizer, Gilead, Merck, Celgene and Janssen. F.P. has participated in speaker bureaus for Angelini, Basilea Pharmaceutica, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Pfizer and Sanofi Aventis, and in advisory boards for

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