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Original article

Efficacy of extended infusion of β-lactam antibiotics for the treatment of febrile neutropenia in haematologic patients (BEATLE): a randomized, multicentre, open-label, superiority clinical trial

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ABSTRACT

Objectives: The efficacy of extended infusions (EI) of β-lactam antibiotics for optimising outcomes in febrile neutropenia is unclear. We assessed whether the administration of β-lactams was more effective in EI than in intermittent infusion (II) for the treatment of febrile neutropenia.

Methods: We performed a randomized, open-label, superiority clinical trial of patients with febrile neutropenia at four Spanish university hospitals. Patients undergoing haematopoietic stem cell transplantation or with acute leukaemia receiving chemotherapy who required empirical antibiotic treatment for febrile neutropenia were randomly assigned (1:1) to receive EI of β-lactam or II after a first dose in bolus. The choice of antipseudomonal β-lactam was left to the discretion of the attending physician. The primary endpoint was treatment success at day 5, defined as defervescence without modifying the antibiotic treatment. Secondary endpoints included adverse events, attainment of the pharmacokinetic/pharmacodynamic target of 50%, 75%, and 100% $f_uT_{>MIC}$, and 30-day mortality.

Results: From November 19, 2019 to June 22, 2022, 295 patients were screened for eligibility, of whom 150 were randomly assigned to receive EI ($n = 77$) or II ($n = 73$) of the antipseudomonal β-lactam of choice. In the intention-to-treat analysis, treatment success at day 5 was achieved in 39/77 patients (50.6%) receiving EI versus 46/73 patients (63.0%) receiving II (risk difference, −12.4%; 95% CI, −29.4 to 4.7; p 0.17). The pharmacokinetic/pharmacodynamic targets of 75% and 100% $f_uT_{>MIC}$ for empirical

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treatment were achieved more frequently in the EI group. No statistically significant differences were found between groups in terms of adverse events or 30-day mortality.
Discussion: Our findings do not support the routine use of empirical EI of β-lactams in febrile neutropenia. Further studies should consider the clinical heterogeneity of febrile neutropenia and focus on patients with sepsis or septic shock and microbiologically documented infections, particularly those with infections caused by microorganisms less susceptible to β-lactams. **Julia Laporte-Amargos, Clin Microbiol Infect 2025;31:211**

Introduction

Febrile neutropenia (FN) is a common complication in patients with haematological diseases, usually managed empirically with antipseudomonal β-lactam antibiotics (BLAs). β-Lactams are time-dependent antibiotics that achieve optimal bactericidal activity when unbound concentrations are maintained above the MIC of the bacteria for a specific fraction of the dosing interval ($\%f_{u}T_{>MIC}$). In patients with severe infections, the β-lactam pharmacokinetic/pharmacodynamic (PK/PD) target associated with better clinical outcomes is still under debate, but emerging evidence suggests that a $100\%f_{u}T_{>MIC}$ may be necessary [1–3].

However, patients with FN may exhibit significant alterations in β-lactam PK that lead to altered concentration-over-time profiles and may be infected by less susceptible pathogens, which may compromise attainment of this PK/PD target [4–8]. A way to overcome this scenario may be extended infusion (EI) administration, as it provides more constant concentrations over time [9–14].

Beyond the theoretical concept, randomized controlled trials (RCTs) evaluating the efficacy of EI of BLA have mainly focused on critically ill patients. Recent data has shown a decrease in 90-day mortality and higher rates of clinical cure and microbiological eradication with the use of continuous infusion [15–17] Conversely, the evidence regarding haematological patients with FN is particularly scarce and contradictory [18–20].

Our hypothesis was that EI of β-lactams may lead to better treatment success in haematological patients with FN compared to intermittent infusion (II) administration.

Methods

Study design

Academic-driven, multicentre, open-label, and superiority RCT of patients with FN (BEATLE study). The study was approved by the Spanish Medicines and Healthcare Products Regulatory Agency, the clinical research ethics committee at Bellvitge Hospital (Ref. AC007/19), and the institutional review boards at each participating site. The detailed study protocol has been registered (ClinicalTrials.gov NCT04233996; EudraCT 2018-001476-37) and published previously [21]. The trial was conducted in accordance with the Declaration of Helsinki principles, the Good Clinical Practices guidelines, and current legislation.

Participants

Adult patients admitted to the haematology wards at four Spanish university hospitals who were undergoing chemotherapy for acute leukaemia or haematopoietic stem cell transplantation, presented FN (defined as axillary temperature ≥38.0 °C and <500 neutrophils/mm^3 or <1000 expected to drop within 24–48 hours), and received empirical therapy with antipseudomonal β-lactams (piperacillin-tazobactam, cefepime, or meropenem), in monotherapy or in combination with another antibiotic, were included. Exclusion criteria were allergy to the study drugs, systemic antibiotic therapy at FN onset, epilepsy, or severe renal impairment (creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation <30mL/min), previous enrolment on the study without resolution of the first episode, or enrolment 5 weeks before the new FN episode. All patients or their legal representatives provided written informed consent.

Randomization

Selected patients were randomized (1:1) to receive the BLA as EI or II in computed-generated variable blocks of 4–6 patients stratified per centre.

Intervention and control

At FN onset, the BLA of choice was administered within 30 minutes in all patients. For patients in the EI group, time was equal to half of the time of the dosing interval. For patients in the II group, the BLA was administered in 30 minutes. Dosage was recommended for treating *Pseudomonas aeruginosa*: piperacillin-tazobactam 4 g/6 h, cefepime 2 g/8 h, and meropenem 1 g/8 h; or adjusted according to renal function (Table S1).

Study procedures

Patients received the BLA under study for 5 days or until one of the following events: (i) modification of the BLA because of clinical criteria; (ii) modification to a nonstudy antibiotic when a microorganism resistant to all study BLA was isolated; (iii) modification to another study BLA when a microorganism resistant to the empirical BLA but susceptible to another study BLA was isolated. In this scenario, measurements and visits started along with the initiation of the second BLA; (iv) severe adverse event; (v) death; (vi) treatment discontinuation due to rapid clinical improvement, hospital discharge, and no need for antibiotic continuation, or (vii) switch to directed oral therapy due to rapid clinical improvement with hospital discharge but still requirement of antibiotic continuation (Table S2). Patients on combination therapy with aminoglycosides received them for 48 hours. Daily clinical assessment was performed for the first 5 days, with a follow-up visit 30-days after randomization.

Microbiological procedures and antibiotic sampling are detailed in the supplementary material (Sections 1.3-1.5, Table S3-S4). Total plasma BLA concentrations were measured using a previously validated ultra-high-performance liquid chromatography coupled to tandem mass spectrometry method [22]. A theoretical protein binding of 30%, 19%, and 2% was applied for piperacillin, cefepime, and meropenem, respectively, to estimate the unbound concentration [23] The empirical MIC target was inferred from the European Committee on Antimicrobial Susceptibility Testing database as the

highest MIC in the susceptible range for *P. aeruginosa* for the chosen dosing (16 mg/L for piperacillin-tazobactam, 8 mg/L for cefepime, and 2 mg/L meropenem) [24]. For patients with a microbiological diagnosis, the MIC of the isolated pathogen was chosen as the directed target.

Outcomes

The primary endpoint was treatment success at day 5, defined as defervescence and no need for antibiotic change. Defervescence was considered as an axillary temperature <37.5 °C for at least 24 hours, assessed at three consecutive time points, with no new documented fever. Treatment failure due to antibiotic change was defined as: (i) modification of the BLA because of clinical criteria; (ii) modification to a nonstudy antibiotic when a microorganism resistant to all study BLA was isolated; (iii) addition of another antibiotic after 24 hours of the initiation of the empirical treatment (Table S2).

Secondary endpoints were: (i) time (hours) until defervescence (without changes in the empirical antibiotic treatment; (ii) time (days) to bacteraemia clearance; (iii) a fall of >50% in the maximum value of C-reactive protein; (iv) time (days) to a fall of >50% in the maximum value of C-reactive protein; (v) clinical resolution rate, defined as improvement or resolution of clinical signs and symptoms with defervescence at days 5 and 30; (vi) achievement of the empirical and directed PK/PD targets of 50%, 75%, and 100% $f_u T_{>MIC}$, overall and by BLA; (vii) adverse events; and (viii) 30-day all-cause mortality.

Statistical analysis

Previously published data suggested that treatment success in the control group was around 45% [18,25]. For an expected treatment success of 70% in the intervention group, the absolute risk reduction would be 25%. Assuming a loss to follow-up of 20%, a

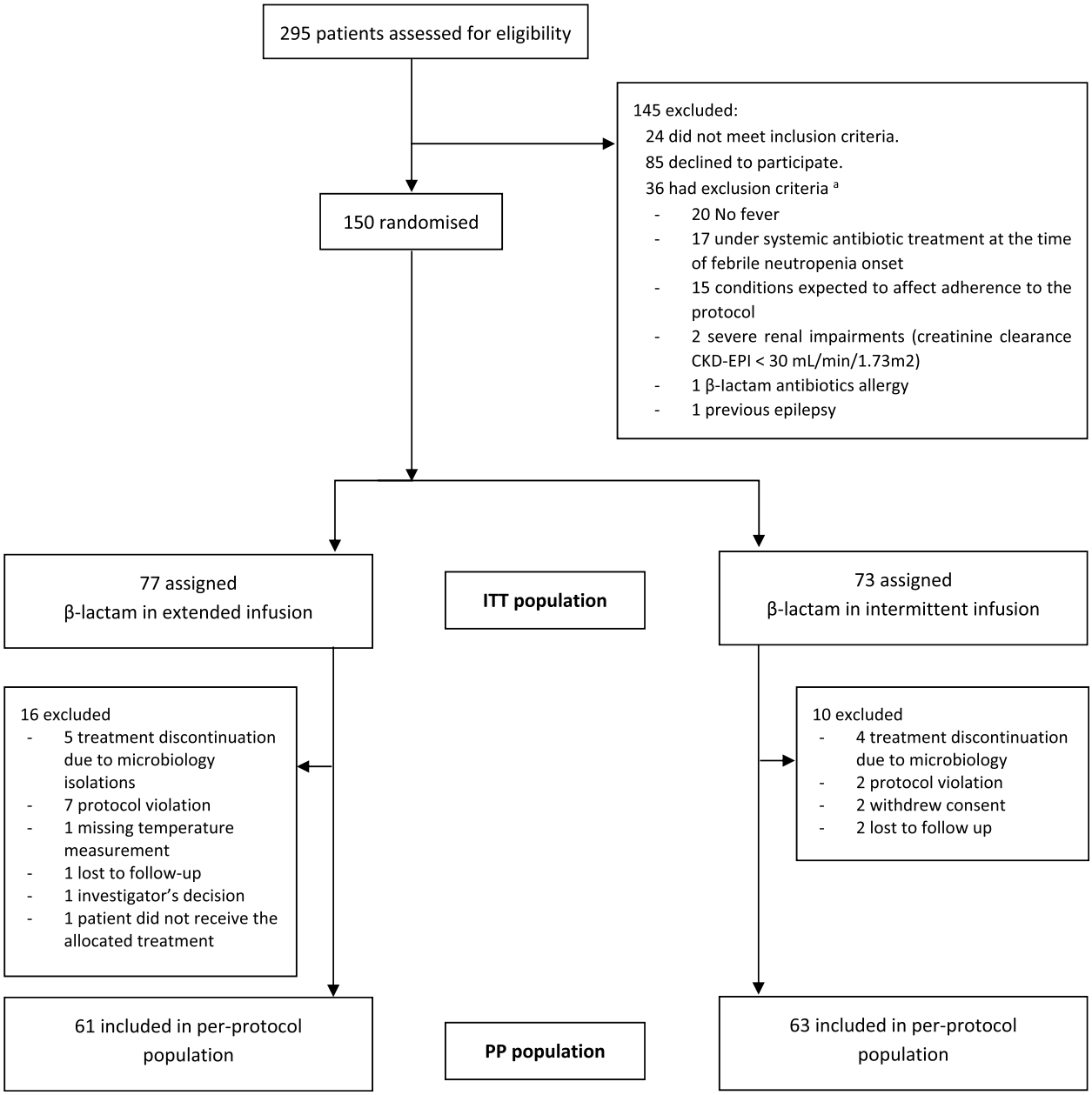

Fig. 1. Trial profile. Flow diagram indicating participant numbers and disposition throughout the course of the trial. [a]Twenty patients presented more than one exclusion criterion.

sample size of 150 participants was calculated to reject the null hypothesis of equal effect with a power of 80% and a significance level of 5%. On March 2022, a planned interim analysis to evaluate the adequacy of the sample size was performed when half of the sample size had been achieved [21]. The independent committee of experts did not recommend increasing the sample size.

Outcomes were analysed by intention-to-treat, including all randomized participants, and per-protocol, including patients without major protocol deviations. All patients who received at least one dose of the study antibiotic were included in the safety analysis. The analysis was repeated in prespecified subgroups according to the clinical presentation (patients with microbiologically documented infection, clinically documented infection, fever of unknown origin or noninfectious fever), according to the BLA under study, and according to whether or not they received combination therapy [21]. For the primary and secondary endpoints, proportions were compared between groups using a two-sided χ^2 test or a Fisher's exact test when applicable. The risk differences for study outcomes were calculated and reported with 95% CI. Kaplan-Meier curves for time-to-event outcomes were estimated and compared using the log-rank test. All analyses were performed with R software version 4.3.0 or later.

Table 1
Baseline characteristics at febrile neutropenia onset in the intention-to-treat population

Characteristic	Extended infusion ($n = 77$)	Intermittent infusion ($n = 73$)
Sex (males)	42 (54.5%)	29 (39.7%)
Age (y)	58.0 (50.0–65.0)	57.0 (48.0–64.0)
BMI (kg/m^2)	27.3 (5.0)	25.6 (4.4)
Glomerular filtration rate (mL/min/1.73m^2) CKD-EPI	103 (33.9)	105 (32.5)
Chronic renal failure (eGFR 30–60 mL/min/1.73m^2)	3 (3.9%)	0
Charlson comorbidity index	3.65 (1.4)	3.38 (1.2)
Previous antibiotics last month	17 (22.1%)	16 (21.9%)
Previous MDR microorganism isolation[a]	6 (7.8%)	7 (9.6%)
Fluoroquinolone prophylaxis	9 (11.7%)	10 (13.4%)
Underlying haematological malignancy		
Acute myeloid leukaemia/myelodysplastic syndrome	26 (33.8%)	32 (43.8%)
Lymphoma	21 (27.3%)	21 (28.8%)
Multiple myeloma	17 (22.1%)	16 (21.9%)
Acute lymphoblastic leukaemia	8 (10.4%)	4 (5.5%)
Other	5 (6.5%)	0
Previous haematopoietic stem cell transplant	10 (13.0%)	9 (12.3%)
Reason for admission		
Treatment for acute leukaemia	21 (27.3%)	15 (20.8%)
Haematopoietic stem cell transplant	56 (72.7%)	57 (79.2%)
Myeloablative conditioning regimen	35/56 (62.5%)	40/57 (70.2%)
Autologous	31/56 (55.4%)	30/57 (52.6%)
Allogenic	25/56 (44.6%)	27/57 (47.4%)
Related HLA-identical donor	5/25 (20.0%)	6/27 (22.2%)
Unrelated donor	14/25 (56.0%)	17/27 (63.0%)
Haploidentical donor	6/25 (24.0%)	4/27 (14.8%)
High risk MASCC score (<21)	37 (48.1%)	42/72 (58.3%)[b]
SOFA score	5.10 (2.0)	5.55 (1.7)
APACHE II score	18.5 (3.9)	18.9 (3.3)
Neutrophils $\leq 100 \times 10^6$/L	64 (83.1%)	65 (89.0%)
Duration of neutropenia previous fever onset (d)	3.00 (1.0–5.0)	3.00 (1.8–5.0)
Source of infection		
Mucositis	9/41 (22.0%)	20/45 (44.4%)
Neutropenic enterocolitis	5/41 (12.2%)	5/45 (11.1%)
Other abdominal source	10/41 (24.4%)	8/45 (17.8%)
Intravascular catheter	4/41 (9.76%)	3/45 (6.67%)
Pneumonia	6/41 (14.6%)	1/45 (2.2%)
Urinary	2/41 (4.9%)	2/45 (4.4%)
Skin and soft tissue	0	2/45 (4.4%)
Other	5/41 (12.2%)	4/45 (8.9%)
Hypotension	12 (16.0%)	11 (15.3%)
Measures of source control: catheter removal	11 (14.3%)	10 (13.7%)
Initial antibiotic therapy		
Cefepime	5 (6.5%)	2 (2.7%)
Cefepime + amikacin	32 (41.6%)	35 (48.0%)
Cefepime + vancomycin	5 (6.5%)	2 (2.7%)
Cefepime + daptomycin	0	1 (1.3%)
Cefepime + amikacin + vancomycin	1 (1.3%)	1 (1.3%)
Cefepime + amikacin + daptomycin	3 (3.9%)	2 (2.7%)
Piperacillin-tazobactam	14 (18.2%)	17 (23.3%)
Piperacillin-tazobactam + amikacin	4 (5.4%)	4 (5.5%)
Piperacillin-tazobactam + vancomycin	3 (3.9%)	2 (2.7%)
Piperacillin-tazobactam + daptomycin	1 (1.3%)	0
Piperacillin-tazobactam + amikacin + daptomycin	1 (1.3%)	0
Meropene	7 (9.1%)	4 (5.5%)
Meropenem + vancomycin	1 (1.3%)	3 (4.11%)

Data are *n* (%), *n*/*N* (%), median (Q1–Q3) or mean ± SD. APACHE II, acute physiology and chronic health disease classification system II; BMI, body mass index; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; MASCC, multinational association for supportive care in cancer; MDR, multidrug-resistant; SOFA, sepsis related organ failure assessment.

[a] Methicillin-resistant *Staphylococcus aureus:* 1 versus 1, *Enterobacterales* MDR: 4 versus 3, *Stenotrophomonas maltophilia:* 1 versus 1.

[b] One patient without neutropenia.

Results

From November 19, 2019 to June 22, 2022, 295 patients were screened for eligibility, of whom 150 were enrolled and randomized to receive either EI ($n = 77$) or II ($n = 73$) of the BLA of choice. The trial profile is shown in Fig. 1, and the enrolment by centre in Table S3.

Patients' baseline characteristics were similar in both groups, except that there were more men and cases of pneumonia in the EI group and more women and cases of mucositis in the control group (Table 1). Microbiological isolation was obtained in 42/150 (28.0%) patients, 30 of whom had bacteraemia, and 14/30 (46.7%) were gram-negative (Table S4-S6). In five patients (3 EI vs. 2 II), the initial BLA was modified to another study drug in view of the microbiological results, and visits were consequently restarted. Accordingly, these patients were included in the intention-to-treat and per-protocol analysis (Table S7). Four patients were switched to oral antibiotics (3 vs. 1) because of clinical improvement and they were considered as treatment successes (Table S8).

In the intention-to-treat population, treatment success at day 5 was achieved in 39/77 (50.6%) patients receiving EI versus 46/73 (63.0%) patients receiving II (risk difference −12.4%; 95% CI, −29.4 to 4.7; p 0.17). A higher proportion of BLA changes was observed in the EI group (31/77 [40.3%] vs. 18/73 [24.7%]; p 0.06) although defervescence was similar in both groups (Table S9). No statistically significant differences were found when analysing the results stratified by clinical presentation, the BLA prescribed, or combined therapy versus monotherapy. Nor were there differences between

Table 2
Primary and secondary endpoints in the intention-to-treat and per-protocol populations.

Intention-to-treat	Extended infusion ($n = 77$)	Intermittent infusion ($n = 73$)	Risk differences % (95% CI)	p
Primary endpoint				
Treatment success at day 5	39 (50.6%)	46 (63.0%)	−12.4 (−29.43 to 4.7)	0.1730
Primary endpoint by subgroups				
Clinical presentation				
Microbiologically documented infection	6/21 (28.6%)	11/21 (52.4%)	−23.8 (−57.37 to 9.76)	0.2086
Clinically documented infection	10/22 (45.5%)	15/25 (60.0%)	−14.5 (−47.13 to 18.04)	0.4813
Fever of unknown origin	22/29 (75.9%)	19/24 (79.2%)	−3.3 (−22.51 to 29.12)	1.0000
Noninfectious fever	1/5 (20.0%)	1/3 (33.3%)	−13.3 (−63.83 to 90.5)	1.0000
Antibiotic treatment				
Piperacillin-tazobactam	17/23 (73.9%)	17/23 (73.9%)	0 (−25.38 to 25.38)	1.0000
Cefepime	19/46 (41.3%)	25/43 (58.1%)	−16.8 (−39.58 to 5.91)	0.1690
Meropenem	3/8 (37.5%)	4/7 (57.1%)	−19.6 (−82.73 to 43.44)	0.6193
Monotherapy	16/26 (61.5%)	14/23 (60.9%)	0.6 (−27.34 to 28.68)	1.0000
Combination with another antibiotic	23/51 (45.1%)	32/50 (64.0%)	−18.9 (−39.95 to 2.14)	0.0878
Secondary endpoint				
Time to defervescense without modifying antibiotic (h)	$n = 39$ 54.0 (32.8–90.6)	$n = 46$ 52.8 (31.7–74.7)	—	0.4943
Time to bacteraemia negativization (d)	$n = 15$ 2.0 (1.0–2.0)	$n = 10$ 1.5 (1.0–2.0)	—	0.4788
Decrease >50% of the maximum value of the C-reactive protein	38 (50.7%)	38 (54.3%)	−3.6 (−21.25 to 14.02)	0.7874
Time to decrease >50% of the maximum value of the C-reactive protein (d)	$n = 38$ 5.0 (3.0–5.0)	$n = 38$ 5.0 (3.0–5.0)	—	0.9236
Clinical resolution rate on day 5	54/75 (72.0%)	56/70 (80.0%)	−8.0 (−23.2 to 7.2)	0.3520
Clinical resolution rate on day 30	69/75 (92.0%)	64/70 (91.4%)	0.6 (−8.98 to 10.13)	1.0000
30-day overall mortality	2 (2.60%)	1 (1.39%)	1.2 (−4.46 to 6.88)	1.0000
Per-protocol analysis	Extended infusion ($n = 61$)	Intermittent infusion ($n = 63$)	Risk differences % (95% CI)	p
Primary endpoint				
Treatment success at day 5	36 (59.0%)	44 (69.8%)	−10.8 (−29.19 to 7.54)	0.2838
Primary endpoint by subgroups				
Clinical presentation				
Microbiologically documented infection	6/13 (46.2%)	10/16 (62.5%)	−16.3 (−59.33 to 26.64)	0.6137
Clinically documented infection	9/18 (50.0%)	15/24 (62.5%)	−12.5 (−47.51 to 22.51)	0.6206
Fever of unknown origin	20/26 (76.9%)	18/20 (90.0%)	−13.1 (−38.36 to 12.21)	0.4350
Noninfectious fever	1/4 (25.0%)	1/3 (33.3%)	−8.3 (−84.83 to 68.16)	1.0000
Antibiotic treatment				
Piperacillin-tazobactam	14/18 (77.8%)	17/21 (81.0%)	−3.2 (−31.86 to 25.51)	1.0000
Cefepime	19/37 (51.4%)	23/36 (63.9%)	−12.5 (−37.76 to 12.69)	0.3972
Meropenem	3/6 (50.0%)	4/6 (66.7%)	−16.7 (−88.32 to 54.99)	1.0000
Monotherapy	14/20 (70.0%)	14/18 (77.8%)	−7.8 (−40.84 to 25.29)	0.7190
Combination with another antibiotic	22/41 (53.7%)	30/45 (66.7%)	−13.0 (−35.9 to 9.88)	0.3116
Secondary endpoint				
Time to defervescens without modifying antibiotic (h)	$n = 36$ 53.5 (32.9–95.9)	$n = 44$ 52.8 (32.9–77.0)	—	0.4653
Time to bacteraemia negativization (d)	$n = 8$ 2.0 (1.0–2.0)	$n = 7$ 1.5 (1.0–2.0)	—	0.8766
Decrease >50% of the maximum value of the C-reactive protein	32 (52.5%)	36 (57.1%)	−4.6 (−23.8 to 14.43)	0.7312
Time to decrease >50% of the maximum value of the C-reactive protein (d)	$n = 32$ 5.0 (3.0–5.0)	$n = 36$ 5.0 (3.0–5.0)	—	0.8591
Clinical resolution rate on day 5	45/61 (73.8%)	52/63 (82.5%)	−8.7 (−24.86 to 7.33)	0.3344
Clinical resolution rate on day 30	57/61 (93.4%)	58/63 (92.1%)	1.3 (−9.12 to 11.88)	1.0000
30-day overall mortality	2 (3.28%)	1 (1.59%)	1.7 (−5.35 to 8.74)	0.6159

Data are n (%), n/N (%), or median (Q1–Q3).

groups in the per-protocol analysis, excluding patients unable to receive the study antibiotic due to resistant isolates (Table 2).

As for the secondary outcomes, there were no statistically significant differences in time to defervescence in patients without changes in the antibiotic treatment (Fig. 2), time to bacteraemia clearance, reduction in C-reactive protein or clinical resolution rate at day 5 or 30. Two patients from the study group and one from the control group died during the 30-day follow-up due to infection-related complications.

EI was advantageous in the attainment of the PK/PD targets of 75 and 100%f_uT $_{>\ MIC}$ for susceptible *P. aeruginosa* (Fig. 3 and Tables 3 and 4). However, in patients with documented microbiology, no statistically significant differences were observed when considering the MIC of the isolated microorganisms, which had a lower MICs than the highest MIC for susceptible *P. aeruginosa* (Table S6).

The proportion of adverse events in the safety population was similar in the two groups (Table S10). Two patients receiving cefepime in EI experienced encephalopathy: one of them had concentrations exceeding 100 mg/mL, and the other had a history of subarachnoid haemorrhage 4 months before admission.

Discussion

The main finding of our RCT is that EI of antipseudomonal β-lactams did not achieve a higher treatment success at day 5 than II in haematological patients with FN. Nor were statistically significant differences found in the per-protocol analysis when noninfectious events were excluded or when data were stratified by type of β-lactam or by combined therapy versus monotherapy.

The rationale of administering BLA in EI is to overcome the potential PK alterations in patients with severe infections to optimize the f_uT $_{>\ MIC}$, especially for difficult-to-treat infections caused by less susceptible pathogens. However, data assessing the impact of this strategy on clinical outcomes in patients with FN are limited and controversial. A single-centre RCT that enrolled 105 patients treated mainly with piperacillin-tazobactam reported a higher treatment success at day 4 with EI (74.4% vs. 55.1%), particularly in patients with documented infections, mainly pneumonia [18]. Similarly, a quasi-experimental retrospective study comprising 164 patients also showed a higher treatment success at day 5 among patients receiving meropenem via EI (68.4% vs. 40.9%) [25].

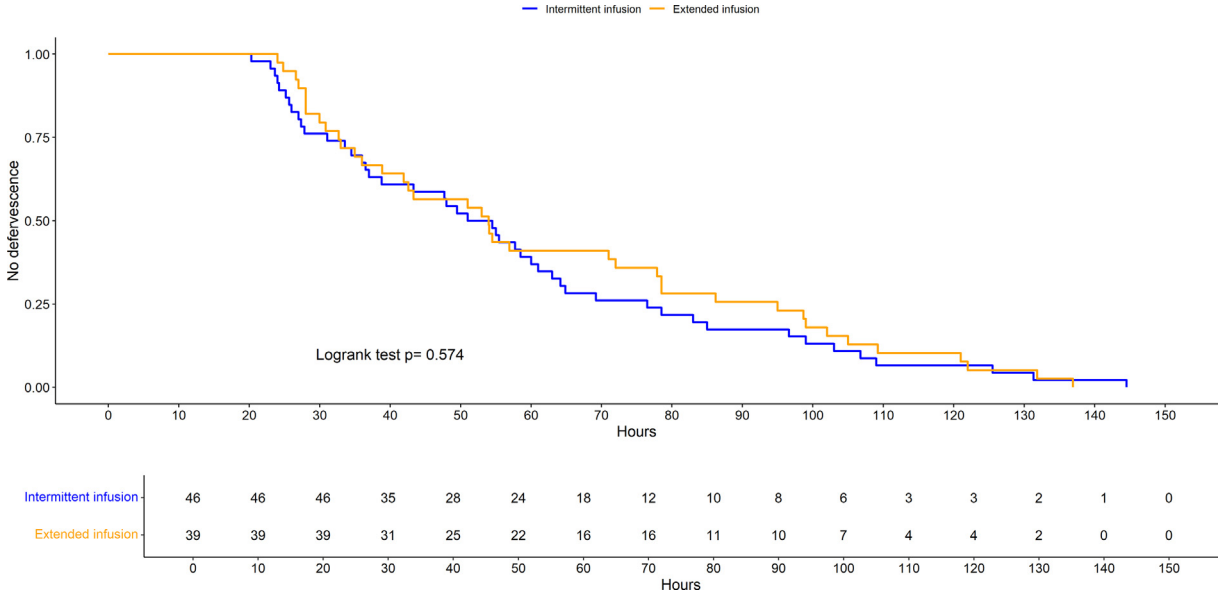

Fig. 2. Time to defervescence.

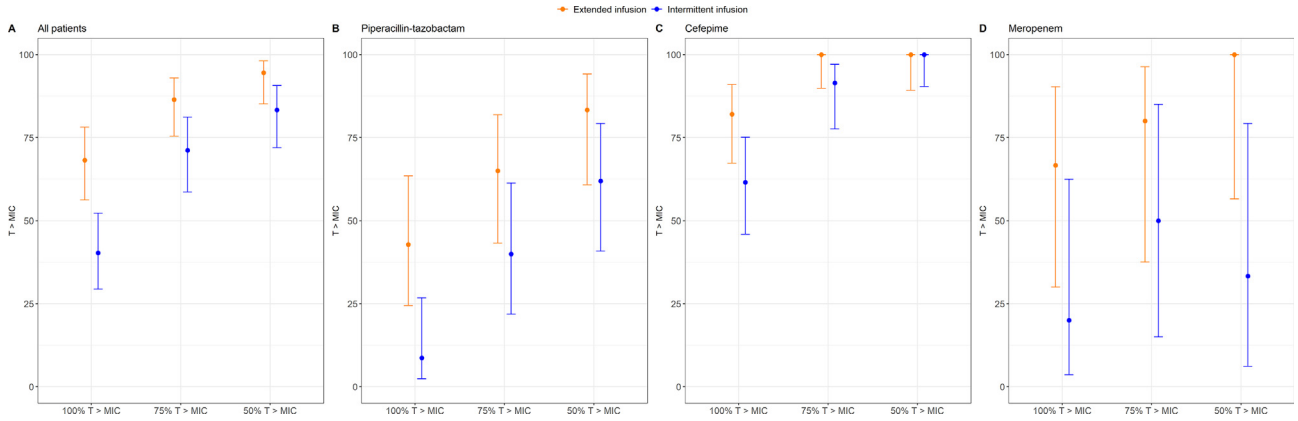

Fig. 3. PK/PD target attainment of empirical treatment.

Table 3
PK/PD target attainment of empirical treatment: unbound antibiotic concentration above the susceptibility breakpoint for susceptible *Pseudomonas aeruginosa* (EUCAST).

Endpoints	Extended infusion *n*/*N* (%)	Intermittent infusion *n*/*N* (%)	Risk differences % (95% CI)	p
All patients				
100% of the dosing interval	45/66 (68.2%)	27/67 (40.3%)	27.9 (10.12–45.64)	0.0023
75% of the dosing interval	57/65 (87.7%)	46/64 (71.9%)	15.8 (0.66–30.97)	0.0434
50% of the dosing interval	62/65 (95.4%)	54/64 (84.4%)	11 (−0.8 to 22.81)	0.0744
Piperacillin-tazobactam				
100% of the dosing interval	9/21 (42.9%)	2/23 (8.70%)	34.2 (5.51–62.81)	0.0235
75% of the dosing interval	14/21 (66.7%)	9/22 (40.9%)	25.8 (−7.68 to 59.2)	0.1655
50% of the dosing interval	18/21 (85.7%)	14/22 (63.6%)	22.1 (−7.64 to 51.79)	0.1905
Cefepime				
100% of the dosing interval	32/39 (82.1%)	24/39 (61.5%)	20.1 (−1.5 to 42.52)	0.0782
75% of the dosing interval	38/38 (100%)	35/38 (92.1%)	7.9 (−3.31 to 19.1)	0.2400
50% of the dosing interval	38/38 (100%)	38/38 (100%)	—	—
Meropenem				
100% of the dosing interval	4/6 (66.7%)	1/5 (20.0%)	46.7 (−23.16 to 100)	0.2424
75% of the dosing interval	5/6 (83.3%)	2/4 (50.0%)	33.3 (−44.86 to 100)	0.5000
50% of the dosing interval	6/6 (100.0%)	2/4 (50.0%)	50 (−19.83 to 100)	0.1333

EUCAST, European Committee on Antimicrobial Susceptibility Testing; PK/PD, pharmacokinetic/pharmacodynamic.

Table 4
PK/PD target attainment of directed treatment: unbound antibiotic concentration above the MIC of the isolated microorganism.

Endpoints	Extended infusion *n*/*N* (%)	Intermittent infusion *n*/*N* (%)	Risk differences % (95% CI)	p
All patients				
100% of the dosing interval	10/12 (83.3%)	6/7 (85.7%)	−2.4 (−38.18 to 33.42)	1.0000
75% of the dosing interval	10/12 (83.3%)	6/7 (85.7%)	−2.4 (−38.18 to 33.42)	1.0000
50% of the dosing interval	10/12 (83.3%)	6/7 (85.7%)	−2.4 (−38.18 to 33.42)	1.0000
Piperacillin-tazobactam				
100% of the dosing interval	3/5 (60.0%)	2/2 (100%)	−40 (−100 to 37.94)	1.0000
75% of the dosing interval	3/5 (60.0%)	2/2 (100%)	−40 (−100 to 37.94)	1.0000
50% of the dosing interval	3/5 (60.0%)	2/2 (100%)	−40 (−100 to 37.94)	1.0000
Cefepime				
100% of the dosing interval	5/5 (100%)	4/5 (80.0%)	20 (−35.06 to 75.06)	1.0000
75% of the dosing interval	5/5 (100%)	4/5 (80.0%)	20 (−35.06 to 75.06)	1.0000
50% of the dosing interval	5/5 (100%)	4/5 (80.0%)	20 (−35.06 to 75.06)	1.0000
Meropenem				
100% of the dosing interval	2/2 (100%)	—	—	—
75% of the dosing interval	2/2 (100%)	—	—	—
50% of the dosing interval	2/2 (100%)	—	—	—

PK/PD, pharmacokinetic/pharmacodynamic.

Conversely, a randomized pilot study including 63 patients with FN treated with cefepime reported a higher clinical success in the II group (87.9%) when compared with the EI group (76.7%), which is nonstatistically significant [26]. Notably, in this last trial, septic patients were excluded, despite being the subgroup that might benefit the most from EI [4].

Assessing the clinical efficacy of a BLA dosing optimization strategy in haematological patients with FN is challenging. FN is a highly heterogeneous clinical syndrome with very broad ranges of disease severity. In FN without clinical severity criteria, 30-day mortality is less than 5% [18,25] and may be largely dependent on the underlying haematological malignancy. Further, noninfectious episodes are common and introduce more complexity in interpretation; in fact, in line with previous studies, only 28% of our patients had microbiologically documented infections [18,25–27]. Finally, haematological patients undergoing chemotherapy or haematopoietic stem cell transplantation are prone to multiple episodes of FN, with profound neutropenia for prolonged periods. In this scenario, demonstrating an all-cause 30-day mortality benefit of EI of BLA in a single episode of FN would require large-scale studies to overcome mortality due to the haematological malignancy itself and other complications.

On contrary, treatment success is one of the most valuable outcomes in clinical practice, as clinical evolution guides maintenance or assessment of antibiotic treatment [27] Previous studies have used treatment success as the primary endpoint to compare the efficacy of the two dosing strategies. However, a standardized definition of treatment success is lacking, and the existing definitions are heterogeneous, mainly composed of multiple variables, some of them subjective, which may have a great impact on nonblinded studies. The variables we chose for defining treatment success, i.e. defervescence and no need for antibiotic change, aimed to be more objective compared with previous definitions. Nevertheless, antibiotic changes were at the discretion of the treating physician and therefore at risk of subjectivity.

A strength of our trial is that it is the first study that reports attainment of the PK/PD targets associated with BLA treatment success [18,19,25,26,28,29]. EI showed a better PK profile, with a significantly higher achievement of the empirical PK/PD target of 75% and 100%$f_u T_{>MIC}$ of susceptible *P. aeruginosa* [24]. These differences were not observed when the PK/PD target was directed to the pathogen MIC in patients with microbiological isolation, mainly due to the fact that the MICs of the isolated pathogens were substantially lower than the highest MIC of susceptible *P. aeruginosa*. However, these better PK/PD profiles suggest that the use of EI of β-lactams may be a good strategy in the empirical management of FN until microbiology results are obtained in patients at high risk of infections caused by less susceptible microorganisms.

Our study has some limitations. First, its open-label design may have introduced a bias in the evaluation of the primary endpoint, as antibiotic escalation could be driven by subjective decisions inherent

to open-label studies. Second, the sample size calculation was based on only two previous studies, with notable differences between arms, and the estimated effect of the intervention on clinical cure was rather ambitious, which may have underpowered the study to detect smaller but clinically significant differences, especially given the therapeutic success rate of 63.0% in the control group. Third, there is a possible centre effect because most patients were enrolled at the promoter centre. Fourthly, unbound plasma concentrations were not measured but estimated from total plasma concentrations [23]. Fifth, there is a potential class effect among the different β-lactams that has not been identified in the study [15]. Finally, the use of combination therapy also limits the interpretation of the results, although combination therapy is reasonably well balanced between groups and the pre-specified sub-analyses did not show any significant differences.

In conclusion, our data do not support the routine use of EI of antipseudomonal BLA in FN. Nevertheless, this strategy may optimize exposure and should be considered in individual cases with documented or suspected infections due to microorganisms with higher MICs. Considering the clinical heterogeneity of FN, larger studies are needed to assess the benefit of BLA EI in FN, and these should focus on patients with sepsis or septic shock and microbiologically documented infections, particularly those caused by microorganisms with higher MICs to BLA.

Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

Financial report

No funding was provided for this study.

Author contributions

J.L.-A., M.U., A.P., J.C., and C.G. designed the study and wrote the trial protocol. J.L.-A., F.C.-T., M.H., P.P.-A., M.A., J.L.d.P., A.T., C.G.-V., and C.G. recruited patients for the study and participated in coordination. R.R.B. measured the β-lactam antibiotic plasma concentrations. F.T. performed the microbiological studies. J.L.-A., M.U., N.P., C.T., J.C., and C.G. had access to all the data and analysed the data. J.L.-A., M.U., J.C., and C.G. wrote the manuscript and were responsible for the decision to submit it. C.G. obtained funding. All authors read and approved the final report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.10.006.

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