Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letter

Evaluating the Use of Meropenem in Hematologic Patients with Febrile Neutropenia: A Retrospective Observational Single-Cohort Study

Keywords: Antibiotic stewardship; Antibiotic resistance; Meropenem; Hematologic disease; Febrile neutropenia.

Published: November 01, 2023 **Received: June 08, 2023** **Accepted: October 26, 2023**

Citation: Stuurman R.A., Jong E., Godschalk P.C.R., Corsten M.F., Nagtegaal J.E. Evaluating the use of meropenem in hematologic patients with febrile neutropenia: A retrospective observational single-cohort study. Mediterr J Hematol Infect Dis 2023, 15(1): e2023067, DOI: http://dx.doi.org/10.4084/MJHID.2023.067

To the editor.

Patients with malignant hematologic diseases or after haematopoietic stem cell transplantation (HSCT) have weakened immune systems due to their primary diagnosis and/or treatment.[1] Treatment can induce periods of neutropenia, defined by an absolute neutrophil count (ANC) below <500 cells/μL.[2,3] In addition to often concurrent mucositis, this predisposes to infections, which often occur in this population.[4] In patients with chemotherapy-induced neutropenia, the prevalence of febrile neutropenia has been suggested to rise up to 80%.[4] Fever caused by an infection is a dangerous complication and can be lethal; therefore, prompt antibiotic treatment is indicated.[3,4]

Meropenem is an ultra broad-spectrum antibiotic in the β-lactam class often used to treat febrile neutropenia.[5,6] Empiric treatment with meropenem reduces mortality risk in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria and other multidrug-resistant (MDR) gram-negative bacteria.[2] However, meropenem use is associated with an increased risk of clostridium infections and candidemia and an increased risk of acute graft-versus-host disease in patients undergoing allogeneic HSCT.[7-12] For these reasons, as well as to promote antibiotic stewardship, the Dutch Working Party on Antibiotic Policy (SWAB) has labelled carbapenems, including meropenem, as a second-line treatment option.[13]

The nationally recommended primary choice of antimicrobial therapy is dependent on a pre-emptive risk stratification based on the expected duration of neutropenia (≤7 days vs. >7 days).[13] In high-risk neutropenic patients, antipseudomonal β-lactams such as ceftazidime and piperacillin/tazobactam are the preferred choice of antibiotic therapy.[13] Standard-risk neutropenic patients with an expected short duration of neutropenia are treated according to their Multinational Association of Supportive Care in Cancer (MASCC) score.

Until 2023, the protocol in our hospital advised treatment of febrile neutropenia in high-risk patients with meropenem for at least 72 hours.[6] As no data are available on local resistance patterns for antipseudomonal β-lactams, making unguided changes to the treatment protocol to adhere to the national guidelines can be challenging in this vulnerable patient population.

This study aims to determine the frequency of bacteria resistant to ceftazidime, piperacillin/tazobactam, and meropenem in diagnostic cultures in haematology patients admitted with febrile neutropenia to our hospital. Doing so can provide insight into the appropriateness of meropenem use and possibilities for responsible adjustments to the current empiric febrile neutropenia treatment protocol.

Methods.

Study design and outcomes. A retrospective, observational, single-centre study was carried out at Meander MC - a teaching hospital in the Netherlands, using a single cohort design of adult patients admitted with hematologic disease and febrile neutropenia between October 2018 and June 2021. The primary outcome was the frequency of bacteria resistant to the antibiotics of interest in diagnostic blood and urine cultures taken on admission for febrile neutropenia. Our antibiotics of interest were ceftazidime, piperacillin/tazobactam, and meropenem.

Only the first diagnostic blood and urine samples, taken after the occurrence of fever, were included in the results. Two other relevant diagnostic cultures, namely a line tip and wound culture, were also included in data collection as their results were the base of treatment evaluation.

Although meropenem has an ultra-broad-spectrum coverage, it does not treat infections caused by some gram-positive cocci, such as *Staphylococcus epidermis*

and *Enterococcus faecalis.*[14] Except for *E. faecalis*, which is sensitive to piperacillin/tazobactam, the bacteria mentioned above were resistant to both meropenem and either of the alternatives.[14] When these gram-positive cocci are either suspected or found, they are treated with different antibiotics, such as vancomycin.[13] To avoid reporting results biased as a higher resistance frequency, we displayed bacteria separately based on their resistance status to meropenem. These are not included in the calculations of resistance percentages to piperacillin/tazobactam and ceftazidime.

Data collection and statistical analysis. Data collection was carried out in accordance with the Dutch Medical Treatment Contracts Act (WGBO). The study was approved by the scientific research committee of the hospital. Data were analysed using SPSS (version 24). Categorical variables were reported as frequencies. Continuous variables were defined as mean and standard deviation when normally distributed or as a median and interquartile range when they were not.

Results.

Population demographics. 100 patients (58 male, 42 female) admitted between October 2018 and June 2021 were enrolled in this study. The median age was 65.0 (54.0-73.8) years, the median BMI was 24.95 (22.3-29.4) kg/m^2 and the median duration of hospital admission was 21.5 (9.3-31.0) days. Additional population demographics are shown in **Table 1**.

Resistance frequencies. Blood and urine cultures were taken in 100 and 62 patients, respectively. Two other diagnostic cultures originated from a line tip and wound. Resistance to ceftazidime was found in seven (7%) patients, divided over seven blood cultures and one wound culture (**Figure 1**). Resistance to piperacillin/tazobactam was confirmed in only a single urine culture from one (1%) patient.

Discussion. The aim of this study was to determine the frequency of bacteria resistant to ceftazidime, piperacillin/tazobactam and meropenem in diagnostic cultures of hematologic patients admitted to our hospital with febrile neutropenia. Retrospective analysis of diagnostic cultures showed a resistance frequency of 7% to ceftazidime and 1% to piperacillin/tazobactam. Furthermore, three diagnostic cultures showed *E. faecalis*, which is susceptible to the latter but a poor target for meropenem. These frequencies support that the hospital's empiric treatment protocol for haematology patients admitted with febrile neutropenia can be safely adjusted from meropenem to piperacillin/tazobactam.

It is important to keep in mind that *Enterobacterales* with intrinsic, chromosomally encoded AmpC beta-lactamase ("AmpC producers"), such as *S. marcescens*, *C. freundii* and *E. cloacae* complex, can develop resistance to penicillins and cephalosporins due to the selection of de-repressed mutants during treatment.[15] The risk of resistance selection is especially high during therapy with third-generation cephalosporins such as ceftazidime, whereas piperacillin/tazobactam is only a weak inducer of AmpC derepression. Data from observational studies suggest that piperacillin/tazobactam may be a treatment option for bloodstream infections with AmpC producers, but no clinical trials are available.[16-19] Therefore, current guidelines for antibiotic use in our hospital do not recommend the use of penicillins (including piperacillin/tazobactam) and cephalosporins for the treatment of infections with AmpC producers and susceptibility results for penicillins, and cephalosporins are not reported to the clinicians. For critically ill patients with febrile neutropenia admitted to the intensive care unit, the first choice of treatment remains a carbapenem.

This study provides data from a relatively large sample readily applicable to the hospital's clinical practice. However, a prospective follow-up study comparing clinical outcomes before and after the suggested treatment adjustments can strengthen the

Table 1. Population demographics and characteristics (n = 100).

Variable	Frequency
Age (years)	
<60 years	35
≥60 years	65
Sex	
Male	58
Female	42
*Primary diagnosis**	
AML	38
NHL	31
MM	11
CLL/HCL	9
MDS	4
ALL	4
RAEB	1
CML	1
Myelofibrosis	1
Vital status	
Alive	86
Death ≤30 days after admission	10
Death during admission	4
Lines	
None	55
Central	44
Midline	1
Duration of hospital admission	
<7 days	25
≥7 days	75
Readmission ≤ 3 months	
No	73
Yes	27

*Acute Myeloid Leukemia (AML); Non-Hodgkin Lymphomas (NHL, all grades), Multiple Myeloma (MM); Chronic Lymphatic Leukaemia (CLL); Hairy Cell Leukaemia (HCL); Myelodysplastic Syndrome (MDS); Acute Lymphatic Leukaemia (ALL); Refractory Anemia with Excess Blasts (RAEB); Chronic Myeloid Leukaemia (CML)

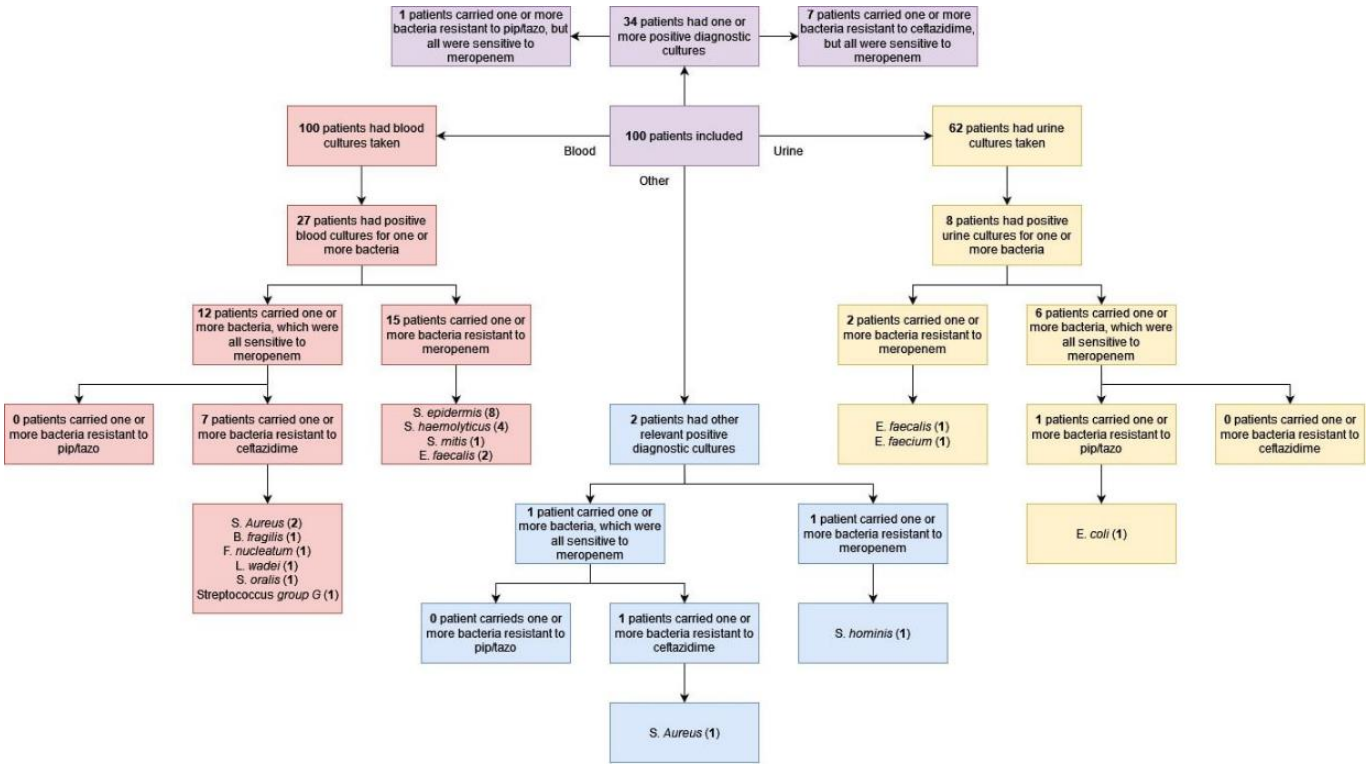

Figure 1. Microbiologic data on diagnostic cultures (blood/urine/other). Other: a line tip and wound culture. Pip/tazo: piperacillin/tazobactam. Only the first cultures taken after diagnosis of febrile neutropenia are included.

recommendations made. These outcomes should involve mortality risk and resistance patterns at a minimum to confirm the expected benefits, including antibiotic stewardship, without impairing clinical outcomes.

Patient characteristics available at admission, such as age, BMI, and recent hospital admissions, hold predictive value and allow for more precise risk stratification.[1,2] Including prospectively validated MASCC scores or other alternatives would allow for more accurate assessments, thus further guiding clinicians to the most appropriate antibiotic therapy.[13,20]

Conclusions. Based on the results of this study, we have changed our protocol of empiric antibiotic therapy of chemotherapy-induced neutropenia from meropenem to piperacillin/tazobactam. Making this carefully considered change helps us promote antibiotic stewardship while preserving our patients' safety.

Acknowledgements. We wish to thank P.C.A.M. Buijtels for her contributions to designing the research protocol and data collection and P.C.M. Pasker-de Jong for her advice in the field of research design.

R.A. Stuurman[1], E. Jong[2], P.C.R. Godschalk[3], M.F. Corsten[2] and J.E. Nagtegaal[4].

[1] Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.
[2] Department of Internal Medicine, Meander Medical Centre, Amersfoort, The Netherlands.
[3] Department of Clinical Microbiology, Meander Medical Centre, Amersfoort, The Netherlands.
[4] Department of Hospital Pharmacy, Meander Medical Centre, Amersfoort, The Netherlands.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Eefje Jong. E-mail: E.Jong@meandermc.nl

References:

1. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematol. 2013;98(12):1826. https://doi.org/10.3324/haematol.2013.091025
2. Khoo AL, Zhao YJ, Teng M, et al. Evaluation of a risk-guided strategy for empirical carbapenem use in febrile neutropenia. Ijantimicag. 2018 Sep;52(3):350-357. https://www.doi.org/10.1016/j.ijantimicag.2018.04.017
3. Schmidt-Hieber M, Teschner D, Maschmeyer G, Schalk E. Management of febrile neutropenia in the perspective of antimicrobial de-escalation and discontinuation. Expert review of anti-infective therapy. 2019 Dec 02;17(12):983-995. https://doi.org/10.1080/14787210.2019.1573670
4. Blennow O, Ljungman P. Infections in Hematology Patients. Concise Guide to Hematology Cham: Springer International Publishing; 2018. p.

503-518.
https://www.doi.org/10.1007/978-3-319-97873-4_38
5. Wang Y, Du Z, Chen Y, Liu Y, Yang Z. Meta-analysis: combination of meropenem vs ceftazidime and amikacin for empirical treatment of cancer patients with febrile neutropenia. Medicine. 2021 Feb 26;100(8):e24883. https://www.doi.org/10.1097/MD.0000000000024883
6. Regelink JC, Godschalk PCR, Russcher M. Richtlijn infectiepreventie en antibioticabeleid hemato-oncologie Meander MC. Personal communication.
7. Ballo O, Kreisel E, Eladly F, et al. Use of carbapenems and glycopeptides increases risk for Clostridioides difficile infections in acute myeloid leukemia patients undergoing intensive induction chemotherapy. Ann Hematol. 2020 Sep 24;99(11):2547-2553. https://www.doi.org/10.1007/s00277-020-04274-1
8. Cornistein W, Mora A, Orellana N, Capparelli FJ, del Castillo M. Candida: epidemiology and risk factors for non-albicans species. Enferm Infecc Microbiolog Clin. 2012;31(6):380-384. https://www.doi.org/10.1016/j.eimc.2012.09.011
9. Ben-Ami R, Olshtain-Pops K, Krieger M, et al. Antibiotic Exposure as a Risk Factor for Fluconazole-Resistant Candida Bloodstream Infection. Antimicrob Agents Chemother. 2012 May 01;56(5):2518-2523. https://www.doi.org/10.1128/AAC.05947-11
10. Zaoutis TE, Prasad PA, Localio AR, et al. Risk Factors and Predictors for Candidemia in Pediatric Intensive Care Unit Patients: Implications for Prevention. Clini Infect Dis. 2010 Sep 01;51(5):e38-e45. https://www.doi.org/10.1086/655698
11. Paul M, Yahav D, Bivas A, Fraser A, Leibovici L, Paul M. Anti-pseudomonal beta-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of beta-lactams. Cochrane library. 2010 Nov 10;2015(2):CD005197. https://www.doi.org/10.1002/14651858.CD005197.pub3
12. Elgarten CW, Li Y, Getz KD, et al. Broad-Spectrum Antibiotics and Risk of Graft-versus-Host Disease in Pediatric Patients Undergoing Transplantation for Acute Leukemia: Association of Carbapenem Use with the Risk of Acute Graft-versus-Host Disease. Transplant Cellular Ther. 2021 Feb;27(2):177.e1-177.e8. https://www.doi.org/10.1016/j.jtct.2020.10.012
13. SWAB. The Dutch Working Party on Antibiotic Policy (SWAB) recommendations for the diagnosis and management of febrile neutropenia in patients with cancer Committee. [Internet]. Available at: https://swab.nl/nl/febriele-neutropenie-algemene-informatie [Accessed February 26th, 2022].
14. Young P, Prisides A. Antibiotic sensitivity overview. [Internet]. Available at: https://drug.wellingtonicu.com/Appendices/5/ [Accessed February 26th, 2022].
15. Macdougall C. Beyond Susceptible and Resistant, Part I: Treatment of Infections Due to Gram-Negative Organisms With Inducible β-Lactamases. J Pediatr Pharmacol Ther. 2011-01-01;16(1):23. https://www.doi.org/10.5863/1551-6776-16.1.23
16. Harris PN, Wei JY, Shen AW, et al. Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by Enterobacter, Citrobacter or Serratia species: a systematic review with meta-analysis. J Antimicrob Chemother 2016;71:296-306. https://doi.org/10.1093/jac/dkv346
17. Cheng L, Nelson BC, Mehta M, et al. Piperacillin-tazobactam versus other antibacterial agents for treatment of bloodstream infections due to AmpC beta-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2017;61:e00276-17. https://doi.org/10.1128/AAC.00276-17
18. Tan SH, Ng TM, Chew KL, et al. Outcomes of treating AmpC-producing Enterobacterales bacteraemia with carbapenems vs. non-carbapenems. Int J Antimicrob Agents 2020;55:105860. https://doi.org/10.1016/j.ijantimicag.2019.105860
19. Drozdinsky G, Neuberger A, Rakedzon S, et al. Treatment of bacteremia caused by Enterobacter spp.: should the potential for ampC induction dictate therapy? A retrospective study. Microb Drug Resist 2021;27:4104. https://doi.org/10.1089/mdr.2020.0234
20. Choi A, Park I, Lee HS, Chung J, Kim MJ, Park YS. Usefulness of complete blood count parameters to predict poor outcomes in cancer patients with febrile neutropenia presenting to the emergency department. Annals of medicine. 2022 Dec 31;54(1):599-609. https://www.doi.org/10.1080/07853890.2022.2031271