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A de-escalation protocol for febrile neutropenia cases and its impact on carbapenem resistance: A retrospective, quasi-experimental single-center study

Abeer Alshukairi[a,*], Haleema Alserehi[a], Aiman El-Saed[b], Mouhammed Kelta[c], Jalil U. Rehman[c], Farrukh A. Khan[c], Hanadi Alsalmi[d], Majda Alattas[e], Muhammad Aslam[c]

[a] *Department of Medicine, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia*
[b] *Department of Community Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt*
[c] *Department of Oncology, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia*
[d] *Department of Infection Control and Hospital Epidemiology, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia*
[e] *Pharmaceutical Care Division, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia*

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Abstract Our objective was to evaluate the impact of using an imipenem de-escalation protocol for empiric febrile neutropenia on the development of carbapenem resistance.

A pre-post intervention design was used. The intervention was adopting the imipenem de-escalation approach, which began on January 1, 2012. A retrospective chart review of cases of febrile neutropenia bacteremia was performed one year before and one year after the intervention. We compared the development of carbapenem resistance between the two study periods.

Seventy-five episodes of febrile neutropenia bacteremia were included in the study. They had similar demographics, clinical features and outcomes. There were 78 and 12 pathogens in the primary and follow-up blood cultures, respectively. Approximately 61% and 66% of the primary and follow-up blood cultures, respectively,

* Corresponding author.
E-mail address: abeer_sh@doctor.com (A. Alshukairi).

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were gram-negative bacteria with similar carbapenem resistance profiles in the two study periods. In our study population, 57% of the gram-negative bacteria were ESBL pathogens. The resistance of the gram-negative bacteria to piperacillin/tazobactam (72% versus 53%, $p = 0.161$), imipenem (16% versus 11%, $p = 0.684$), and meropenem (8% versus 16%, $p = 0.638$) did not significantly change after our policy change.
In conclusion, the use of the carbapenem de-escalation approach for febrile neutropenia in our institution was not associated with an increase in carbepenem resistance. Future prospective multi-center studies are recommended to further confirm the current findings.

Introduction

Febrile neutropenia is a common complication during treatment of hematological malignancies and hematopoietic cell transplant. Several antibiotics are approved as an empiric therapy for febrile neutropenia (cefepime, piperacillin-tazobactam, meropenem, and imipenem) [1,2]. The choice of antibiotic therapy for febrile neutropenia varies from center to center because of the local epidemiology of bacterial resistance [1,2]. Multidrug-resistant, gram negative bacteria are becoming increasingly isolated from patients with febrile neutropenia in various centers worldwide [3]. In centers with a high prevalence of extended beta-lactamase-producing pathogens, carbapenem seems to be a reasonable empiric therapy for febrile neutropenia, followed by a de-escalation approach. This approach is useful to prevent mortalities related to the inappropriate use of empiric antibiotics. However, surveillance for the development of multi-drug-resistant pathogens is recommended when adopting this approach [4]. The association of the use of carbapenem in patients with febrile neutropenia and the emergence of carbapenem-resistant gram-negative bacteria has not been fully established. According to the antibiogram results provided by our microbiology laboratory, there is a 60% gram-negative bacterial resistance rate to piperacillin-tazobactam and Cefepime in the hematology unit in our hospital. Before January 2012, no clear guidelines had been adopted for patients with empiric febrile neutropenia. Multiple antibiotics, including ceftazidime, cefepime, piperacillin-tazobactam, imipenem and meropenem, were used based on physician decision. Since January 2012, we have adopted a new policy, which is the use of carbapenem and amikacin as the initial empiric therapy for febrile neutropenic patients with de-escalation to piperacillin-tazobactam in the absence of documented extended spectrum beta-lactamase producing pathogens.

This study aimed to determine if the use of carbapenem for febrile neutropenia in our hematology center was associated with the emergence of bacterial resistance, especially carbapenemase-producing, gram-negative pathogens.

Methods

Population

We reviewed the data provided by the infection control department in our institution for all patients with hematological malignancies and hematopoietic cell transplantation with febrile neutropenia and bacteremia admitted to our hospital from January 1, 2011, until December 31, 2012. All episodes of febrile neutropenia bacteremia were included. Patients with multiple episodes of febrile neutropenia bacteremia were also included.

Design

A pre-post intervention design was used. The intervention was adopting an imipenem de-escalation approach, which began on January 1, 2012. It was achieved by changing the febrile neutropenia protocol, educating physicians and nurses about adherence to the protocol and auditing the compliance of the staff. We compared the data from two different time periods. The first period was before our policy change from January 1, 2011, until December 31, 2011, during which there were no antibiotic guidelines for febrile neutropenia. The second period was after our policy change and the adoption of a de-escalation approach from January 1, 2012 until December 31, 2012. The term initial antibiotic regimen was defined as the date on which an empiric antibiotic started with the onset