American Journal of Infection Control ■■ (2017) ■■-■■

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Implementation of an antimicrobial stewardship program for patients with febrile neutropenia

Bahar Madran RN [a], Şiran Keske MD [a], Gizem Tokça RN [a], Ebru Dönmez RN [a], Burhan Ferhanoğlu MD [b], Mustafa Çetiner MD [c], Nil Molinas Mandel MD [d], Önder Ergönül MD, MPH [e,*]

[a] *Infectious Diseases Department, American Hospital, Istanbul, Turkey*
[b] *Hematology Department, American Hospital, Istanbul, Turkey*
[c] *Internal Medicine and Hematology Department, School of Medicine, Koç University, Istanbul, Turkey*
[d] *Medical Oncology Department, American Hospital, Istanbul, Turkey*
[e] *Infectious Diseases and Clinical Microbiology Department, School of Medicine, Koç University, Istanbul, Turkey*

Key Words:
Febrile
neutropenia
antimicrobial
stewardship
outcome

Background: We aimed to describe the effectiveness of our standardized protocol for febrile neutropenia (FN), which was targeted to minimize unintended outcomes and reduce antimicrobial consumption.
Methods: The study was performed in a private hospital with 300 beds. We included all adult hematologic and oncologic cancer inpatients admitted between January 1, 2015-December 31, 2015, and January 1, 2016-May 31, 2017. The outcomes of the study were fatality, infections, and adherence to the antimicrobial stewardship program (ASP).
Results: We included 152 FN attacks of 95 adult inpatients from hematology and oncology wards; of these, 43% were women, and the median age was 57 years. The case fatality rate was 30% in the pre-ASP period and decreased to 11% in the post-ASP period ($P = .024$). The appropriate adding or changing ($P = .006$) and appropriate continuation or de-escalation or discontinuation of antimicrobials improved ($P < .001$). In the post-ASP period, *Staphylococcus* spp infections (from 22% to 8%, $P = .02$) and gram-negative infections decreased (from 43% to 20%, $P = .003$). In the multivariate analysis, appropriate continuation or de-escalation or discontinuation was increased in the post-ASP period (odds ratio [OR], 4.3; 95% confidence interval [CI], 1.82-10.41; $P = .001$), and gram-positive infections were decreased (OR, 0.32; 95% CI, 0.11-0.95, $P = .041$). Vancomycin and fluoroquinolone use decreased significantly.
Conclusions: After implementation of the ASP, the case fatality rate among the patients with FN decreased. Appropriate antimicrobial use increased and overall antimicrobial consumption was reduced. Bacterial infections and *Candida* infections decreased.

Fever occurs frequently during chemotherapy-induced neutropenia. Nearly 80% of the patients with hematologic malignancies, and 10%-50% of those with solid tumors, will develop fever during neutropenia associated with chemotherapy.[1] Fever during chemotherapy-induced neutropenia may be the only symptom of a severe underlying infection because signs and symptoms of inflammation typically are weakened. Physicians must be aware of the infection risks, diagnostic methods, and antimicrobial therapies required for management of febrile patients through the neutropenia period. The mortality rate, related to a febrile neutropenia (FN) episode, has been variably reported between 2% and 20%.[2,3] Because of the high case fatality rate (CFR), implementation of an appropriate clinical algorithm is of vital importance. In particular, the antimicrobial treatment should be closely monitored to prevent development of unintended outcomes and antimicrobial resistance.

Algorithmic approaches to fever and neutropenia, infection prophylaxis, diagnosis, and treatment have been established during the last 40 years, but should be modified by updated clinical evidence and experience of over time.[4] Clinically documented infections occur in 20%-30% of febrile episodes; common sites of

* Address correspondence to Önder Ergönül, MD, MPH, Koç University, School of Medicine, Infectious Diseases and Clinical Microbiology Department, Istanbul, Turkey.
E-mail address: oergonul@ku.edu.tr (Ö. Ergönül).
Conflicts of interest: None to report.

0196-6553/
https://doi.org/10.1016/j.ajic.2017.09.030

tissue-based infection include the intestinal tract, lung, and skin.[5] The etiologic agents may change according to geographic location, for instance gram-negative microorganisms are the predominant agents in South European countries, including Turkey.[6,7] We aimed to optimize clinical outcomes and minimize unintended consequences, such as *Clostridium difficile* and *Candida* spp infections, by implementing an antimicrobial stewardship program (ASP) in our hospital. Through this study, we describe the effectiveness of the ASP among patients with FN.

METHODS

Study population

The study was performed in a private foundation hospital with 300 beds. We included all the hematologic and oncologic cancer inpatients with FN admitted between January 1, 2015-December 31, 2015, and January 1, 2016-May 31, 2017.

Implementation of the ASP

The infection control team (ICT) of the hospital organized weekly meetings with the related physicians and nurses from the infectious diseases, clinical microbiology, hematology, oncology, and pediatrics departments at the end of December 2015. The ICT is responsible for surveillance, isolation, monitoring of hand hygiene, monitoring of antimicrobial resistance and antimicrobial use, preparation of clinical pathways and guidelines, occupational infections, and education of health care workers. An active laboratory supported with necessary cultures, molecular analysis including rapid multiplex polymerase chain reaction, and biomarkers was part of the ASP. A dedicated group prepared a clinical pathway for adult inpatients by reviewing published guidelines[8] (Fig 1). The data were collected with a daily electronic surveillance system; interim analyses were shared quarterly with the participating departments. The rate of appropriateness in starting, adding, switching, de-escalating, and discontinuing antimicrobials was analyzed. The outcomes of the study were fatality, infections, and adherence to the ASP. The adherence to the ASP was assessed by the ICT (Fig 1). After implementation of the ASP, we prospectively followed-up patients from January 1, 2016-May 31, 2017, to see the efficacy of the ASP.

Definitions

Fever among hematology and oncology patients was defined as a single tympanic temperature measurement of ≥38.3°C or a temperature of ≥38°C sustained over a 1-hour period. Neutropenia was defined as absolute neutrophil count (ANC) of <1,000 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 hours.[9] The Multinational Association of Supportive Care in Cancer (MASCC)[8] risk index score was applied to determine the risk of serious complications during FN; episodes were classified as high risk if the score was <21 points and as low risk if the score was ≥21 points. Positive blood culture result was obtained by 2 separate blood samples from 2 different sites. Infected patients with clinical conditions and isolated agent were included, and colonization was excluded.

Antimicrobial appropriateness was assessed in 3 phases: (1) empirical antimicrobial use (Fig 1, first step in the ASP), (2) add or change antimicrobial (Fig 1, second step in the ASP), and (3) appropriate continuation or de-escalation or discontinuation (Fig 1, third step in the ASP).

Statistical analysis

Mean comparisons for continuous variables were done using independent group *t* tests. Proportion comparisons for categorical variables were done using χ^2 tests; however, Fisher exact test was used when data were sparse. A multivariate analysis to describe the changes after the ASP was modeled, and logistic regression was performed. Independent variables included in the model were gram-negative and gram-positive infections, *Candida* infections, appropriate duration of antimicrobials, and MASCC score <21 (high risk). Significance was set as $P < .05$ using 2-sided comparisons. Stata 14 (StataCorp, College Station, TX) software package was used in the analysis. The Institutional Review Board of Koc University approved the study (reference no. 2017.162.IRB1.016).

RESULTS

We included 152 FN attacks of 95 adult inpatients (50 patients with 81 FN attacks in the pre-ASP period and 45 patients with 71 FN attacks in the post-ASP period) from the hematology and oncology wards; of these, 43% were women, and the median age of the patients was 57 years (range, 21-82 years). The ANC was <100 cells/mm^3 among 54% of the FN attacks in the pre-ASP period, and 63% in the post-ASP period ($P = .289$). The rank-sum test of the neutrophil counts by the Kruskal-Wallis test was not statistically different ($P = 0.084$). Duration of neutropenia per FN attacks was not significantly different (4.9 vs 3.5 days, $P = .10$) (Table 1). The CFR was 30% in the pre-ASP period and significantly decreased to 11% in the post-ASP period ($P = .024$) (Table 1).

The appropriateness of empirical antimicrobial use (step 1) between the 2 phases was not significantly different; however, appropriate adding or changing antimicrobials (step 2) ($P = .006$) and appropriate continuation or de-escalation or discontinuation of antimicrobials (step 3) improved significantly ($P < .001$) (Table 2).

The total number of infections per FN attacks decreased from 86% to 45% after ASP implementation ($P = .003$). In the post-ASP period, *Staphylococcus* spp infections per FN attacks significantly decreased from 22% to 8% ($P = .02$) (Table 3), and gram-negative infections decreased from 43% to 20% ($P = .003$) (Table 3).

In the multivariate analysis, appropriate continuation or de-escalation or discontinuation (step 3) was significantly increased in the post-ASP period (odds ratio [OR], 4.3; 95% confidence interval [CI], 1.82-10.41; $P = .001$) (Table 4). In the post-ASP period, the number of gram-positive infections was decreased significantly (OR, 0.32; 95% CI, 0.11-0.95; $P = .041$) (Table 4). The sensitivity of the model, the area under the receiver operator curve, was calculated as 73%.

The most striking decrease in antibiotic consumption was detected in vancomycin and fluoroquinolone. Vancomycin use was decreased from 95 daily defined dose (DDD) (25% of FN days) to 47 DDD (17% of FN days, $P = .01$). Fluoroquinolone use was decreased from 88 DDD (24% of FN days) to 40 DDD (15% of FN days, $P = .004$). Using piperacillin-tazobactam or carbapenem as empirical agents in FN attacks was increased from 80% to 97% ($P < .001$). Echinocandin use was increased from 20% to 35% of the FN attacks ($P < .001$). Metronidazole use increased from 7% to 9% ($P = .299$).

DISCUSSION

Our study findings demonstrated the significant beneficial effect of implementation of the ASP among patients with FN. This was a