PROGRAM PROFILE

Implementation of a Protocol for Management of Febrile Neutropenia in the Emergency Department at Veteran Health Indiana

Lori Melikian, PharmD, BCOP[a]; Susan Bullington, PharmD, BCOP[b]; Brent Harris, PharmD, BCPS[c]; Cole Smith, PharmD, BCPS[a]; Justin Roberts, PharmD, BCPS[a]; Chad Naville-Cook, PharmD[a]; Brooke Crawford, PharmD, BCOP[a]

Background: Febrile neutropenia (FN) is a life-threatening oncologic emergency requiring timely evaluation and treatment. Unrecognized fever and infection can progress quickly and have been shown to increase morbidity and mortality in patients with malignancy. It is critical to identify patients with neutropenic fever on presentation to the emergency department (ED) and to initiate treatment immediately.

Observations: This quality improvement initiative sought to optimize ED care of patients presenting with FN. Delays in antibiotic prescribing for patients with FN presenting to the ED were identified. A protocol was implemented to streamline clinical decision making and decrease the time from triage to the first dose of antibiotics in the ED. Key interventions included obtaining ED staff support, developing a standard empiric therapy protocol, increasing prescriber awareness of the neutropenic fever protocol and integrating it into the electronic health record. Before the protocol, the mean time from triage to the first dose of antibiotics was 3.3 hours with only 6% of patients receiving appropriate empiric therapy within 1 hour. Postimplementation, the average time to antibiotics decreased to 2.3 hours. In the postimplementation group, 17% of patients within 1 hour.

Conclusions: Early identification and timely empiric antibiotic therapy are critical to improving outcomes for patients presenting to the ED with FN. Additional optimization of the order sets along with increased protocol comfort and staff education will help to further reduce the time to antibiotic administration in alignment with guideline recommendations.

Author affiliations can be found at the end of this article.
Correspondence: Lori Melikian (lori.melikian@gmail.com)

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Febrile neutropenia (FN) is a life-threatening oncologic emergency requiring timely evaluation and treatment. Chemotherapy-induced neutropenia is a major risk for life-threatening infection, and fever may be the only sign.[1,2] Unrecognized fever can progress to sepsis and may result in increased morbidity and mortality. FN is defined as the presence of fever with a single temperature of ≥ 38.3 °C or a sustained temperature > 38 °C sustained over 1 hour with an absolute neutrophil count (ANC) of < 500 cells/mm^3 or < 1000 cells/mm^3 and expected to decrease to < 500 within 48 hours.[2,3] It is critical to quickly identify these patients on presentation to the emergency department (ED) and take appropriate steps to initiate treatment as soon as possible. To streamline care, the American Society of Clinical Oncology (ASCO) recommends that laboratory assessments be initiated within 15 minutes of triage and empiric antibiotic therapy be administered within 1 hour.[2]

In alignment with the Infectious Disease Society of America (IDSA) guidelines, the National Comprehensive Cancer Network (NCCN) highlights the importance of the initial assessment of fever and neutropenia and presents available treatment options for both inpatient and outpatient management of FN.[1] Once patients are identified, the appropriate laboratory tests and physical assessments should be initiated immediately. These tests include a complete blood count with differential, complete metabolic panel (CMP), and blood cultures from 2 separate IV sites.[1-3] The guidelines offer additional suggestions for cultures and radiographic assessments that may be completed based on clinical presentation.

Several available studies provide insight into methods of protocol creation and possible barriers to timely management. Previous research showed that an FN protocol for pediatric oncology patients aimed at antibiotic administration within 1 hour showed significant improvement from 35.0% to 55.4% of patients being treated on time.[3,4] Prescribers became more comfortable in using the protocol, and timing improved as the study progressed. Barriers noted were inconsistent ED triage, rotating ED staff, and limited understanding of the protocol.[3] Yoshida and colleagues worked with the same population. Over the course of 1 year, 60% of patients were receiving antibiotics within 1 hour. The mean time decreased from 83 to 65 minutes, which the study investigators noted would continue to decrease with increased protocol comfort and use.[5] Mattison and colleagues used nursing staff to identify patients with FN and begin antibiotic

treatment. On triage, nurses took note of a temperature of > 38 °C or a sepsislike clinical picture that initiated their antibiotic proforma.[4,6] This resulted in 48.1% of patients receiving antibiotics within 15 minutes and 63.3% overall within 30 minutes of arrival.[5] Other barriers to consider are ED crowding and the admission of higher acuity patients, which may delay the treatment of patients with FN.

The US Department of Veterans Affairs (VA) Richard L. Roudebush VA Medical Center (RLRVAMC) in Indianapolis, Indiana is a level 1A facility serving about 62,000 veterans annually and more than 13,000 unique veterans visiting the ED. RLRVAMC ED staff rotate often so the creation of a process will facilitate appropriate treatment as quickly as possible. The purpose of this protocol was to improve the mean time from triage to administration of antibiotics for patients with FN presenting to the ED.

IMPLEMENTATION

To quantify the perceived delay in antibiotic prescribing, a pre- and postprotocol retrospective chart review of patients who presented with FN to the RLRVAMC ED was conducted. Patients were identified through the electronic health record (EHR) based on 3 criteria: recorded/reported fever as defined above, ANC < 1000 cells/mm^3, and administration of cancer treatment (IV and oral) within 4 weeks. The data collected in the postimplementation phase were identical to the pre-implementation phase. This included timing of blood cultures, choice/appropriateness of antibiotics based on guidelines, and length of admission. The pre-implementation period started on August 1, 2018, and ended on August 1, 2019, to allow for an adequate pre-implementation sample size. The protocol was then implemented on October 1, 2019, and data collection for the postimplementation phase began on October 1, 2019, and ended on October 1, 2020.

The protocol was accompanied by EHR order sets initiated by both nurses and health care practitioners (HCPs), including physicians, nurse practitioners, and physician assistants. The nursing order set consisted of vitals and appropriate laboratory monitoring, and the practitioner order set housed medication orders and additional clinical monitoring for more patient-specific scenarios. On identification of at-risk patients, the nursing staff could initiate the neutropenic fever protocol without consulting an HCP. The patient was then assigned a higher acuity rank, and the HCP was tasked with seeing the patient immediately. In conjunction with a complete physical assessment, the HCP ordered appropriate antibiotics through the designated order set to streamline antibiotic selection. Antibiotic options included cefepime or piperacillin-tazobactam, and vancomycin when clinically indicated. Alternatives for patients allergic to penicillin also were available. The protocol intended to streamline workup and antibiotic selection but was not designed as a substitute for solid clinical decision making and complete assessment on behalf of the HCP; therefore, additional workup may have been necessary and documented in the EHR.

Findings

This patient population comprised 17 patients pre-implementation and 12 patients postimplementation, most of whom had solid tumor malignancies (88.2% and 83.3%, respectively) receiving platinum, taxane, or antimetabolite-based chemotherapy. In the pre-implementation group, most patients (70.5%) coming through the ED were treated with palliative intent. Only 25% of these received any prophylactic granulocyte-colony stimulating factor (G-CSF) based on risk for FN. The mean time from triage to the first dose of antibiotics decreased from 3.3 hours before protocol implementation to 2.3 hours after. Only 6% in the pre-implementation group compared with 17% in the post-implementation group received the first dose of antibiotics within the recommended 1-hour interval from triage. The most common antibiotics administered were cefepime and vancomycin. Eleven patients in each group (65% and 92%, respectively) were admitted to the inpatient service for further care, with 10 and 8 patients, respectively, experiencing a hospitalization > 72 hours. Of note, 41% of patients died pre-implementation vs 17% postimplementation.

INTERPRETATION

The goal of this protocol was to optimize ED care of patients presenting with FN to better align with guideline-recommended time lines and antibiotics. The mean time from triage to administration of antibiotics decreased by 1.0 hour from the pre- to postimplementation phase, similar to the study by Mattison and colleagues.[3] When removing an outlier from

the postimplementation group, the mean time from triage to first dose further decreased to 1.8 hours. The percentage of patients receiving antibiotics within 1 hour of triage nearly tripled from 6% to 17%. Additionally, the percentage of patients empirically treated with appropriate antibiotics consistent with NCCN/ASCO/IDSA guidelines increased from 65% to 83%. Although goals for the optimization of care have not yet been reached, this protocol is the first step in the right direction.

Limitations

Several limitations and concerns arise when implementing a new protocol or workflow process. Overall, these limitations may contribute to delays, such as the willingness of team members to use an unfamiliar protocol or issues locating a new protocol. The nursing staff is challenged to triage patients quickly, which may add to an already busy environment. Frequent physician turnover may require more frequent education sessions. Also, a lag time between implementation and using the protocol may result in decreased protocol use during the designated postimplementation data collection phase.

On review, ED staff were excited to find a protocol that streamlined decision making and increased awareness for patients at risk. The COVID-19 pandemic may have been a confounder for the postimplementation phase. Data may have been skewed as some patients might have elected to stay at home to avoid potential COVID-19 exposure in the ED. Additionally, increased ED use by patients with COVID-19 may have resulted in longer wait times for an available bed, thereby minimizing the impact of the protocol on time from triage to administration of antibiotics. COVID-19 may also have contributed to postimplementation mortality. Of note, barcode medication administration (BCMA) was implemented in the ED in May 2019, which may account for undocumented delays in antibiotic administration as staff may have been unfamiliar with BCMA workflow.

Due to the retrospective nature of a chart review, the data rely on the timely input and accuracy of documented information. Data after the patient's ED encounter (except inpatient hospitalization and deaths during the implementation period) were not collected due to the scope of the program being limited to the ED only. Last, this protocol was implemented at a single site, and the generalizability to implement the same protocol at other VA medical centers may be limited. After reaching out to other VA sites and several non-VA facilities, we were unable to find a site with a similar protocol or program emphasizing the importance of timely care, although there may have been established laboratory test and medication order sets within the EHR.

Future Direction

The newly established FN order sets will continue to streamline clinical decision making and antibiotic selection in this population. In our study, we learned that most patients coming through the ED were being treated with palliative intent. As a result, these patients also may have a higher risk for complications like FN. We hope to further analyze the impact on this group and consider the role of empiric dose reduction or increased G-CSF support to minimize FN.

More than half of the patients who were admitted to the inpatient service, remained in extended care for > 72 hours. Inpatient recovery time may cause delays in future cancer treatment cycles, dose reductions, and contribute to an overall decline in performance status. Six patients in the pre-implementation phase and 1 in the postimplementation phase were eligible for outpatient management per independent Multinational Association of Supportive Care in Cancer assessment. To increase comfort, a future goal would be to create an outpatient treatment order set on discharge from the ED to help identify and outline treatment options for low-risk patients. In addition to the ED, training staff in clinics with a similar protocol may enhance the identification of patients with FN. This may require a tailored protocol for this location using health technicians in taking vital signs before the HCP visit.

This protocol helped establish "code sepsis." Code sepsis alerts are broadcast to alert pertinent members of the health care team to provide immediate medical attention to the veteran. Pharmacy can expedite the compounding of antibiotics and record review while radiology prioritizes the portable X-ray for quick and efficient imaging. The nursing team comes ready to administer antibiotics once cultures are drawn. The HCP's attention is focused on the physical examination to determine any additional steps/care that need to be accomplished. At our site, we

plan to continue HCP, nursing, and other team member education on this oncologic emergency and the availability of a streamlined protocol. We would like to re-assess the data with a long team study now that the protocol has been in place for 3 years. We hope to continue to provide strong patient care with enhanced adherence to guidelines for patients with FN presenting to RLR-VAMC.

CONCLUSIONS

Early identification and timely empiric antibiotic therapy are critical to improving outcomes for patients presenting to the ED with FN. The neutropenic fever protocol reduced time to antibiotics by about 1 hour with a higher percentage of patients receiving them in < 1 hour. Additional optimization of the order sets along with increased protocol comfort and staff education will help further reduce the time to antibiotic administration in alignment with guideline recommendations.

Author affiliations

[a]Veteran Health Indiana, Indianapolis
[b]Veterans Health Administration, National TeleOncology Hub
[c]University of Kentucky Healthcare Markey Cancer Center, Lexington

Author contributions

All authors had full access to the data and a role in writing the manuscript.

Author disclosures

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Ethics and consent

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol was reviewed and approved by the Indiana University Institutional Review Board and the Veteran Health Indiana Research and Development Committee.

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