Implementation of an Evidence-Based Order Set to Impact Initial Antibiotic Time Intervals in Adult Febrile Neutropenia

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eutropenia, one of the most common side effects of chemotherapy, places patients with cancer at increased risk for systemic infection (sepsis) and infectionrelated death. Chemotherapy depletes infection-fighting resources, specifically neutrophils, and infection may be masked by the absence of the normal febrile response (National Comprehensive Cancer Network [NCCN], 2011). Fever related to neutropenia (febrile neutropenia) is a major reason for hospitalization of chemotherapy recipients. In addition to increased healthcare costs, delays in chemotherapy decrease overall quality of life and may prevent optimal treatment outcomes (Coughlan & Healy, 2008; Donohue, 2006; Kuderer, Dale, Crawford, Cosler, & Lyman, 2006; Nirenberg et al., 2006a). Patients who develop febrile neutropenia following chemotherapy require hospitalization to receive antibiotic therapy. Delays in initiation of antibiotics can occur at any point in the admission process, increasing the patient's risk for sepsis and death (Baltic, Schlosser, & Bedell, 2002). The purpose of this project was to evaluate the effects of the implementation of a standardized order set on the time interval in initiation of antibiotic therapy for adult patients with cancer and febrile neutropenia who were admitted to the oncology unit of an urban hospital.

Febrile Neutropenia

NCCN guidelines (2011) define a fever as a single temperature of 38.3°C or higher orally or 38°C or higher over one hour. Infection may be subtle in patients with a low absolute neutrophil count because of a compromised immune response, with fever often being the only sign of a serious infection (Camp-Sorrell, 2005; Coughlan & Healy, 2008; Kannangara, 2006). Febrile neutropenia is defined by the presence of fever in a patient who has an inadequate amount of circulating neutrophils to fight infection (Book,

Purpose/Objectives: To evaluate the impact of the implementation of a standardized order set on the time interval in initiation of antibiotic therapy for adult patients with cancer and febrile neutropenia.

Design: Practice change.

Setting: The oncology unit of an urban hospital in the southeastern United States.

Sample: Adult patients with cancer and febrile neutropenia admitted six months prior to (n = 30) or during the three months following (n = 23) implementation of the order set.

Methods: Literature regarding febrile neutropenia, use of order sets, and change process was reviewed. In addition, a retrospective and concurrent chart review was conducted for adult patients admitted with febrile neutropenia. Time intervals were analyzed using SPSS® software, version 18.

Main Research Variables: Initial antibiotic times, order-set use, and length of stay.

Findings: An overall reduction in time intervals for initiation of antibiotic therapy was observed for presentation (t = 2.25; degrees of freedom [df] = 37; p = 0.031) and order (t = 2.67; df = 40.17; p = 0.012) to antibiotic administration, with an order-set usage of 31% in the inpatient unit and 71% in the emergency department.

Conclusions: Findings in the presence of low order-set usage suggest that staff education and placement of the order-set antibiotics in unit-based medication dispensing machines helped reduce time intervals for initial antibiotic therapy.

Implications for Nursing: The use of an evidence-based approach to nursing care is essential to achieving the best outcomes for patients with febrile neutropenia. Incorporation of current evidence into an order set to guide clinical practice and comprehensive nurse, pharmacy, and physician education are needed for the successful implementation of evidence-based practice changes.

2008) or an absolute neutrophil count lower than 500/mcl (NCCN, 2011). Although 6% of febrile neutropenic events occur during the first cycle of chemotherapy treatment, about 11% of patients are at risk for experiencing a febrile

event during the first three treatment cycles (Crawford et al., 2008). Febrile neutropenia is an oncologic emergency; therefore, assessment and early intervention are essential to avoid progression of an infection to sepsis or death (Cull & Nolan, 2009; Kuderer et al., 2006).

A number of cancer-, patient-, and treatment-related factors increase the risk of developing febrile neutropenia. Patients who are older than 60 years, are women, and have comorbidities, inadequate immune systems or low albumin levels, aggressive or metastatic cancers, and lymphoma or other bone marrow diseases are at increased risk. Treatment regimens that include bone marrow radiation or aggressive chemotherapy predispose the patient to severe neutropenia. Febrile neutropenia also occurs more frequently among patients who previously have been treated with chemotherapy and have a history of prior significant neutropenia (Klastersky et al., 2000; Nirenberg et al., 2006a).

The skin is the body's primary defense mechanism to prevent the entrance of pathogens. The use of chemotherapy, radiation, or a combination of the two to treat cancers disrupts the skin's protective barriers, increasing the patient's risk for infection. Oral mucositis, one of the most common side effects of chemotherapy, provides pathogens with an easy portal of entry to the body and requires diligent oral hygiene to prevent infection. Diarrhea, another common side effect of cancer treatment, may cause erosions along the intestinal tract that allow normal body flora to cause infection. Disruption of the pulmonary and genitourinary mucosa provides other opportunities for pathogen entry. The presence of any of those conditions increases the patient's risk for febrile neutropenia. Assessment and prompt treatment of those complications are essential to lowering the patient's risk of developing an infection (Coughlan & Healy, 2008; Viscoli, Varnier, & Machetti, 2005).

Clinical Significance

Delays in treatment for febrile neutropenia are associated with negative patient outcomes. The febrile neutropenia mortality rate in patients with cancers with solid tumors is about 50%, whereas an estimated 70%–75% of patients with acute leukemia die as a result of neutropenia-related events (Nirenberg, Mulhearn, Lin, & Larson, 2004). A neutropenic patient who lives alone, does not have insurance, or is unaware of the significance of fever in the presence of neutropenia may delay seeking treatment until the infection is severe (Nirenberg et al., 2006b). Failure to inform the physician office or emergency room staff of their neutropenic status may also cause delays in assessment, treatment, and initiation of antibiotic therapy (Cull & Nolan, 2009). Organizational reasons for delays in early initiation of antibiotic therapy include system issues with antibiotic orders, delays in transfer from the emergency department to the inpatient unit, issues with the pharmacy's process for filling medications, or a delay in the administration of the medication by the patient's nurse (Baltic et al., 2002).

For patients who develop febrile neutropenia, prompt assessment and initiation of treatment with appropriate antibiotic therapy is essential to ensuring positive outcomes. The use of a standardized order set for this population can ensure that patients receive prompt treatment for infection (Baltic et al., 2002; Nirenberg et al., 2006a).

Theoretical Framework

The concepts of adult learning theory (Knowles, Holton, & Swanson, 2005) and Lewin's change theory (Dulaney & Stanley, 2005; Marquis & Huston, 2009; Simms, 2006; Wirth, 2004) were used to lead the development and implementation of an order set to guide the care of adult patients with febrile neutropenia who were admitted to the oncology unit. Adult learning theory states that internal experiences influence an individual's willingness to learn. According to Knowles et al. (2005), adult learning is problem-centered and focuses on the practical application of information. The need to know is satisfied once the individual identifies the rationale for how the information is useful. Internal motivation, self-concept, prior experience, and readiness to learn all affect the individual's learning experience (Knowles et al., 2005).

The three stages of Lewin's change theory (unfreezing, moving, and refreezing) guided this evidence-based change process (Dulaney & Stanley, 2005; Marquis & Huston, 2009). The theory incorporates organizational culture and past experiences that influence the change process (Wirth, 2004). During *unfreezing*, a situation needing change is recognized and individuals or groups are motivated to take action. *Moving* is an active process where decisions and plans are made, restraining and driving forces are identified and addressed, and the new practice is implemented. Finally, *refreezing* occurs once the new process becomes common practice (Marquis & Huston, 2009; Simms, 2006).

Review of Evidence

Timing of Initial Antibiotic Therapy

Extensive research has identified appropriate antibiotics for prophylaxis and treatment of febrile neutropenic episodes, and those antibiotics have been incorporated into national treatment guidelines (NCCN, 2011; Rolston, 2004). Appropriate laboratory tests, including cultures, are determined based on the patient's presenting signs and symptoms. Guidelines recommend beginning an appropriate antibiotic soon after patient assessment; however, no specific time frame for initial administration has been established (Baltic et al., 2002; Craig et al., 2007; Koh & Pizzo, 2002; NCCN, 2011; Nirenberg et al., 2004). Terms

such as "timely" (Glasmacher et al., 2005; Vogtlander et al., 2004; Zuckermann et al., 2008), "prompt" (Craig et al., 2007; Rolston, 2004), and "immediate" (Natsch, Kullberg, Meis, & van der Meer, 2000) have been used to describe timing of antibiotic therapy initiation for patients with febrile neutropenia.

The accuracy of diagnosis and the time intervals between diagnosis and initial antibiotic administration have been examined in the literature. Natsch et al. (2000) found that median intervals from admission to start of antibiotics began at five hours and decreased to 3.2 hours following staff education. Perrone, Hollander, and Datner (2004) reported that the average time from initial triage to administration of the first antibiotic was about two hours and 50 minutes. Nirenberg et al. (2004) stated that the length of time from patient arrival to physician examination in a large emergency department was a median of 75 minutes; however, the time between arrivals to start of antibiotic therapy was 210 minutes. Of concern, patients with significant cancer or comorbidities had longer wait times before initiation of antibiotic therapy than patients with less advanced disease (Nirenberg et al., 2004).

Initiating antibiotic therapy in a timely manner has been associated with variables that individually or collectively can become barriers to early treatment of febrile neutropenia. Those variables can be categorized as patient-related, staff-related, and procedure-related (Baltic et al., 2002; Cull & Nolan, 2009; Perrone et al., 2004; Vogtlander et al., 2004). Patient-related variables (e.g., lack of knowledge related to the effects of chemotherapy and the importance of prompt reporting of even a low-grade fever) affect overall delays in treatment, but do not directly impact antibiotic time intervals once the patient has presented to the hospital (Nirenberg et al., 2004). However, addressing patient education indirectly may ensure early initiation of antibiotic therapy if patients report their chemotherapy history during the triage process (Cull & Nolan, 2009).

Staff-related barriers include failure to recognize the urgency of initiation of antibiotic therapy, failure of the pharmacist to schedule the first dose of antibiotic to be given immediately, and poor timing of administration with meals or only during daytime hours (Natsch et al., 2000; Perrone et al., 2004; Vogtlander et al., 2004). An additional pharmacy concern is related to adjusting the dosage of antibiotic based on the patient's renal function (Vogtlander et al., 2004). Nursing delays in establishing IV access and collecting ordered cultures also are associated with a lack of urgency to initiate antibiotics (Perrone et al., 2004).

Procedure-related barriers include delays in nursing triage and physician assessment of patients with febrile neutropenia. Other significant causes of antibiotic delay include sending the patient for radiology studies or transfer within departments before giving the initial antibiotic (Vogtlander et al., 2004). Implications from the findings suggest that interventions to improve initial antibiotic

timing should address identified barriers prior to implementing the interventions to improve patient outcomes.

Order-Set Usage

The use of order sets has been identified as one method of standardizing care and improving outcomes for specific patient populations, including those with febrile neutropenia. Barriers to physician compliance with order sets include internal factors (e.g., physician personal preferences, concerns with lack of autonomy of practice) and external factors (e.g., convenience, change in prior practice, inadequate communication of order-set availability) (Zuckermann et al., 2008). Time intervals for initial antibiotic administration improve with partial

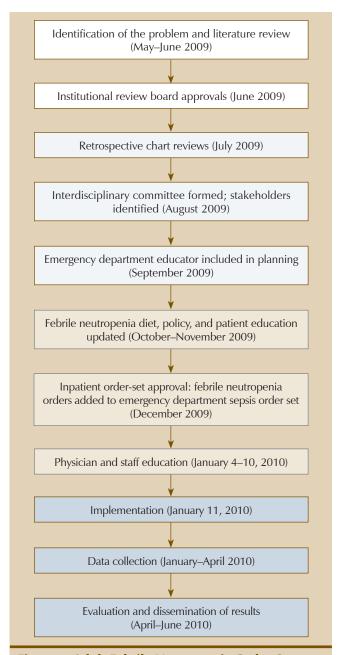


Figure 1. Adult Febrile Neutropenia Order-Set Project Timeline

compliance with standardized order-set use (Baltic et al., 2002; Vogtlander et al., 2004; Zuckermann et al., 2008). Consideration of physician-sensitive barriers when planning order-set implementation may improve compliance and help achieve desired patient outcomes.

Standardization of orders reduces medication errors and decreases overall cost of antibiotic therapy (Sano, Waddell, Solimando, Doulaveris, & Myhand, 2005). Development of order sets that use appropriate antibiotics given on a suitable schedule can decrease time intervals significantly and may reduce overall antibiotic use (Vogtlander et al., 2004; Zuckermann et al., 2008). Order-set inclusion of antibiotic adjustment guidelines for renal

impairment can decrease pharmacy order processing time, potential dose-related complications, and length of stay (Vogtlander et al., 2004).

Staff education and willingness to change practice directly affect the use of order sets. Standardization of care through clinical pathways that include order sets helps staff improve triage assessment and begin antibiotic administration in a shorter time frame (Salter, 2005). Improved interdisciplinary communication also directly increases the effectiveness of order sets in reducing antibiotic time intervals (Baltic et al., 2002; Salter, 2005; Zuckermann et al., 2008). Careful planning and presentation of staff and physician education and consideration of all

Section 1. Patient Demographic Characteristics							
1. Entry to system:	ntry to system: Emergency department Direct admittance Outpatient oncology 2. Admitted from: Home Facility		3. Ethnicity: Caucasian African American Hispanic Asian Other		4. Gender: ☐ Male ☐ Female		5. Age range (years): 18-25 26-40 41-59 60 or older
6. Time of presentation:	Time of presentation: 7. Length of stay:			8. Activity level: ☐ Self-care ☐ Assistance ☐ Total care			
9. Insurance type: Privat	e 🗖 Medica	are 🗖 Medio	caid 🗖 None	☐ Other:			
Section 2. Disease Charact	eristics						
1. Type of cancer: Solid tumor Leukemia Advanced cancer (stage)			2. History: Neutropenia Chemotherapy Fever Date of last chemotherapy: Radiation Type of last chemotherapy:			emotherapy:emotherapy:	
3. Was the patient transferred to critical care unit for sepsis? ☐ Yes ☐ No							
4. Comorbidities: Cardiovascular: Pulmonary: Myocardial infarction Chronic obstructive Hypertension Asthma Other: Obstructive sleep Cancer Immune system: Diabetes: Type 1 Type			□ Urinary tract infection □ End-stage renal disease apnea □ Dialysis Liver: □ Open wounds			nal disease Is	
Section 3. Laboratory Values and Antibiotic Administration							
1. Laboratory values on admission: White blood cell: Absolute neutrophil count: Platelet count: Albumin: 4. Cycle time (minut				 5. Where was antibiotic administered? Emergency department Inpatient unit 6. Order set used? Yes No 			
Comments:							

Figure 2. Febrile Neutropenia Admission Data Collection Tool

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the variables that impede compliance with order-set use is essential to achieving desired patient outcomes (Baltic et al., 2002; Natsch et al., 2000).

Synthesis of Relevant Literature

Prompt assessment and implementation of interventions that are based on established national guidelines are the keys to effective treatment and positive patient outcomes in febrile neutropenia (Cull & Nolan, 2009; NCCN, 2011). Although no standardized timeframe has been demonstrated to be optimal, experts agree that early intervention with appropriate antibiotic therapy decreases patients' risk of sepsis and death (Perrone et al., 2004; Vogtlander et al., 2004; Zuckermann et al., 2008). Delays in implementing treatment in the emergency department are problematic for this population, and changes that improve time to assessment and antibiotic therapy are appropriate for consideration as evidence-based practice projects (Baltic et al., 2002).

Practice Questions

Considering the importance of early treatment of febrile neutropenia on patient outcomes, this project was designed to answer the following questions. Does the implementation of an order set affect the mean time interval between patient presentation and initiation of antibiotic therapy for adult patients with febrile neutropenia admitted to the adult oncology unit? In addition, does the implementation of an order set affect the average length of stay for adult patients with febrile neutropenia on the oncology unit?

Implementation

An interdisciplinary team approach was chosen for implementation of the project. The use of interdisciplinary teams is an effective method of successfully initiating a change in clinical practice (Maxwell & Stein, 2006). The success of any change process depends on the collective efforts of team members working toward a common goal (McCallin, 2006). Therefore, key stakeholders who were interested in the project and were willing to share their expertise were recruited to become team members. Regular meetings were scheduled, and a timeline for completion of the project was established (see Figure 1).

Design

A retrospective chart review was conducted of all patients admitted to the adult oncology unit with a diagnosis of cancer and febrile neutropenia in a six-month period. The review identified the time interval between admission to the emergency department or direct admission to the oncology unit and the initiation of antibiotic therapy, as well as length of stay.

Setting and Sample

The chart review included all adult patients (aged 18 years or older) with a diagnosis of cancer and febrile neutropenia who were admitted to a 31-bed adult oncology unit in an urban 600-bed hospital in the southeastern United States during a six-month time interval prior to the implementation of the order set (n = 30) or during the three months following implementation (n = 23). Patients who were younger than age 18, had cancer and febrile neutropenia but were admitted to the critical care unit, or had febrile neutropenia without a cancer diagnosis were excluded. Two patients also were excluded from the postintervention data analysis: one already was receiving antibiotics within the same drug category, thus requiring a significant delay in administration of the new antibiotic, and one patient's written antibiotic order was not timed.

Protection of Human Participants

Data collected in the study were reported in the aggregate without patient identifying information to protect anonymity. The project was approved by the investigational review boards of Presbyterian Hospital–Charlotte (where the project was conducted), the University of Alabama in Huntsville (where the principal investigator was a doctor of nursing practice student), and Queens

Table 1. Demographic Characteristics of Sample Before and After Order-Set Implementation

Characteristic	Before (N = 30)	After (N = 23)
Gender		
Male	15	13
Female	15	10
Age (years)		
18–25	7	2
26–40	2	4
41–59	8	3
60 or older	13	14
Ethnicity		
Caucasian	16	15
African American	13	2
Hispanic	_	5
Asian	1	1
Other	_	_
Cancer type		
Leukemia	9	14
Advanced cancer	7	_
Solid tumor	4	3
Hodgkin lymphoma	2	_
Non-Hodgkin lymphoma	7	3
Other	1	3
Origin		
Direct admittance	16	10
Emergency department	13	13
Outpatient oncology	1	_
Site of antibiotic administration		
Inpatient unit	21	16
Emergency department	9	7

Table 2. Antibiotic Time Intervals						
Variable	Admittance to Administration (Minutes)	Order to Administration (Minutes)				
Emergency departmen	t					
Preorder set	188	71				
Postorder set	115	22				
Inpatient unit						
Preorder set	228	204				
Postorder set	163	108				

University of Charlotte (where the principal investigator is a nursing faculty member).

Data Collection

An investigator-developed tool was used to collect data from the medical record and was designed to maintain patient confidentiality (see Figure 2). Demographic, history, laboratory values, and data related to the timing of initial antibiotic therapy were obtained. After implementation, a chart review was conducted using the same data collection tool to establish initial antibiotic time intervals and whether or not the order set was used for the patient.

Procedure

Data from the retrospective chart review indicated that an improvement in practice was needed. An interdisciplinary team including a clinical nurse specialist (doctor of nursing practice student), three nurse educators, two clinical pharmacists, an oncology nurse practitioner, and two staff nurses was formed. Physician participation was solicited from the infectious disease, medical oncology, and emergency departments. Theoretical frameworks of Knowles' adult learning theory and Lewin's change theory provided the foundation for the interdisciplinary group to plan, develop, and implement the practice change.

The interdisciplinary team reviewed current practices, compared actual practice to NCCN practice guidelines, and developed an admission order set. Recognition that many of the patients were admitted through the emergency department led the group to include the emergency department educator and physicians in the development process. Based on the recommendation of the emergency department physicians, orders specific to patients with febrile neutropenia were added to the current emergency department sepsis order set. After reviewing current evidence, the hospital's neutropenia policy and procedures, dietary guidelines, patient education materials, and neutropenic precaution signs were revised by the team and approved through appropriate channels.

A major barrier that impeded progress was a delay in timely response of the assigned medical oncologist and emergency room physician to questions and reviews of early order-set drafts. The team initially believed that a separate order set would be required for use in the emergency department. Direct involvement of an emergency department physician resulted in a decision to incorporate appropriate febrile neutropenia orders within the existing sepsis order set. The order set then was ready for implementation within two weeks.

Medical oncologists and emergency department physicians requested that all three network hospitals begin use of the order set concurrently to decrease physician confusion during the admission process. Physician and nursing staff education occurred in all three locations and in the oncology physicians' offices prior to implementation of the order set. The education plan consisted of group and one-on-one inservices, posterboard presentations, and follow-up inservices by the clinical nurse specialist and oncology nurse educator. Simultaneous education and roll-out of the order sets provided consistency in patient care and ease of decision making regarding choice of treatment orders for the admitting physician. Postimplementation data were obtained only from the units where initial data were collected. Concurrent chart review allowed oversight of the change process and provided the data required to determine whether the order set positively impacted the time interval of antibiotic therapy.

Evaluation

Analysis of Data

Retrospective chart reviews from August 2008 through March 2009 were conducted by computer retrieval for patients who were admitted to the adult oncology unit and who had discharge International Classification of Diseases, Ninth Revision (ICD-9), diagnosis codes of neutropenia 288.0–288.09, fever 780.6, and a diagnosis of cancer. Thirty patients were admitted to or were on the unit at the time of febrile neutropenia diagnosis during the initial period. Twenty-three patients admitted in the three months following implementation were included in the postimplementation chart reviews. Table 1 shows demographic characteristics

Table 3. Group Statistics From Independent- Samples T Tests						
Antibiotic Time Interval	N	$\overline{\mathbf{X}}$	SD	SEM		
Admittance to administration						
Preorder set	26	211.12	99.17	19.45		
Postorder set	13	137.3	90.85	25.7		
Order to administration						
Preorder set	25	161.64	128.48	25.7		
Postorder set	23	80.35	78.37	16.34		
SEM—standard error of the mean						

Table 4. Independent-Samples T Test for Equality of Means						
Antibiotic Time Interval	t	df	р	X Diff	SED	95% CI of the Difference
Admittance to administration Order to administration		37 40.17		73.73 81.29	32.8 30.45	[7.28, 140.18] [19.76, 142.83]

CI—confidence interval; df—degrees of freedom; SED—standard error of difference; \overline{X} Diff—mean difference

for both groups. For time intervals for initial antibiotic administration, see Table 2.

Time to Antibiotic Administration

Independent-samples t tests were completed to evaluate the difference between cycle times prior to and following the implementation of the order set. Results indicated a statistical significance between the cycle time from order written to initial antibiotic administration (t = 2.67; df = 40.17; p = 0.012). A statistical difference was found for time from presentation to initial antibiotic administration (t = 2.25; df = 37; p = 0.031). Tables 3 and 4 display the group distributions and independent-samples test results.

Length of Stay

A Pearson correlation was completed to compare length of stay with cycle times from presentation and order written to initiation of antibiotic therapy. In the preorder-set period, the mean length of stay was 11.33 days and the cycle time from order to antibiotic administration was 161.64 minutes. Length of stay and cycle time from order to antibiotic administration were significant at the 0.05 level (r = 0.496, p = 0.012) in the preorder-set sample. The finding indicates that as time from order of antibiotic to administration increases, length of stay also increases. That pattern was not seen in the postorder-set group, where the length of stay was 17.43 days and the cycle time from order to antibiotic administration was 80.35 minutes. Several confounding variables may have influenced that result because the postorder-set sample included more newly diagnosed patients with acute leukemia who received induction chemotherapy and required longer lengths of stay. Three of those patients had unusually long lengths of stay (50, 60, and 64 days, respectively) because of complications of sepsis and severe thrombocytopenia related to their chemotherapy treatment.

Implications for Nursing Practice

The literature supports the premise that the introduction of standardized order sets can decrease initial antibiotic time intervals and improve the communication process between disciplines, thus positively affecting lengths of stay, costs of cancer care, and ultimately the mortality rates of patients with neutropenia (Baltic et al., 2002; Kuderer et al., 2006; Salter, 2005; Zuckermann et al., 2008). Establishment of the need for an order set to guide clinical practice is the first step in improving patient outcomes. The ultimate success of any order set depends on its ease of ac-

cess, physician compliance, and comprehensive staff and physician education (Natsch et al., 2000; Zuckermann et al., 2008).

The initial evaluation quickly identified a need for improving the care of patients with chemotherapy-induced neutropenia. Having the data available at the onset of the project was invaluable in securing the support of physicians and nurses (Camp-Sorrell, 2005; Cull & Nolan, 2009; Eaton & Tipton, 2009). Although the evidence-based project significantly reduced time intervals to treatment, the outcomes of those interventions may have been influenced by changes other than the order set itself. Physician and staff education raised awareness of the problem and increased the likelihood that early antibiotic administration became a priority in the care of this population. Medical oncologists' collective decision that antibiotics may be administered for this population prior to drawing blood cultures if patients had difficult IV access, along with a pharmacy decision to place cefepime and doripenem in the unit-based medication dispensing machines, helped to reduce barriers to timely antibiotic administration.

The use of an evidence-based approach to nursing care is necessary for achieving the best outcomes for patients with febrile neutropenia. Comprehensive interdisciplinary staff education is essential to the successful implementation of any evidence-based practice change. Incorporation of current evidence into an order set to guide clinical practice was an effective method of improving patient care, and the success of this project provides a foundation for future evidence-based projects aimed at improving the care of vulnerable patients with cancer.

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