Implementation of a Pathway for the Treatment of Fever and Neutropenia in Pediatric Patients With Cancer

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Abstract
Fever and neutropenia is an oncologic emergency. Time-to-antibiotics (TTA) refers to the amount of time from initial provider evaluation for fever and neutropenia to intravenous antibiotic administration. Research supports that rapid time-to-antibiotics (RTTA) is associated with improved patient outcomes. This quality improvement project evaluated the success of implementing an RTTA pathway in pediatric oncology patients with fever and neutropenia. The setting was an advanced practice nurse–managed pediatric ambulatory infusion center where patients with fever and neutropenia were often evaluated and treated. In order to improve TTA, a multidisciplinary pathway was implemented with a goal of TTA that was less than 60 minutes from initial provider evaluation. Implementation of the RTTA pathway included discussion of shared expectations with the pharmacy and education departments and discussion of shared expectations with the bedside nurses and advanced practice nurses staffing the unit. Additionally, a preliminary lab test was utilized. Success of the implementation was evaluated through 2 measures: TTA and nurses’ knowledge of fever and neutropenia and the importance of RTTA. The aims of this project were to improve TTA as well as nurses’ knowledge of fever and neutropenia and the importance of RTTA, and both these aims were successfully attained.

Keywords
evidence-based practice, infection, oncologic emergency, nurse practitioner

Introduction
According to the American Childhood Cancer Organization (2014), approximately 13,400 American children aged birth to 19 years are diagnosed with cancer each year. The chemotherapy that many of these patients receive leads to neutropenia (Williams et al., 2014). Fever and neutropenia is considered a life-threatening, medical emergency and a leading cause of morbidity and mortality among pediatric cancer patients (Hakim & Gaur, 2011; Volpe et al., 2012). Neutropenia requiring treatment is defined as an absolute neutrophil count (ANC) less than or equal to 500 cells per cubic millimeter. The risk of serious bacterial infection increases with the presence of neutropenia (Volpe et al., 2012). Neutropenia can also obscure the traditional signs and symptoms of infection as it limits inflammation. Therefore, infection may go unnoticed in these patients (Hakim & Gaur, 2011).

In about half of pediatric patients with fever and neutropenia, clinically suspected or microbiologically proven bacterial infection is present (Hakim & Gaur, 2011). In one study, 22% of pediatric patients (93, total N = 423) with fever and neutropenia had documented bacteria in their blood (Agyeman et al., 2014). Because of the rate of infection in this population, rapid evaluation and intervention are necessary in cases of fever and neutropenia. The standard of care in these pediatric patients is rapid time to empiric broad-spectrum intravenous (IV) antibiotics with continuation of antibiotic therapy until recovery of the ANC (Freifeld et al., 2011). Rapid time-to-antibiotics (RTTA) equates to antibiotic administration within 60 minutes of initial provider evaluation for fever and neutropenia.

RTTA is an effective treatment in cases in which bacterial infection is eventually documented (Agyeman et al., 2014). Because of the implications RTTA has for positive outcomes in patients with fever and neutropenia, time-to-antibiotics (TTA) is a widely applicable measure of quality in pediatric cancer care (Fletcher et al., 2013; McCavit & Winick, 2012). The Clinical Practice Guideline of the

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Infectious Diseases Society of America recommends “immediate” administration of empiric antibiotics to patients with fever and neutropenia (Freifeld et al., 2011). Rapid administration of empiric IV antibiotics is considered a national benchmark of quality care in pediatric cancer patients among members of the Children’s Oncology Group (McCavit & Winick, 2012). Research on TTA with fever and neutropenia has demonstrated improved morbidity and mortality in those who experience RTTA on hospital presentation (Fletcher et al., 2013; Perron, Emara, & Ahmed, 2014). The available research supports that a delay (more than 60 minutes from presentation) in TTA is independently associated with adverse events including mortality, intensive care unit (ICU) admission, and hypotension requiring fluid administration (Fletcher et al., 2013; Lin, Weinstein, & Hota, 2008; Perron et al., 2014; Williams et al., 2014).

Numerous investigators have demonstrated the efficacy of RTTA in vulnerable populations (Fletcher et al., 2013; Lin et al., 2008; Perron et al., 2014; Williams et al., 2014). Several studies that specifically involve neutropenic patients support the benefit of RTTA. The most applicable are those that involve the treatment of cancer patients with neutropenia with suspected or known infection (Fletcher et al., 2013; Lin et al., 2008; Perron et al., 2014; Williams et al., 2014). RTTA in neutropenic pediatric patients with known or suspected infection is associated with improved outcomes (Fletcher et al., 2013; Williams et al., 2014). RTTA in pediatric cancer patients with fever and neutropenia is associated with a reduction in mortality rate, fewer ICU admissions, and less need for fluid resuscitation (Fletcher et al., 2013).

The remainder of the available literature focuses on adults. In adults with fever and neutropenia, RTTA is associated with eliminating mortality and ICU admissions (Williams et al., 2014). Other studies on TTA in adult neutropenic patients with actual or suspected infection do not specifically evaluate administration in less than 60 minutes but rather focus on the effects of more prolonged delays of hours to days (Lin et al., 2008; Perron et al., 2014). Additionally, a benefit of preventing delayed TTA is decreased length of hospital admission (Perron et al., 2014). Prevention of delayed TTA has been shown to have the greatest benefit for the most severely neutropenic patients (ANC less than 100; Lin et al., 2008).

Further evidence that involves cancer patients with fever and neutropenia, specifically, is limited. However, evidence that supports the importance of RTTA in vulnerable nononcology populations who are at risk for serious infections such as bacteremia, septic shock, meningitis, and pneumonia substantiates the importance of preventing delayed TTA. Several studies on TTA in patients who have sepsis support that RTTA is associated with improved patient outcomes (Gajeski et al., 2010; Jalili et al., 2013; Kumar et al., 2006). In patients with severe sepsis or septic shock, RTTA has shown to improve mortality rates (Gajeski et al., 2010). Delayed TTA in an interval of even 60 to 120 minutes has been associated with greater risk of mortality when compared with RTTA (Jalili et al., 2013). In adult patients with bacterial meningitis, delayed TTA of more than 60 minutes from hospital presentation has been associated with unfavorable outcomes that range from a persistent vegetative state to a disability preventing return to work or school (Koster-Rasmussen, Korshin, & Meyer, 2008). When investigating TTA with even more prolonged delays, incremental delays past 6 hours are associated with increased fatality rates (Prouix, Frechette, Toye, Chan, & Kravcik, 2005). Battlemann, Callahan, and Thaler (2002) report on TTA in adult patients with pneumonia requiring inpatient admission. Their findings also support prevention of delayed TTA in this population. While the TTA with this population often far exceeded a goal of 60 minutes, antibiotic administration in less than 8 hours of hospital presentation was associated with shorter length of hospital stay (Battlemann et al., 2002).

In many hospitals that provide care to patients with fever and neutropenia, the delay in TTA is due to a prolonged time interval while waiting for lab results, pharmacy issues, and communication between the medical and nurse teams (Cash, Deloach, Graham, Shirm, & Mian, 2014). Root cause analysis in this quality improvement (QI) project set in the ambulatory infusion center (AIC) identified pharmacy, lab, and nurses’ workflow issues as sources of delayed TTA. Specifically, time for delivery of antibiotics from the pharmacy to the unit was prolonged in some instances. Wait times for lab results in order to determine the ANC from a complete blood count (CBC) with differential was often more than 1 hour. Nurses’ workflow problems resulted from nurses’ assignments, prioritization of care, as well as delays in the advanced practice nurse (APN) evaluating the patient and placing orders. The aims of this QI project were to successfully implement a pathway to achieve TTA in less than 60 minutes from presentation for outpatient evaluation of fever and neutropenia in pediatric oncology patients, and improved bedside nurses’ knowledge of fever and neutropenia and the importance of RTTA.

**Materials and Methods**

**Setting and Sample**

This project was implemented in the AIC of a large urban academic freestanding pediatric hospital that provides comprehensive cancer care. Located within the hospital building, this unit serves the infusion needs of various types of pediatric patients, primarily oncology, but also...
includes hematology, gastroenterology, genetic, rheumatology, and immunology patients. Oncology patients receive outpatient chemotherapy regimens in addition to blood product transfusions. This AIC is managed by APNs. These AIC APNs also evaluate oncology patients for acute illness in order to avoid potential emergency department visits. One APN staffs the unit of 26 beds while infusions were in process. An attending physician is available for consultation should the APN required assistance with patient care.

The patient sample was composed of pediatric oncology patients with fever and neutropenia. This sample included patients referred to the AIC by their primary oncology providers for evaluation of fever and neutropenia as well as patients who presented for treatments such as chemotherapy or a blood product transfusion, who then developed fever while in the AIC. Inclusion criteria included any oncology patient age birth through 18 years, undergoing treatment with chemotherapy, and with fever and neutropenia who received IV antibiotic therapy while in the AIC. Patients were excluded from the project if they did not have an implanted vascular access device.

The nurse sample was a convenience sample of the unit bedside nurses. The unit is staffed by 6 to 8 bedside nurses who are trained in pediatric infusion medicine, most with a strong oncology background as well. The bedside nurse to patient ratio is typically 1 bedside nurse to 2 or 3 patients.

**Measures**

TTA was tracked via retrospective chart review. A report in the electronic medical record was run that filtered patient records between specific dates with a diagnosis “fever and neutropenia” or “fever.” These charts were then reviewed utilizing the reports of orders placed, lab results, and the medication administration record. Once the RTTA pathway was implemented, all fever and neutropenia patients admitted to the AIC were tracked for the time of the initial provider evaluation, time of labs ordered, time of preliminary ANC results, time of antibiotic administration, and ultimate disposition. Times were logged on a computerized spreadsheet.

Nurses’ knowledge of patients with fever and neutropenia and the importance of RTTA was measured using a 9-item multiple-choice print Fever and Neutropenia Questionnaire, which was distributed to the bedside nurses pre- and posteducation. Each multiple-choice question pertained to facts regarding patients with fever and neutropenia and their care. The Fever and Neutropenia Questionnaire was developed from standards of care and best practices and was reviewed by a pediatric oncologist to establish content validity. Each completed Fever and Neutropenia Questionnaire was reviewed and responses were marked as correct or incorrect. Each Fever and Neutropenia Questionnaire was scored and the scores were tabulated on a computerized spreadsheet including the responses to each item.

**Procedures**

Institutional internal review board approvals were obtained prior to initiation of this project. To improve TTA in patients with fever and neutropenia, the RTTA pathway was implemented to decrease delays in time to lab results, time to antibiotic delivery from pharmacy, and time to administration of the antibiotic. Prior to implementation of the RTTA pathway, shared expectations were discussed with pharmacy. The expectation for pharmacy was delivery of an antibiotic to the unit within 15 minutes of the APN placing the order. To improve lab result times, a preliminary ANC test was utilized in the RTTA pathway rather than awaiting the results of a CBC with manual differential. The institution had already established expectations with the lab to provide preliminary ANC results within 15 minutes from sample receipt.

Once shared expectations were established with other disciplines, nurses’ workflow issues were addressed. Prior to any education or discussion about the new pathway, the Fever and Neutropenia Questionnaire was distributed to the bedside nurses. Bedside nurses were asked to label the Fever and Neutropenia Questionnaire with a self-assigned 4-digit numeric identifier in order to maintain anonymity. Education was then provided to the bedside nurses staffing the unit. A bulletin board highlighting key concepts about fever and neutropenia was placed in the bedside nurses’ break room in a highly visible location. Bedside nurses also received a brief in-service education from a unit APN informing them of the goals of the RTTA pathway and the plan for implementation. These bedside nurses then completed the same Fever and Neutropenia Questionnaire after education, labeling their sheet of paper with the same 4-digit identifier.

Shared expectations were discussed with all APNs staffing the unit. Bedside nurses were to page the APN within 5 minutes of a patient arriving for evaluation, or becoming febrile if already in the unit for treatment. Urgent APN response was expected with rapid order entry including an order for the preliminary ANC test run by the lab. The APN placing the orders for antibiotics would notify the pharmacist via phone that an antibiotic was ordered for a patient with fever and neutropenia as soon as the order was placed in the electronic medical record. To incorporate process improvement for pharmacy, lab, and bedside nurses’ workflow, and to provide safe patient care, the multidisciplinary RTTA pathway was followed. Figures 1 and 2 show the care of the patient...
with fever and neutropenia prior to and after implementation of the RTTA pathway.

**Statistical Analysis**

Mean TTA, in minutes, was calculated for pre- and post-pathway patient groups. Given the difference in variance between the 2 groups, a Welch’s $t$ test was used to determine the statistical significance of the difference between the 2 means. Mean times, in minutes, were also calculated for time from initial provider evaluation to lab order entry, time from lab order entry to lab results, and time from lab results to antibiotic administration for both the pre- and post-pathway groups. Not all times were available for all patients as some patients had a known ANC prior to evaluation and did not require CBC results prior to ordering IV antibiotics.

Mean scores on the Fever and Neutropenia Questionnaires were calculated in both the pre- and post-education groups. The mean scores were then compared using a paired T test in order to determine the statistical significance of the difference in scores between the 2 groups.

**Results**

In the pre-pathway group there were a total of 16 patients with fever and neutropenia who received IV antibiotics over the 13-month review period. The mean TTA in this group was 79.6 minutes with a standard deviation of 40.4 minutes. Four patients in this group did not have a known ANC prior to presentation to the AIC. In the post-pathway group there were 9 patients with fever and neutropenia who received IV antibiotics over a 4-month period. In this group, the mean TTA was 41.2 minutes with a standard deviation of 23.9 minutes. Of these patients, there were 4 who did not have known ANC results prior to presenting to the AIC.

Because there was a difference in variance between the 2 groups, a Welch’s $t$ test was utilized to determine the statistical significance of the difference between the means. The 2tailed $t$ test value was 2.98 with a difference between the means of 38.4 minutes ($p = .0068$), 95% confidence interval 11.7 to 65.1 minutes, indicating the RTTA pathway was successful at reducing the TTA.

For the patient sample, individual times of initial provider evaluation, lab order entry, preliminary ANC results, and antibiotic administration were compared in the pre- and post-pathway implementation groups. In both the pre- and post-pathway groups, all but 4 patients in each group did not require preliminary ANC results prior to initiation of antibiotics because ANC results were already known prior to the AIC visit.

As shown in Figure 3, in the pre- and post-pathway groups, mean time from patient presentation to initial
provider evaluation was similar, 9.75 minutes and 10.25 minutes, respectively. Time from lab order to lab result improved from the pre-pathway to the post-pathway group, 63.25 minutes to 27 minutes, respectively. Mean time from lab result to antibiotic administration improved from 49 minutes in the pre-pathway group to 7.5 minutes in the post-pathway group.

For the nurse sample, 12 bedside nurses completed the Fever and Neutropenia Questionnaire both pre- and post-education. Of the 12 nurses, all were White females with a bachelor’s degree as the highest level of education. All but 1 nurse had greater than 10 years of nursing experience. Mean scores on the 9-item Fever and Neutropenia Questionnaire were calculated for both the pre- and post-education groups. In the preeducation group, the mean score was 7.5 correct responses with a standard deviation of 1.09. In the posteducation group, the mean score was 8.92 correct responses with a standard deviation of 0.29. The mean scores were then compared using a paired t test. The 2-tailed t test value was 5.45 with a difference between the means of −1.42 (P = .0002), 95% confidence interval −1.99 to −0.84, indicating the in-service education and poster board provided improved the nurses’ knowledge of this patient population and the importance of RTTA.

Discussion

The aims of this QI project were to successfully implement a pathway to achieve TTA in less than 60 minutes from presentation for outpatient evaluation of fever and neutropenia in pediatric oncology patients, and to improve bedside nurses’ knowledge of fever and neutropenia and the importance of RTTA. Both these aims were attained. In the patients, while sample sizes were small in both the pre- and post-pathway groups, the results were statistically significant. In the pre-pathway group, there was wide variance in the TTA. TTA in most cases was more than 60 minutes. In the post-pathway implementation group, there was less variance, and TTA was consistently less than 60 minutes. The mean TTA post-pathway implementation was decreased and variance improved. There was also consistent improvement in all service times (time from initial provider evaluation to lab order entry, time from lab order entry to lab result, time from lab result to antibiotic administration) in the post-pathway group compared with the pre-pathway group, indicating compliance among all disciplines with shared expectations.

In the nurse sample, knowledge of fever and neutropenia and the importance of RTTA improved with education. Mean scores were consistently higher on the 9-item Fever and Neutropenia Questionnaire posteducation. The difference in mean scores between the pre- and posteducation groups was statistically significant, indicating that the poster board and in-service education was effective in improving nurses’ knowledge of fever and neutropenia and the importance of RTTA.

This evidence-based QI project led to an improvement in TTA and nurses’ knowledge, which has implications for improved patient outcomes. RTTA in pediatric cancer patients with fever and neutropenia is associated with a reduction in mortality rate, fewer ICU admissions, and less need for fluid resuscitation (Fletcher et al., 2013). Thus, RTTA in this unit could lead to more favorable outcomes.

There were limitations to this project. The first is that the sample sizes in all groups were small. Larger sample sizes would provide greater power indicating greater generalizability of the results. Future projects should include larger numbers of patients and involve more nurses.
Larger sample sizes could be accomplished by developing a multicenter QI project or by extending the length of the patient enrollment time period.

Tracking TTA could potentially serve as a motivator for all disciplines to meet the expectations of time. A concern is sustainability of these results after the QI project was completed. It is possible that when times are no longer being tracked, the consistency of TTA may change. Potential means to avoid this are routine chart audits and educational updates provided to staff.

This QI project, an APN developed pathway that successfully improved TTA in patients with fever and neutropenia, in this unique unit was innovative. The collaboration of multiple disciplines throughout the steps of the RTTA pathway was effective in improving TTA. This project could be extended to include other units in this particular institution, including the inpatient oncology unit and the ICU. Once the pathway is successfully implemented institution-wide and evaluated, it could also be implemented in other pediatric institutions. A multicenter QI project could allow for extensive data collection in which data regarding patient outcomes could also be tracked. With larger sample sizes and a longer time period for enrollment, the correlation between TTA and patient outcomes such as length of inpatient admission, need for ICU admission, and mortality rates could be determined. Data collected from this project and future studies will supplement the evidence base to support RTTA in pediatric oncology patients with fever and neutropenia.

Conclusion

The QI project in this APN-managed pediatric AIC successfully accomplished the aims of improved TTA in patients with fever and neutropenia, and improved bedside nurses’ knowledge of patients with fever and neutropenia. If the success of this project is sustained there is potential for data collection on a larger scale involving other units within the institution and other centers. Future research on this topic is needed to continue to build the evidence base in the literature that supports the importance of RTTA in pediatric patients specifically. This evidence could influence policy development and potentially decrease both morbidity and mortality in this vulnerable pediatric population.

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