Chapter 15
Implementation of Evidence-Based Care in Pediatric Hematology/Oncology Practice

Eric J. Werner and Dana E. Ramirez

Timely Antibiotic Administration in Febrile Immunocompromised Patients

Febrile illnesses are a common part of a child's life and, in the vast majority of instances, do not represent life-threatening illness. Within the pediatric hematology/oncology community, however, there are several populations who have an increased risk for life-threatening infection, in particular, those with neutropenia, functional or anatomic asplenia, and central venous catheters. When such patients present with fever, it is often to facilities that manage large numbers of febrile children, only a small proportion of which have these risk factors, so processes need to be implemented, monitored, and improved to achieve rapid patient evaluation and treatment for this population.

E.J. Werner, MD, MMM (✉)
Chief Medical Quality Officer and Member, Division of Pediatric Hematology/Oncology, Children's Specialty Group, Norfolk, VA, USA

Co-Chief Medical Information Officer, Children's Hospital of The King's Daughters, Norfolk, VA, USA

Professor of Pediatrics, Eastern Virginia Medical School, Norfolk, VA, USA
e-mail: Eric.werner@chkd.org

D.E. Ramirez, MD
Director, Pediatric Residency, Associate Professor of Pediatrics, Eastern Virginia Medical School, Norfolk, VA, USA

Associate Medical Director for Quality and Patient Safety, Children's Hospital of The King's Daughters, Norfolk, VA, USA

Member, Division of Pediatric Emergency Medicine, Children's Specialty Group, Norfolk, VA, USA
e-mail: dana.ramirez@chkd.org

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Time to Antibiotics in Pediatric Cancer Patients with Febrile Neutropenia

Populations and Locations of QI Projects

Factors other than the absolute neutrophil count alone contribute to a patient's risk for bacteremia. While a risk stratification tool has become standard for adult patients with fever and neutropenia, it has several components that make it not applicable for a pediatric population [1]. There have been many stratification tools aimed at the pediatric population validated and reported, but none has yet been found to have reliability across a broad range of clinical environments [2]. Hence, most of the quality improvement projects to date have not separated "high-risk" from "low-risk" febrile neutropenia patients.

There are three locations where time to antibiotic administration can be analyzed; the emergency department, the ambulatory oncology clinic, and inpatient areas. Time from initial fever, which is usually in the home, until antibiotic administration would be a worthwhile target for reduction. Some issues affecting this time have been described [3]. However, other than patient/family education, most of these are currently out of control of the health system. Therefore, majority of the literature thus far available on time to antibiotics (TTA) in pediatric hematology/oncology patients has been from quality improvement projects within emergency departments, inpatient units, and/or ambulatory clinics.

Goals and Outcomes of QI Projects

Based on adult guidelines, a goal of less than 1 h for administration of antibiotics in febrile, immunocompromised pediatric patients is widely cited [4]. Some recent pediatric data supports this goal time frame. Using a composite adverse event outcome measure (in-hospital mortality, PICU admission, and/or fluid resuscitation), Fletcher et al. found that febrile neutropenic cancer patients who had a time to antibiotics (TTA) of 61–120 min had an increased odds ratio of this adverse outcome when compared to those who received antibiotics in ≤60 min [5]. Looking at a similar population treated in an ambulatory pediatric oncology clinic, Salstrom et al. analyzed the outcomes of 143 patients who had a TTA <60 min to 77 patients with a TTA over 60 min and found a 20% decrease in ICU admissions [6]. They also found one death in the shorter TTA group compared with three in the longer group.

The comparative TTA in reported febrile neutropenia quality improvement studies is shown in Table 15.1 [6–17]. There was an 53% decrease in the average TTA reported in these studies. Seven of the projects achieved the goal of ≤60 min, and three additional institutions were within 10 min of this goal. The majority of quality improvement interventional studies were performed in the emergency department. While the inclusion criteria, such as the definition of neutropenia, vary within these reports, many share quality improvement methods (Table 15.2). For instance, these include standardized processes such as algorithms and/or clinical pathways, multidisciplinary involvement in design, standardized patient/parent/caregiver and staff education, and sharing of data with key stakeholders. Iterative process improvement trials using the plan-do-study-act approach have been utilized [8]. Common factors delaying TTA included failure to rapidly identify and triage at-risk patients; time for laboratory

Table 15.1 Time to antibiotics (TTA) in pediatric cancer patients with febrile neutropenia

Author	Year	Location	TTA before QI process (Min)	TTA after QI process (Min)	Percent decrease
Amado [7]	2011	PICU	164	55	66%
Pakakasam [14]	2011	ED	180	75	58%
Burry [10]	2012	ED	216	Not stated	–
Volpe [8]	2012	ED	99	49	51%
Dobrasz [13]	2013	ED1	103	44	57%
Dobrasz [13]	2013	ED2	141	61	57%
Cash [11]	2014	ED	154	95	38%
Vedi [15]	2014	ED1	148	76	49%
Vedi [15]	2014	ED2	221	65	71%
Cohen [12]	2015	ED	97	64	34%
Salstrom [6]	2015	Hem/Onc Clinic	134	54	60%
Jobson [9]	2015	ED	65	30	54%
Dandoy [17]	2016	ED	137	<50	>63%
Green [16]	2016	Inpatient	99	50	49%

Table 15.2 Quality improvement techniques to reduce time to antibiotics in febrile neutropenic pediatric cancer patients

Clinical practice guidelines or management algorithm
Multidisciplinary involvement in process design
Data sharing with key stakeholders
Staff and patient/parent/caregiver education
Process improvement methodology such as Lean
“Sign and hold” orders
Release of auto-diff results without manual confirmation
Rapid identification and triage of at-risk patients
Availability of antibiotics near the patient treatment areas
Patient/parent/caregiver application of topical anesthetic cream prior to arrival in clinic
Documentation and discussion of an inpatient patient-specific fever plan

results, primarily absolute neutrophil counts, to complete; delays in obtaining antibiotic orders; and/or availability of the antibiotic for infusion [6, 8, 9]. Examples of process improvements used to overcome such obstacles include tools to rapidly identify at-risk patients [8, 13, 17], having parents apply topical anesthetic cream prior to ED arrival [6], not waiting for blood count results to start antibiotics in selected patient groups [12], and maintaining a stock of antibiotics in the treatment area [9].

Time to Antibiotics in Other Pediatric Hematology/Oncology Populations

The incidence of bacteremia in febrile children with sickle cell disease has been reported to be as high as 3–5% [18]. The rate may be lower now due to vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* and the use of prophylactic penicillin in young children with sickle cell disease. Still, bacteremia is still a major concern in this population [18, 19]. While to our knowledge, there are no studies

that look at time to antibiotic versus clinical outcome in febrile sickle cell disease patients, administration of parenteral broad spectrum antibiotics in less than 60 min to febrile sickle cell disease patients has been identified as a quality indicator of high importance for this disorder [20]. Quality improvement studies for time to antibiotics are lacking in this population but have been done for time to pain medication [21, 22].

Using a series of interventions in a population of febrile pediatric patients with central venous catheters in a pediatric academic emergency department, Jobson et al. increased the percentage who had a TTA <60 min from 66 to 99%, sustained for over 2 years, and decreased the mean TTA from a mean of 65 to 30 min. Of note, a baseline racial disparity in the TTA disappeared after these interventions. Key components identified included standardized processes, patient identification cards, and communication of the data with providers and staff [9].

Sepsis in the Hematology/Oncology Patient

Defining Sepsis

As mentioned previously, there is a population of hematology/oncology patients, specifically those with neutropenia, functional or anatomic asplenia, or central venous catheters who are at increased risk of life-threatening infections. Before addressing how to identify and treat these patients, there must first be an understanding of the definitions associated with life-threating infection. At the 2005 International Pediatric Sepsis Consensus Conference, definitions [23] (see Fig. 15.1) were created for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock in the pediatric population. SIRS requires the presence of at least two of the following: fever/hypothermia, tachypnea/respiratory failure, leukopenia/bandemia, and tachycardia/bradycardia. Sepsis is defined as the presence of a suspected or confirmed infection combined with SIRS. Severe sepsis includes sepsis with either cardiovascular dysfunction, respiratory distress syndrome, or dysfunction of at least two other organ systems. Figure 15.2 describes the definition of organ dysfunction in the pediatric population [23]. Finally, septic shock is defined as persistent hypotension despite fluid resuscitation or evidence of tissue hypoperfusion (e.g., altered mental status, decreased urinary output) [23] (Fig. 15.1).

Early Goal-Directed Therapy

Early goal-directed therapy (EGDT) has been of primary focus from the Surviving Sepsis Campaign, an international collaborative that created guidelines for management of severe sepsis and septic shock revised in 2012 and again in 2016. Principles of EGDT include providing oxygen, aggressive fluid resuscitation, early antibiotic administration, inotropic support for fluid-resistant shock, and steroid administration for inotropic resistant shock [24]. The newest guidelines used large validated adult data to change the guidelines emphasizing infection and dysfunction of two organ

SIRS[a]

The presence of at least two of the following four criteria, **one of which must be abnormal temperature or leukocyte count:**

- Core[b] temperature of > 38.5°C or < 36°C.
- Tachycardia, defined as a mean heart rate > 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-h time period **OR for children < 1 year old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-h time period.**
- Mean respiratory rate > 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or > 10% immature neutrophils.

Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

Sepsis

SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Organ dysfunctions are defined in Table 15.4.

Septic shock

Sepsis and cardiovascular organ dysfunction as defined in Table 15.4.

Modifications from the adult definitions are highl ighted in boldface.

[a]See Table 15.3 for age-specific ranges for physiologic and laboratory variables; [b]core temperature must be measured by rectal, bladder, oral, or central catheter robe.

Fig. 15.1 Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock. Reprinted with permission from [23]

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 h

- Decrease in BP (hypotension) < 5th percentile for age or systolic BP <2 so below normal for age[a]

OR

- Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)

OR

- Two of the following

  Unexplained metabolic acidosis: base deficit >5.0 mEq/L

  Increased arterial lactate >2 times upper limit of normal

  Oliguria: urine output < 0.5 mL/kg/hr

  Prolonged capillary refill: >5 s

  Core to peripheral temperature gap > 3°C

Respiratory[b]

- PaO_2/FIO_2 <300 in absence of cyanotic heart disease or preexisting lung disease

OR

- $PaCO_2$ > 65 torr or 20 mm Hg over baseline $Paco_2$

OR

- Proven need[c] or > 50% FIO_2 to maintain saturation ≥92%

OR

- Need for nonelective invasive or noninvasive mechanical ventilation[d]

Neurologic

- Glasgow Coma Score ≤11 (57)

OR

- Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline

Hematologic

- Platelet count <80,000/mm^3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)

OR

- International normalized ratio >2

Renal

- Serum creatinine ≥2 times upper limit of normal for age or twofold increase in baseline creatinine

Hepatic

- Total bilirubin ≥4 mg/dL (not applicable for newborn)

OR

- ALT 2 times upper limit of normal for age

BP, blood pressure; ALT, alanine transaminase.

[a]See Table 15.2; [b]acute respiratory distress syndrome must include a Pao_2/FIO_2 ratio :S200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure (Refs. 58 and 59). Acute lung injury is defined identically except the Pao_2/FIO_2 ratio must be ≤300 mm Hg; [c]proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required; [d]in postoperative patients, this requirement can be met if the patient has developed an acute inflammatory infectious process in the lungs that prevents him or her from bein extubated.

Fig. 15.2 Organ dysfunction criteria. Reprinted with permission from [23]

Table 15.3 Surviving sepsis campaign bundles

To be completed within 3 h:
(1) Measure lactate level
(2) Obtain blood cultures prior to administration of antibiotics
(3) Administer broad spectrum antibiotics
(4) Administer 30 mL/kg crystalloid for hypotension or lactate 4 mmol/L
To be completed within 6 h:
(5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation)
to maintain a mean arterial pressure (MAP) ≤ 65 mm Hg
(6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/L (36 mg/dL): - Measure central venous pressure (CVP)[a] - Measure central venous oxygen saturation (ScvO2)[a]
(7) Remeasure lactate if initial lactate was elevated[a]

[a]Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg,ScvO2 of ≥70%, and normalization of lactate
Modified from [33]

Table 15.4 Pediatric advanced life support septic shock (SS) guidelines

Timely recognition of septic shock	Initiation of interventions/frequent reassessment
Placement of PIV	Within 5 min of recognition
20 cc/kg isotonic crystalloid fluid	Within 5 min of recognition then reassess
Antibiotic administration	Within 60 min of recognition
Vasoactive agent administration	Within 60 min of recognition

Modified from [26–28]

systems as the best indicators of sepsis [25]. While the Surviving Sepsis Campaign guidelines have been used as a gold standard for sepsis evaluation and treatment, the definitions are not pediatric specific, and the Goldstein criteria [23] remain the most frequently cited pediatric sepsis definitions. In 2010, the addition of pediatric recommendations were released by the American Heart Association as part of Pediatric Advanced Life Support [26] and further revised in 2015 [27, 28] (see Table 15.4).

When focusing on pediatric specific literature, studies have reported a noteworthy increase over the past decade in the number of sepsis cases identified in pediatric hospitals [29]. Yet, the rate of sepsis in the pediatric population differs from study to study likely due to a myriad of factors including different patient populations, study design, reporting bias, detection bias, differing sets of diagnostic criteria, and differing sources of data [30].

Early identification of the febrile patient who is likely neutropenic, functionally or anatomically asplenic, has an indwelling central venous line, or is immunosuppressed is critical to assess for SIRS, sepsis and septic shock in the hematology/oncology population. Once suspicion of sepsis is identified, initial management should include EGDT with concentration on frequent assessment [26–28]. Intravenous access must be quickly established followed by a 20 mL/kg bolus with isotonic fluid and timely reassessment for tissue hypoperfusion [28]. Additional fluid boluses should be considered based on these frequent assessments [27].

Compared with adults, children can remain in compensated shock with persistent tachycardia. They may also present later with hypotension as a sign of irreversible cardiovascular collapse [26]. The pediatric consensus guidelines are designed to identify patients with compensated septic shock allowing for early intervention to prevent cases of profound decompensation [23].

During fluid resuscitation, the clinician should also remain aware of the patient's respiratory status. The Fluid Expansion as Supportive Therapy [31] trial looked at treatment of children with a febrile illness complicated by impaired consciousness, respiratory distress or both, and impaired perfusion. The trial concluded that early fluid therapy increased mortality [31]. However, further review of subsequent literature analyzing the FEAST trial was included in the Pediatric Advanced Life Support: 2015 International Consensus on Cardiopulmonary Resuscitation which does not recommend limiting resuscitation fluids for children in septic shock but does recommend utilizing caution if the resuscitation occurs in a place with extremely limited critical care resources [27, 28].

The other principles of EGDT: providing oxygen, early antibiotic administration, and inotropic support for fluid-resistant shock [24], also should each be addressed as soon as signs of SIRS/sepsis/septic shock are recognized. As oxygen delivery is dependent on cardiac output and the oxygen-carrying capacity of blood, oxygen delivery can be increased by first providing 100% inspired oxygen and additionally by volume expansion with rapid infusion of isotonic fluid or packed red blood cells when indicated by hemoglobin and hematocrit results. The administration of intravenous antibiotics must be administered within the first hour of suspected sepsis or septic shock [32].

Performance Improvement

Poor patient outcomes from sepsis can be mitigated with early identification of sepsis and subsequent timely initiation of proven therapies [33]. The Surviving Sepsis Campaign 2012 recommendations include the utilization of performance improvement methods to improve patient outcomes [32]. The original campaign implemented a set of goals in the form of a bundle in multiple hospital settings and demonstrated not only improved quality of treatment of sepsis but additionally decreased mortality [33] (see Table 15.3).

Implementation of standardized sepsis protocols in pediatrics foster improved recognition of septic patients [34, 35] and more timely delivery of critical interventions [34, 36] in both inpatient and emergency department settings. Early identification of patients who may require EGDT for possible sepsis can be achieved by training staff on age-appropriate vital signs and abnormal variation in vital signs based on temperature elevation [34–36]. Additional training must focus on compliance with current treatment guidelines. Paul et al. were able to increase compliance with PALS sepsis guidelines with the use of QI methodology [36]. As pediatric institutions continue to undertake development of plans for adapting and sustaining

sepsis protocols, collaboration and continued quality improvement will remain vital to reaching the goal of enhancing outcomes. In addition to institutional quality improvement efforts, national and international efforts may offer the opportunity for more rapid learning through shared quality improvement collaboration as done in the past by the Surviving Sepsis Campaign [32] and currently by the Children's Hospital Association Improving Sepsis Outcomes Collaborative [37].

Safe Handoffs in Pediatric Hematology/Oncology

All care providers must transition the care of their patients to an oncoming provider at the end of a clinical shift. Hematology/oncology patients frequently have complicated conditions; thus, it is important for providers to be competent in patient handovers.

A successful handoff is defined by The Joint Commission's Center for Transforming Healthcare as "a transfer and acceptance of responsibility for patient care that is achieved through effective communication. It is a real time process of passing patient-specific information from one caregiver to another or from one team of caregivers to another to ensure the continuity and safety of that patient's care [38]. In 2006, The Joint Commission identified handoffs as a major risk to patient safety. In response one of its national patient safety goals was for hospitals "to implement a standardized approach to "hand off" communications, including an opportunity to ask and respond to questions." [39, 40] When a provider relinquishes the care of a hematology/oncology patient to another provider, the effective transfer of information becomes critical to patient safety, and the loss of critical information can lead to medical error and adverse events [41].

Increased attention to handoffs occurred when the American Council for Graduate Medical Education (ACGME) restricted resident work hours to 80 h per week in 2003 and then added additional restrictions in 2011 [42, 43]. This resulted in a significant increase in the number of patient transitions of care. The increased number of patient handoffs subsequently led to delayed care [44], delayed disposition [45], redundancy in work [46], and uncertainty regarding future care [47].

Currently, the ACGME requires residents to be competent at handing over patients [48]. Yet, initial exploration of resident ability to transition patients demonstrated that interns often overestimate the effectiveness of their handoffs. Additionally, in one study residents reported that a patient was harmed 50% of the time on their previous rotation due to a handoff error [49]. To achieve handoff consistency among residents in an academic institution, it has been suggested that standardization of handoffs and a content checklist are crucial to appropriate communication [50].

As research progressed in the field of handoffs, communication was noted to be an essential part of an effective handoff (1, Joint Commission 2007). Poor communication has been cited by The Joint Commission as the root cause of up to two-thirds of sentinel events [51]. In addition, it has been estimated that up to one quarter

I	Illness Severity	• Stable, "watcher," unstable
P	Patient Summary	• Summary statement • Evens leading up to admission • Hospital course • Ongoing assessment • Plan
A	Action List	• To do list • Time line and ownership
S	Situation Awareness and Contingency Planning	• Know what's going on • Plan for what might happen
S	Synthesis by Receiver	• Receiver summarizes what was heard • Asks questions • Restates key action/to do Items

Fig. 15.3 Elements of the I-pass handoff tool. Reprinted from [54] with permission from the I-PASS Study Group

of all malpractice claims are a direct result of communication errors [52]. To improve communication, one suggested strategy is the utilization of mnemonics which can provide structure and act as a memory aid [53]. In pediatrics, the I-Pass mnemonic [54] (Fig. 15.3) and the use of checklists [50] have established improvement in handoffs. The I-Pass mnemonic, when implemented as part of a handoff bundle to include standardized communication, training, as well as efforts to minimize distraction, ultimately revealed decreased rates of medical errors [41]. Measurement of improvement in communication can be done using a Likert scale to score elements of communication such as confidence, organization, and included/excluded content [50] (Fig. 15.4). Additionally, for improved handoff communication, one should strive to communicate face to face which has proven to be the superior method of communication when compared with phone, email, and paper communication [55].

Two additional factors that can weaken handoff quality are lack of formal training [39] and lack of standardized tools to assess handoffs [53, 56] Thus, whether a health system ultimately chooses to utilize a checklist or a mnemonic for care transition, it is imperative that all providers receive standardized training on the tool.

Transfer of Care Global Evaluation Scale

Evaluator: _____ Date _____

Evaluates _____ ◻ intern ◻ resident ◻ student ◻ other _____

Situation: ◻ End of shift ◻ Transfer between services ◻ Admission

Type: ◻ face-to-face ◻ phone ◻ Notes

Organization

1	2	3	4	5
Information followed a logical order for the patient.		The learner seemed to follow a series of topics; however, there were some items/topics out of order.		The learner provided information that was disjointed and unorganized.

Economy

1	2	3	4	5
The learner provided the ideal amount of information.		The learner included a fair amount of extraneous information		The learner provided far too much extraneous information.

Confidence

1	2	3	4	5
The learner spoke without hesitation.		The learner was occasionally hesitant.		The learner was frequently hesitant.

	1	2	3	4	5
Presentation Order Presents sickest patients first	Always	Usually	Sometimes	Rarely	Never
Seeks Comprehension Ensures that recipient understands information and concerns/plans for next shift	Always	Usually	Sometimes	Rarely	Never
Professionalism Appropriate comments re: patient, family, staff, etc	Always	Usually	Sometimes	Rarely	Never

Overall Rating: _____

Fig. 15.4 Reprinted with permission from [50]

By providing standardization, providers obtain structure so that the "rules" of interaction (e.g., content and order) do not need to be negotiated; if no information is given, it implies there was nothing that required mention, and information is conveyed more efficiently and reliably [56]. One must also develop an assessment tool for ongoing evaluation and improvement [53]. For example, a global assessment tool (Fig. 15.4) encourages evaluation by direct observation [50].

Once the health system has determined the tool, education, and assessment that will be implemented, there are some general strategies that will be undertaken to make handoffs as successful as possible. These include being clear, concise, and organized and asking the receiver if they have any questions after each patient; being certain to impart critical data including pertinent positives and negatives about the patient; allowing the appropriate amount of time to relay information; and doing it where interruptions are minimized. For instance, implement a page-free zone or a designated quiet space in which to handover patients. Identify and present the most critical patients first when the receivers' attention is at its best. Finally, the receiver should be empowered to not accept a poor patient handoff and to ask clarifying questions.

Influenza Vaccination in Pediatric Hematology/ Oncology Practices

Influenza, a common upper respiratory tract infection, can cause major complications, especially in the immune compromised host [57, 58]. Complications include respiratory failure, secondary pneumonia and bacteremia, and prolonged viral shedding. Cancer treatment delays are common [59]. Therefore, preventing this infection in children with sickle cell disease or cancer is of high importance. The percentage of patients in each of these groups who did receive the appropriate influenza vaccine in the recommended time frame for each year is a good process measure for influenza prevention.

Influenza Vaccination in Pediatric Cancer Patients

Pediatric cancer patients are at increased risk for severe influenza-related illness. Two studies in the recent era assessed influenza complications in hospitalized pediatric oncology patients. In a 5-year period with 27 clinical encounters due to influenza, 63% of which were treated with antiviral medication, Tasian et al. [59] found that 15% required mechanical ventilation, 22% required oxygen support, 15% developed bacteremia, and 11% had hospitalizations in excess of 30 day. The influenza vaccination status of these patients was not reported. In a similar 5-year period, Kersun et al. [60] describe 39 patients, 46% of which had received immunization. Of these, 20% had respiratory complications, 10% intensive care admissions, and 5% died.

Treatment with antiviral agents such as oseltamivir or zanamivir for specific strains of influenza and in appropriately aged patients can decrease the severity of infection and complication rate for pediatric cancer patients infected with influenza [58]. However, because complications exist even in treated patients, the potential for cancer treatment interruption, and possible exposure of other at-risk patients to the illness, prevention is a better strategy. As infection of patients can occur from healthcare personnel, universal vaccination of pediatric hematology/oncology providers and staff should be performed [58].

Influenza Vaccination Safety and Efficacy in Pediatric Cancer Patients

Overall, patients receiving chemotherapy have a decreased serologic response to influenza vaccine when compared to healthy children. Patients with AML or within 1 year of stem-cell transplant have lower response rates [58]. Mavinkurve-Groothuis et al. [61] found that 92% of patients with a normal absolute lymphocyte count for

age had a protective immune response to H1N1 vaccine as opposed to 33% with a low absolute lymphocyte count. They did not find a difference between hematologic malignancy (mostly ALL) and solid tumor patients in response to H1N1 vaccine. None of their patients with an absolute T-cell count below 200 per microliter achieved protective levels. Older age or perhaps the larger dose administered to older children may predict a higher vaccine response rate in children with ALL [62, 63]. It is not clear that the serologic titer associated with a protective effect in healthy individuals is applicable to pediatric oncology patients [58, 63]. Children who have completed therapy for cancer, with the exception of stem-cell transplant patients, have a better response to immunization [63].

The adverse reaction rate to inactivated influenza vaccine is not higher in pediatric cancer patients than in the general population [58, 63]. Thus, despite lower serologic response rates for children on chemotherapy compared to the general pediatric population, that a significant proportion of on-therapy patients do respond, that off-therapy patients respond well, the low adverse reaction rate and the significant morbidity of influenza in this population give strong support to the recommendation that this population be vaccinated against this infection with the inactivated form of the vaccine.

Influenza Vaccination Rates in Pediatric Oncology Patients

Despite the above reasons for vaccinating pediatric cancer patients against influenza, vaccination rates in this population have been disappointing [58, 60]. Some of the stated barriers to adequate vaccination are noted in Table 15.5. Adult survivors of childhood cancer who are also at high risk for influenza-related complications due to late effects of their cancer treatments also have a low rate of vaccination [64].

Freedman et al. [65] used five interventions to increase influenza vaccination rates in their pediatric oncology program: (a) parent/family education, (b) use of the electronic health record to identify vaccine-eligible patients, (c) brightly-colored identification bracelets attached to vaccine-eligible patients in the ambulatory environment, (d) inclusion of influenza vaccine in the discharge order set, and (e) provider education. As a result, when compared to the prior year's population, there was a significant increase in the percentage of fully immunized patients (64.5% vs. 44.4%, $p = 0.001$) and a proportionate decrease in unimmunized patients (45.2% vs. 22.5%, $p = 0.001$). The percentage of patients who were partially immunized did not change significantly (13.0% vs. 10.4%, $p = 0.19$). They demonstrate, as with most

Table 15.5 Barriers to influenza vaccination in pediatric cancer patients

Parental concern about vaccine side effects
Parental fear that vaccination will cause influenza illness
Provider belief that vaccination is ineffective
System failure to identify unimmunized children
System failure to administer vaccine to eligible children

quality improvement projects to improve adherence in pediatrics, multidisciplinary and patient/parent/family education, and systemic factors need to be addressed.

Influenza Vaccination in Pediatric Sickle Cell Disease

Sickle cell disease (SCD) patients are also at increased risk for adverse outcomes from influenza infection [57]. The hospitalization rate for influenza illness in children with sickle cell disease is 56 times that of children without SCD and even higher for children identified as having homozygous HbSS disease [66]. Influenza can cause acute chest syndrome [67].

Influenza vaccine is both safe and effective in SCD. Unlike pediatric cancer patients, the large majority of children with SCD achieve protective antibody titers in response to inactivated influenza vaccine [68–71]. Purohit et al. [68] did report a decreased response to inactivated H1N1 in SCD patients on chronic transfusion. Hydroxyurea use and splenectomy did not appear to impact response [68, 69]. The vaccine is well tolerated in this population [69–71]. The inactivated trivalent influenza vaccine does not appear to increase the rate of hospitalization for vaso-occlusive crisis within 2 weeks of administration [72]. Because of the morbidity of influenza in SCD patients and the proven efficacy and safety of the inactivated vaccine, the CDC, AAP, and WHO all recommend influenza vaccination for sickle cell disease [57]. An annual influenza vaccine is a recommended quality measure for sickle cell disease [20].

Despite this recommendation, adherence with influenza vaccination in children remains poor [73]. An analysis of a Wisconsin Medicaid database showed that over a 5-year period, only 30% of children with SCD received 80% of their influenza vaccines annually, while 46% received less than 50% [74]. Barriers likely are quite similar to those described for pediatric cancer patients, although concern of poor response should not be a factor. Additional factors include that the seasonal availability of the vaccine may not coincide with the patient's clinic visit and primary care or specialty provider's assumptions that the other will manage this aspect of the patient's care [75].

Improvement in Influenza Immunization in Pediatric Sickle Cell Disease Patients

Quality improvement methods have been used in increase influenza immunization in other high-risk pediatric populations [65, 76]. Repeated contact with a hematologist was shown to increase the likelihood of influenza immunization in sickle cell disease patients, suggesting that information provided from this source is valued [77]. Zimmerman et al. [78]. identified tools to facilitate three major approaches to increasing influenza vaccination rates among high-risk pediatric populations including

Table 15.6 Strategies to increase influenza vaccination in children and adolescents with sickle cell disease [79]

Patient/parent and provider education
Enhanced electronic health record
Establishment of patient registry
Use of care coordinators

sickle cell disease in a low-income urban environment. These tools included parent information devices (e.g., flyers, posters, letters, etc.), increased access to immunizations (walk-in and Saturday clinics), and systems-based interventions including electronic provider reminders, staff education, and standing orders. While these interventions nearly doubled the immunization rate, going from 10.4 to 18.7%, it remained quite poor. Recently, Sobota et al. [79] used four strategies (Table 15.6) to increase both the rate of influenza immunization and the timing of this vaccination in their SCD patients treated in an urban pediatric hematology ambulatory environment. Implemented and refined over a 2-year period, these approaches dramatically increased the influenza vaccination rate from 45 to 90%. The immunization rate exceeded 80% even for patients 18–21 years of age. An additional secondary goal was to have patients receive their immunization early in the season. Seventy-one percent were immunized by mid-November of the last year reported.

Despite data demonstrating safety and utility, albeit the latter perhaps less well demonstrated for pediatric cancer than SCD patients, there appears to be significant opportunity for improvement. Two recent publications, one for each population, have demonstrated that dedicated teams adequately resourced and using systems-based approaches can achieve high influenza immunization rates. Implementation of such practices and use of evolving tools such as interoperable vaccine registry databases to identify unimmunized patients, secure provider-to-provider electronic communication to facilitate care coordination between practices, and electronic patient portals to send education and reminders to patients may soon help achieve similar vaccination rates across all pediatric hematology/oncology practices.

Iron Overload and Its Management

Iron homeostasis is a complex process that tightly regulates iron absorption and iron excretion, with relatively small quantities of this element moving in either direction on a daily basis [80]. In the average adult, iron balance is achieved by the absorption of 1–2 mg/day of iron from the gut and the loss of 1–2 mg/day of iron, primary from shedding of GI mucosal cells and blood loss [81]. As there are no physiologic pathways to increase iron excretion, the main control mechanism is to limit iron absorption from the diet through a complex series of interacting regulating proteins, principally hepcidin and ferroportin [82, 83]. Causes of iron overload are shown in Table 15.7. As each unit of red blood cells transfused contains 200–250 mg of iron, [84] a 60-kg individual transfused 2 units/month receives roughly 7–8 mg/day of iron. More than one mechanism may be present in any given patient. For example, patients with the more severe thalassemic disorders, especially β-thalassemia major,

Table 15.7 Causes of iron overload

1. Defects in iron metabolism regulatory proteins. Example hereditary hemochromatosis
2. Excessive iron intake. Example transfusional iron overload
3. Ineffective erythropoiesis. Example thalassemia intermedia
4. Combination of factors. Examples: a. Thalassemia with transfusional therapy b. Long-term therapeutic doses of iron in patients with hereditary hemochromatosis or thalassemia

have both ineffective erythropoiesis and frequent transfusions [85]. Ineffective erythropoiesis causes suppression of hepcidin synthesis leading to increased GI iron absorption and iron overload, even without or with only limited red blood cell transfusion. When the amount of iron in the plasma exceeds the transferrin binding capacity, labile plasma iron can induce free radicals which cause oxidative intracellular damage, in particular, in the liver, heart, pancreas, and endocrine organs [86].

Determination of iron overload is made by measurement of iron levels in various organs. Serum ferritin can reflect iron overload but correlates poorly with hepatic and most importantly cardiac iron deposition. Liver iron concentration by liver biopsy has long been the gold standard but is invasive. Recently, MRI techniques ($R2^*$) have been shown to correlate well with hepatic liver iron concentration as determined by liver biopsy [81]. Cardiac iron as determined by $T2^*$ has also been shown to be predictive of cardiac dysfunction [81, 84] It is very important that the MRI unit and technique have appropriate validation and calibration [81]. Symptomatic cardiac overload can occur even without major hepatic disease, especially if there is ineffective erythropoiesis or the patient has undergone chelation with desferrioxamine that preferentially removes hepatic iron [84].

Management of Iron Overload

Non-pharmacologic techniques include ingesting tea, which can inhibit iron absorption [87], dietary restriction of iron-containing foods, and carefully counseling patients to avoid iron supplements. In most instances, such interventions will not be adequate to prevent iron overload. Use of exchange transfusions rather than simple transfusions to remove aging erythrocytes has been shown to be effective in reducing iron overload for patients on chronic transfusion regimens but requires adequate venous access and increases the donor exposures [88].

Three iron chelators are currently licensed in the United States. Desferrioxamine has been available for decades. It is typically administered as a 12-h subcutaneous infusion 4–5 times/week. Higher-dose, intravenous infusions may also be used for selected patients [89]. Desferrioxamine has been associated with several significant toxicities including retinal damage, hearing loss, bone changes, local reactions at the infusion site, poor growth, Yersinia infections, and allergic reactions [84, 86]. High doses can cause neurologic and pulmonary toxicity [84]. While effective for

hepatic iron overload, desferrioxamine is not always effective at limited cardiac iron overload, and patients have developed fatal cardiac disease while on the medication [84]. Not surprisingly, poor adherence to desferrioxamine regimens has long been recognized [86, 90].

Deferiprone (DFP) is an oral iron chelator approved by the FDA in 2011 [86]. Due to a short half-life of 4 h, it is typically taken three times daily. DFP may have advantages over DFO for management of cardiac iron overload [84, 91]. Toxicities include nausea and vomiting, arthropathy, zinc deficiency, and elevated liver enzymes. The most serious toxicity is neutropenia or agranulocytosis that occurs in approximately 1% of drug recipients and requires close monitoring of blood counts throughout treatment [84].

Deferasirox (DFX), approved by the FDA in 2005, has a longer experience in the United States but not in Europe. DFX promotes fecal iron excretion. Its half-life permits once-daily dosing. DFX has been shown to be effective in reducing hepatic and cardiac iron in pediatric and adult patients with transfusion-iron overload [84]. Common toxicities include gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), rash, hearing loss, and cytopenias. Significant hepatic and renal toxicity has been noted, and a "Black Box" warning exists for renal and hepatic failure, with frequent laboratory testing recommended. A Black Box warning also exists for GI hemorrhage but this problem is noted more frequently in the elderly.

Alternating or combined chelator trials have been performed, albeit generally in small numbers of patients, and further trials are needed to determine the optimal approach for management of iron overload in children [84, 92, 93].

Medication Adherence with Chelation Therapy

To date, several studies have focused on medication adherence. There are some studies noted below that also measured clinical outcome measures such as hepatic iron concentration or hospitalization rates.

Not surprisingly for a medication with a requirement for long-term painful subcutaneous infusions, early on nonadherence to desferrioxamine regimens was identified as a barrier to its effectiveness [90]. A series of large studies put the estimated adherence with DFO at 59–78% [94]. Nonadherence is associated with an increased incidence of poor outcomes including death [94, 95]. Based on survey responses in a multinational study, Ward et al. found that outside of India and Iran where access to medication was the most frequent reason for missing doses, the patient's beliefs and feelings about the medication and medication side effects were the most common reasons. Additionally, age was also correlated with nonadherence with children under 10 years having the highest rate of adherence, while patients over 18 years of age had the lowest rate [96]. Adherence has been shown to be better for deferiprone than desferrioxamine [97].

An Iranian study reported increase patient self-reported adherence to DSX as compared with DFO [98]. As part of a larger study of adherence to chelation in

thalassemia patients, Trachtenberg et al. found that adherence did increase for a subset who changed from DFO to DSX. Predictors of poor adherence included side effects, smoking, age, and difficulties with DFO [99]. Using a medication possession ratio and analysis of Medicaid claims from three states, Jordan et al. found a higher adherence rate and decreasing hospitalization rate for sickle cell disease patients on DSX compared with DFO [100]. Compliance with chelation therapy had a more significant role in prevention of iron-induced cardiac disease than choice of chelation agent in transfused adults with beta thalassemia major [101].

Improvement Trials in Chelation Adherence

While nonadherence is well documented in patients with transfusional iron overload, and several contributing factors have been identified, there are relatively few studies of effective interventions. Pakbaz et al. used a Numerical Likert Scale adherence assessment tool and then discussion of hepatic iron content results, education regarding chelation, and barrier to adherence solutions to improve adherence and decrease hepatic iron in a subgroup of 15 patients who had serial measurements over 15 months [102].

Iron overload remains a major problem for many populations with impact on quality and quantity of life, particularly for those patients on chronic transfusion therapy. Medication non-adherence contributes significantly to adverse patient outcome. Factors associated with decreased adherence to chelation regimens are similar to other disorders including patient beliefs, side effects, decreased access to medication, and regimens that are difficult to understand or complete. Access to oral iron chelation agents appears to increase medication adherence, but concerns about toxicity have prevented consensus that these should be the front line agents for all such patients [93]. Few studies have been performed in this population to increase adherence, and these are limited to small patient numbers and short term interventions.

Conclusion

Efficacy of evidence-based care is dependent upon its reliable delivery. Many of the quality improvement activities cited in this chapter used common tools in the quality improvement toolbox including identified measurable targets for improvement, multidisciplinary team approaches to design and implementation, standardized processes, patient/parent/caregiver engagement, and iterative cycles of improvement activity. More in-depth discussion of quality improvement science and some of its potential applications in pediatric hematology/oncology is found elsewhere in this book. However, many opportunities remain for future development and implementation of improvement methods for these and many other areas within our specialty.

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