American Journal of Infection Control 44 (2016) 1650-5

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Bacterial bloodstream infections in pediatric allogeneic hematopoietic stem cell recipients before and after implementation of a central line-associated bloodstream infection protocol: A single-center experience

Alicia K. Chang MD [a], Marc D. Foca MD [a], Zhezhen Jin MD [b], Rahul Vasudev MD [a], Mary Laird RN, PNP [c], Sharon Schwartz RN, PNP [c], Mahvish Qureshi MD [a], Michelle Kolb RN, PNP [c], Anya Levinson MD [a], Monica Bhatia MD [a], Andrew Kung MD, PhD [a], James Garvin MD, PhD [a], Diane George MD [a], Phyllis Della-Latta PhD [d], Susan Whittier PhD [d], Lisa Saiman MD, MPH [a,e], Prakash Satwani MD [a,*]

[a] *Department of Pediatrics, Columbia University, New York, NY*
[b] *Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY*
[c] *Department of Nursing, New York-Presbyterian Morgan Stanley Children's Hospital, New York, NY*
[d] *Department of Pathology, Columbia University, New York, NY*
[e] *Department of Infection Prevention and Control, New York-Presbyterian Hospital, New York, NY*

Key Words:
Children
Bone marrow transplantation
Sepsis

Introduction: There are only few reports describing the influence of central line-associated bloodstream infection (CLABSI) prevention strategies on the incidence of bacterial bloodstream infections (BBSIs).
Methods: We performed a retrospective cohort study among pediatric recipients of allogeneic hematopoietic stem cell transplantation (allo-HCT) to assess potential changes in BBSI rates during 3 time periods: pre-CLABSI prevention era (era 1, 2004-2005), CLABSI prevention implementation era (era 2, 2006-2009), and maintenance of CLABSI prevention era (era 3, 2010-2012). BBSI from day 0-365 following allo-HCT were studied. The comparison of person-years incidence rates among different periods was carried out by Poisson regression analysis.
Results: The mean age of patients was 10.0 years. During the study period, 126 (65%) of 190 patients had at least a single BBSI. From day 0-30, day 31-100, day 101-180, and day 181-365, 20%, 28%, 30%, and 17% of patients, respectively, experienced BBSIs. The rate of *Staphylococcus epidermidis* and gram-negative pathogens significantly declined from 3.16-0.93 and 6.32-2.21 per 100 person-months during era 1 and era 3, respectively ($P = .001$).
Conclusions: Patients undergoing allo-HCT during era 3 were associated with decreased risk of BBSI ($P = .012$). Maintenance of CLABSI protocols by nursing staff and appropriate education of other care providers is essential to lower incidence of BBSI in this high-risk population, and further strategies to decrease infection burden should be studied.

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is an established treatment option for patients with various malignant and nonmalignant diseases. However, certain risk factors unique to the allo-HCT recipients increase their susceptibility to bacterial bloodstream infections (BBSIs), which contribute significantly to their morbidity and mortality.[1-3] These factors change during different stages of immune reconstitution, further complicating

* Address correspondence to Prakash Satwani, MD, Division of Pediatric Blood and Bone Marrow Transplantation, New York-Presbyterian Morgan Stanley Children's Hospital, Columbia University, 3959 Broadway, CHN 10-02, New York, NY 10032.
E-mail address: ps2087@columbia.edu (P. Satwani).
Conflicts of Interest: None to report.

0196-6553/
http://dx.doi.org/10.1016/j.ajic.2016.04.229

implementation of infection prevention. Early in the pre-engraftment period, mucosal breakdown and neutropenia can contribute significantly to the development of BBSIs, whereas later in the postneutrophil engraftment phase, acute graft-versus-host disease and prolonged indwelling central venous lines (CVLs) can contribute to the development of BBSIs.[3-7]

Various prevention practices have been established to reduce the risk of BBSIs in allo-HCT recipients. Both gut decontamination and antibacterial prophylaxis aim to decrease early infections.[2,8] However, both of these practices are not used widely in children and are associated with the risk of developing antibiotic-resistant bacterial infections.[2,8] Central line-associated bloodstream infection (CLABSI) bundle protocols have been used to standardize line insertion and maintenance prevention and reduce the rate of CLABSIs.[9-11]

According to National Healthcare Safety Network data, the incidence of CLABSIs in oncology patients and the pediatric intensive care population is similar.[8] Reports describing the efficacy of CLABSI prevention practices exist for the intensive care unit setting[11]; however, there are few reports describing the association of CLABSI-prevention strategies on the incidence of BBSI in pediatric allo-HCT populations.[9] Assessing this association is complicated by changes in the CLABSI case definitions, the complexity of distinguishing secondary BSIs from CLABSIs, and potential imprecision in identifying CLABSIs. Thus, monitoring BBSIs may be a complementary strategy to monitor the influence of CLABSI-prevention strategies over time. We established a CLABSI-prevention protocol at our children's hospital to reduce both community- and health care-onset CLABSIs, and found that CLABSI rates significantly declined from 10.03-3.00 CLABSIs per 1,000 CVL-days.[9] CLABSI prevention efforts have continued, but the influence on BBSIs has not been assessed. Thus, the aims of the current study were to describe the epidemiology of BBSIs (hospital and community acquired) over time, including the incidence and pathogens associated with BBSIs, and to assess potential risk factors for BBSIs, including the timing after allo-HCT. We hypothesize that BBSIs have continued to decline at our institution since 2010 associated with maintenance of CLABSI prevention bundles.

METHODS

Study design and patient population

We performed a retrospective cohort study among pediatric recipients of allo-HCT to assess potential changes in BBSI rates from April 2004-October 2012. Conditioning regimens were as previously published.[5] In brief, the myeloablative conditioning regimen consisted of total body irradiation (TBI-12 Gray) + 1-2 high-dose alkalytors or busulfan + high-dose alkalytor. Myeloablative but reduced-toxicity regimens consisted of fludarabine + single high-dose alkalytor busulfan or cyclophosphamide. Reduced-intensity regimens consisted of fludarabine + half-dose busulfan or fludarabine + cyclophosphamide or melphalan.[12,13] Immunotherapy with conditioning regimens consisted of either alemtuzumab (anti-CD52 monoclonal antibody) or rabbit antithymocyte globulin. The institutional review board of our institution approved this study with a waiver of informed consent.

A description of our CLABSI bundle was previously published by our team.[9] In brief, CLABSI standardized procedures for dressing changes (including frequency, method of skin disinfection, and type of dressing) and for obtaining blood from the CVL (including flushing and cap changes). The CLABSI team educated the inpatient and outpatient nursing staff on the selected maintenance principles and used a mannequin to simulate appropriate practices and to evaluate and document competency. The CLABSI team developed a checklist for these practices and used it to monitor the staff, scoring adherence to the checklist components as well as overall compliance with the maintenance bundle.[9]

Infection prophylaxis

During the study period, patients were hospitalized in protective isolation, defined as single hospital rooms with high-efficiency particulate air filtration systems and positive pressure. Most received sargramostim (granulocyte-macrophage colony stimulating factor) daily from day 0 until the white blood cells reached $\geq 0.3 \times 10^9$/L $\times$ 2 days and then filgrastim (granulocyte colony stimulating factor) was started until an absolute neutrophil count of $\geq 2.5 \times 10^9$/L was achieved for 3 days.[14] Viral prophylaxis was provided as previously described.[15] As we recently described,[5] patients did not receive prophylactic antibacterial agents unless febrile, in which case piperacillin-tazobactam was started initially. Additional agents were added in a stepwise fashion (vancomycin and antifungal therapy) if patients were persistently febrile without a source. Patients with positive blood cultures were treated for a minimum of 10-14 days and febrile nonneutropenic patients with negative cultures were treated for 48-72 hours. Febrile neutropenic patients received early post-allo–HCT antibiotics until achievement of neutrophil engraftment.[5] The antibacterial coverage (empiric and treatment) has been consistent at our center for the past 15 years. Initially, fungal prophylaxis consisted of intravenous liposomal amphotericin B (3 mg/kg/d) starting on day 0 through day 100. Since 2007, most patients have received intravenous liposomal amphotericin B (1.5 mg/kg) until day 45 and then micafungin (1-1.5 mg/kg) until day 100 for fungal infection prophylaxis.

Blood cultures and antimicrobial susceptibility

All positive bacterial blood cultures from day 0-365 were reviewed. Per the treating clinician, blood cultures were obtained at onset of fever (>38°C) or if a patient showed signs of clinical decompensation; for example, hypotension, respiratory distress, or altered mental status. The same bacterial species isolated > 7 days apart was considered 2 BBSIs. Antibiotic susceptibilities were performed using the most current Clinical and Laboratory Standards Institute guidance. Bacteria reported as intermediate were considered resistant.[16]

Study definitions

The diagnosis and grades of acute graft-versus-host disease were as defined by Glucksberg et al:[17]

- Absolute neutrophil count: The product of the white blood cell count (cells per liter) and the fraction of polymorphonuclear cells and bands.
- Neutrophil engraftment: Achievement of absolute neutrophil count > 0.5×10^9/L for 3 consecutive days following allo-HCT.

Oral mucositis was graded according to the World Health Organization classification by the bone marrow transplant physicians.[18,19] Oral mucositis was graded daily.

The case mix index is a relative value assigned to a disease-related group of patients in a hospital setting reflecting similar condition,[20] morbidity, and need for resources (https://www.cms.gov).