Effect of cefepime prophylaxis on bacterial bloodstream infections in neutropenic patients with acute myelogenous leukemia

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BACKGROUND

- Bacteremia is a major cause of morbidity and mortality among children with acute myelogenous leukemia (AML)[1,2]
- Data evaluating the utility of bacterial prophylaxis in pediatric AML patients are limited[3-5]
- The benefit of bacterial prophylaxis in AML patients must be weighed against the risks of broad-spectrum antimicrobial use, such as *C. difficile* infection (CDI) and emergence of antimicrobial resistance
- Children's Health (CH) implemented routine use of cefepime 50 mg/kg (max 2000 mg) IV q12h as bacterial prophylaxis for AML patients undergoing induction or intensification chemotherapy during periods of functional neutropenia or neutropenia in April 2014

OBJECTIVES

- **Primary:** Compare frequency of documented bloodstream infections (BSIs) before (PRE; Jan 2010 to Mar 2014) and after (POST; Apr 2014 to Dec 2018) implementation of routine bacterial prophylaxis
- **Secondary**: Compare total antibiotic utilization, frequency of antibiotic resistance, and occurrence of neutropenia-associated *C. difficile* infection

METHODS

- Observational, retrospective cohort study
- Inclusion: Patients < 21 years of age with AML admitted at CH from January 2010 through December 2018 with absolute neutrophil count (ANC) <500 cells/μL; days between initiation of cytotoxic chemotherapy and achieving this ANC were also counted as periods of functional neutropenia
- Exclusion: Patients with mixed phenotype acute leukemia
- BSIs with multiple isolated pathogens were counted as single episodes

RESULTS

Table 1. Baseline Demographics

	PRE (n=38)	POST (n=52)
Gender, male, n (%)	17 (45)	26 (50)
Age (y) at AML diagnosis, median (range)	4.5 (0.16-17)	10 (0.33-17)
Race, n (%)		
White	25 (66)	34 (65)
Black or African American	4 (10)	13 (25)
Asian	3 (8)	2 (4)
Hispanic/Latino	5 (13)	0
American Indian/Alaska Native	0	1 (2)
Unknown/not reported	1 (3)	2 (4)
Ethnicity, Hispanic, n (%)	13 (34)	16 (31)

Table 2. Outcomes

	PRE (n=38)	POST (n=52)	p-value
Neutropenia days, median (IQR)	88.5 (66-117.8)	80.5 (62.25-105.8)	0.39
Neutropenia episodes, median (IQR)	4 (3-4)	3 (2-4)	0.02
Febrile neutropenia episodes, median (IQR)	3 (2-4)	1 (1-2)	<0.0001
Neutropenia episodes with BSI, median (IQR)	1 (1-2)	0 (0-0)	<0.0001
BSI / 1000 neutropenia days†	15.5	2.8	<0.0001
Antibiotic days / 1000 neutropenia days	760	970	<0.0001
Patients with CDI while neutropenic, n (%) ‡	3 (8)	10 (19)	0.22

†Incidence rate ratio 0.18, 95% CI 0.09-0.33; ‡OR 2.78, 95% CI 0.69-9.90

Figure 1. Isolated bacterial pathogens in neutropenia-associated BSIs

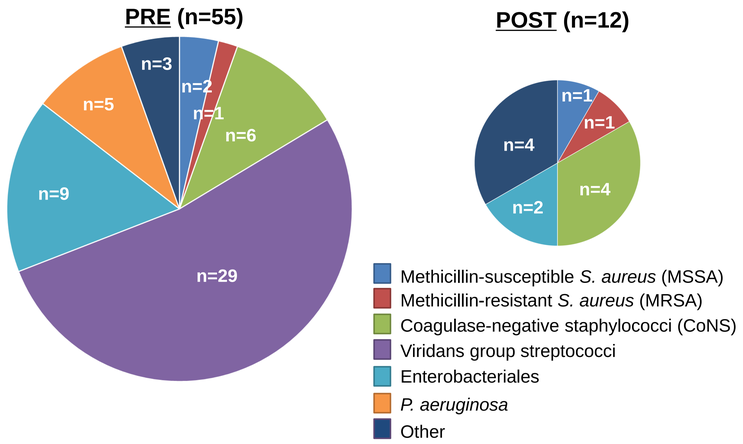

Table 3. Cefepime susceptibility among isolated bacterial BSI pathogens

Isolated pathogen	PRE		POST	
	Total isolated	Cefepime S, n (%)	Total isolated	Cefepime S, n (%)
Methicillin-susceptible *S. aureus* (MSSA)	2	2 (100)	1	1 (100)
Methicillin-resistant *S. aureus* (MRSA)	1	NA	1	NA
Coagulase-negative staphylococci (CoNS)	6	0	4	1 (25)
Viridans group streptococci	29	27 (93)	0	--
Enterobacteriales	9	7 (78)	2	1 (50)
Escherichia coli	1	0	2	1 (50)
Klebsiella pneumoniae	6	5 (83)	0	--
Enterobacter spp.	1	1 (100)	0	--
Citrobacter spp.	1	1 (100)	0	--
P. aeruginosa	5	5 (100)	0	--
Other				
Rothia spp.	1	1 (100)	2	2 (100)
Granulicatella adiacens	0	--	1	0
Group G streptococci	1	1 (100)	0	--
Clostridium tertium	1	1 (100)	1	1 (100)

Cefepime S=cefepime susceptible; NA=not applicable due to inherent resistance

DISCUSSION/CONCLUSIONS

- Universal cefepime prophylaxis for children with AML and disease- or chemotherapy-induced neutropenia was associated with a significant reduction in frequency of febrile neutropenia and incidence of neutropenia-associated BSIs
- Limitations of this study include its retrospective and observational design and small patient numbers; whether findings can be extended to patients with other types of malignancies is also unknown
- Antimicrobial susceptibility of bacterial BSI pathogens in the POST group suggests that universal cefepime prophylaxis did not substantially increase the frequency of cefepime-resistant Gram-negative organisms
- Routine bacterial prophylaxis did not significantly increase the frequency of *C. difficile* infection

REFERENCES:
1. Ammann RA, Laws HJ, Schrey D, et al. Bloodstream infection in paediatric cancer centres – leukemia and relapsed malignancies are independent risk factors. *Eur J Pediatr*. 2015;174(5):675-686.
2. Sung L, Buxton A, Gamis A, et al. Life-threatening and fatal infections in children with acute myeloid leukemia: a report from the Children's Oncology Group. *J Pediatr Hematol Oncol.* 2012;34(1):e30-e35.
3. Wolf J, Tang L, Flynn PM, et al. Levofloxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia. *Clin Infect Dis.* 2017;65(11):1790-1798.
4. Inaba H, Gaur AG, Cao X et al. Feasibility, efficacy and adverse effects of outpatient antibacterial prophylaxis in children with acute myeloid leukemia. *Cancer*. 2014;120(13):1985-1992.
5. Alexander S, Fisher BT, Gaur AH et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation. *JAMA.* 2018;320(10):995-1004.

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