The Impact of an Empiric Neutropenic Fever Practice Guideline on Vancomycin-resistant *Enterococcus* Rates in Pediatric Oncology Patients

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INTRODUCTION

Febrile neutropenia is associated with increased risk of mortality in oncology patients. Institutions rely on hospital-specific practice guidelines for empiric antibiotic recommendations. There are limited data regarding the impact of stewardship guidelines on the development of antimicrobial resistance in pediatric oncology patients.

Although studies in adults have shown no survival benefit with upfront early vancomycin initiation, at Boston Children's Hospital (BCH) prior to 2012, a few cases of serious *Bacillus* species infections led to widespread and prolonged empiric vancomycin use.

In 2012 the neutropenic fever practice guideline was revised in efforts to curb unnecessary vancomycin exposure.

OBJECTIVE

To evaluate the impact of an empiric neutropenic fever practice guideline on vancomycin utilization and vancomycin-resistant *Enterococcus* (VRE) rates in a pediatric oncology population.

MATERIALS & METHODS

In 2012, BCH adopted a novel approach to empiric antibiotic management for febrile neutropenia:

	2008-2012	2012-present
Risk Stratification[1]	None	Based on clinical criteria
Anti-pseudomonal agent	ceftazidime	cefepime
Additional abdominal coverage	Switch to piperacillin-tazobactam + gentamicin	Add metronidazole
Vancomycin initiation criteria	Clinical criteria[2]	All high risk patients x 48 hours
Antibiotic discontinuation	ANC > 500	ANC > 200
Hospital discharge	ANC > 500	APC > 100 (Standard risk)

1 High Risk Patients include those with sepsis, typhlitis, who are on intensely myelosuppressive chemotherapy regimens, or who have AML or Down Syndrome
2 SSTI, recent high dose cytarabine, MRSA colonization, suspected infection with Bacillus spp, shock

Study Design

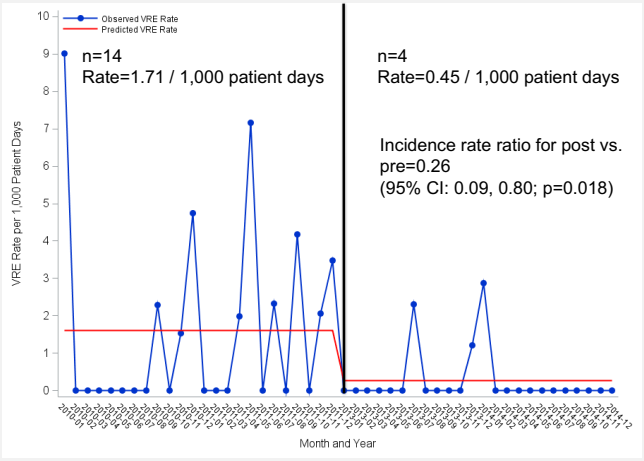
- Retrospective, quasi-experimental study, using interrupted time series analysis.
- All pediatric oncology patients ≤ 18 years admitted to BCH between 2008 – 2016 with fever (T >38.5x1, >38.0 x2) and neutropenia (ANC ≤ 500 /mm^3) were included.
- Admissions with antibiotic receipt or positive microbiologic data were recorded.
- Segmented Poisson regression was created to compare VRE rates between pre- and post-intervention periods.

RESULTS

Characteristic	n (%) or Median (Q1, Q3) Pre-(2010-2011)	Post (2013-2014)	P-value
Patients	N = 185	N = 188	
Age (years) at 1st FN episode	7.0 (3.0, 12.4)	6.78 (3.5, 12.7)	0.69
Female gender	89 (48%)	80 (43%)	0.30
Race			0.03
White	125 (68%)	118 (63%)	
Black / African American	12 (6%)	9 (5%)	
Asian	10 (5%)	10 (5%)	
Other	9 (5%)	28 (15%)	
Unknown	29 (16%)	23 (12%)	
Underlying oncologic diagnosis			0.04
Acute lymphoblastic leukemia (ALL)	74 (40%)	66 (35%)	
Acute myelogenous leukemia (AML)	10 (5%)	19 (10%)	
Solid Tumor	74 (40%)	89 (47%)	
Hodgkin's Lymphoma	5 (3%)	4 (2%)	
Non-Hodgkin's Lymphoma (NHL)	8 (4%)	7 (4%)	
Acute Promyelocytic Leukemia (APML)	6 (3%)	0 (0%)	
Other	8 (4%)	3 (2%)	
Admissions per Patient	3 (2, 6)	3 (2, 6)	0.86
FN Episodes per Patient	2 (1, 3)	2 (1, 3)	0.49

Characteristic	n (%) or Median (Q1, Q3) Pre-(2010-2011)	Post-(2013-2014)	P-value
Admissions	N=765	N=830	
Length of Stay (d)	4 (3, 9)	4 (2, 8)	0.08
FN Episode during Admission	382 (50%)	385 (46%)	0.16
FN Episodes	N=409	N=417	
Episode Length (d)	6 (4, 10)	5 (4, 9)	0.04
Admitting Location			0.17
Oncology floor	378 (93%)	389 (93%)	
ICU or ICP	30 (7%)	28 (7%)	
Risk Classification			0.58
Standard	207 (51%)	219 (53%)	
High	202 (49%)	198 (47%)	
Sepsis	27 (13%)	23 (12%)	
Typhlitis	2 (1%)	5 (3%)	
ALL (all phases but continuation)	132 (65%)	120 (61%)	
AML (all phases but maintenance)	33 (16%)	42 (21%)	
Relapsed AML, ALL	14 (7%)	37 (19%)	
Down Syndrome	1 (<1%)	7 (4%)	
Advanced stage NHL, recurrent NHL or Hodgkin's disease with intensively myelosuppresive chemo	26 (13%)	20 (10%)	

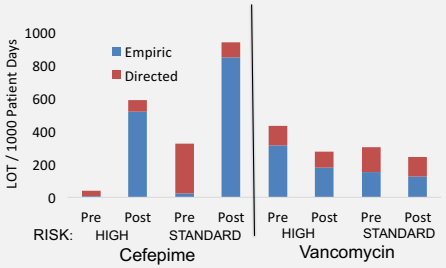
VRE Rates



RESULTS

Characteristic	Pre-(2010-2011)	Post-(2013-2014)
Infection during an FN Episode		
No Infection	249 (61%)	293 (70%)
Infection	160 (39%)	124 (30%)
Clinically Suspected	79 (49%)	39 (31%)
Microbiologically Documented	66 (41%)	66 (53%)
30 Day Mortality	8 (4%)	5 (3%)

Antimicrobial Utilization



- Overall antimicrobial utilization decreased in high risk patients from 2283 to 1872 DOT/1000 episode days.
- While more high risk patients received vancomycin post-intervention (127, 64%) compared to pre-intervention (88, 44%), the total duration of empiric vancomycin use decreased from a median 6 days (range 4-12) to 3 days (range 3-4).

CONCLUSIONS

Although the proportion of patients receiving empiric vancomycin in the post-intervention period was higher, total duration of vancomycin therapy was decreased.

Implementation of a FN guideline limiting vancomycin exposure was associated with a decreased incidence of VRE among pediatric oncology patients.

Antimicrobial stewardship interventions are feasible in immunocompromised patients and can impact antibiotic resistance.

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