Implementation of a Pragmatic Biomarker-Driven Algorithm to Guide Antibiotic Use in the Pediatric Intensive Care Unit: The Optimizing Antibiotic Strategies in Sepsis (OASIS) II Study

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Background

- Antibiotic overuse in the pediatric intensive care unit (PICU) is common. Reliable approaches are needed to promote safe antibiotic discontinuation.
- In prior work we developed a biomarker-based algorithm that identified children with suspected sepsis at low risk of bacterial infection if they had a CRP < 4 mg/dL and procalcitonin < 1 ng/mL at SIRS onset, no evidence of focal infection on exam, and negative cultures at 48 hours.
- We evaluated the effectiveness of this algorithm to reduce broad-spectrum antibiotic use in the PICU.

Objectives

- To assess the effect of a biomarker-based algorithm on broad-spectrum antibiotic prescribing in the PICU.

Methods

Study design: Retrospective pre/post study design. Antibiotics were given per usual practice during the non-intervention period T1 (Aug 2012 – May 2015). During intervention period T2 (June 2015 – May 2016), PICU clinicians were encouraged, but not required, to stop antibiotics in "low-risk" patients: CRP <4 mg/dL and procalcitonin (PCT) <1 ng/mL at SIRS onset (day 0) and no pathogen or focal signs of bacterial infection identified by day 2. Weekly emails were sent to PICU clinicians as reminders of the algorithm. Antimicrobial stewardship program practitioners used their standard evaluation processes for antibiotic approvals in both T1 and T2.

Primary outcome(s): Broad-spectrum length of therapy (LOT) and days of therapy (DOT) on days 3-9 following SIRS onset.

Study population: Children <=18 years of age admitted to the PICU with new onset SIRS who had blood cultures drawn and started on broad spectrum IV antibiotics.

Exclusion criteria: ANC< 500 cells/uL, HSCT or SOT, DNR order, evaluation for infection started at another hospital, infection identified prior to SIRS onset, admitted to the PICU <3 days (i.e. decision to stop/continue antibiotics made outside of the PICU).

Study definitions: Infection was identified on Day 0-2 using modified NHSN criteria; equivocal cases were adjudicated by 3 study members (KD, MR and SC). Day 0 defined as day of SIRS onset.

Statistical analysis: Time series analyses adjusting for significant covariates and confounders compared LOT from T1 to T2 in patients with no identified bacterial infection. We also calculated the incidence rate ratio (IRR) of LOT and DOT in the subset of patients who met our low-risk criteria.

Results

Table 1. Patient and clinical characteristics of the study population.

Characteristic	Period T1 (n=507, 71.1%)	Period T2 (n=206, 28.9%)	p-value
Infection, n (%)			
Yes	174 (34.3)	82 (39.8)	0.17
Age in years, median, (IQR)	4.6 (1.4, 12.9)	4.0 (1.6, 12.7)	0.98
Gender, n (%)			
Female	243 (47.9)	87 (42.2)	0.17
Race, n (%)			
Asian	25 (4.9)	9 (4.4)	
Black	189 (37.3)	60 (29.1)	0.17
White	184 (36.3)	90 (43.7)	
Other/Unknown	109 (21.5)	47 (22.8)	
Hispanic Ethnicity, n (%)	79 (15.6)	26 (12.6)	0.48
PELOD 2 score median, (IQR)	6 (4, 9)	6 (4, 9)	0.62
Any Complex Chronic Condition, n (%)	414 (81.7)	167 (81.1)	0.85
Malignancy	38 (7.5)	17 (8.3)	0.73
Positive viral panel, n (%)	196 (38.7)	90 (43.7)	0.21
Surgery, n (%)	46 (9.1)	27 (13.1)	0.11
Other Diagnostic Procedure, n (%)	23 (4.5)	12 (5.8)	0.47

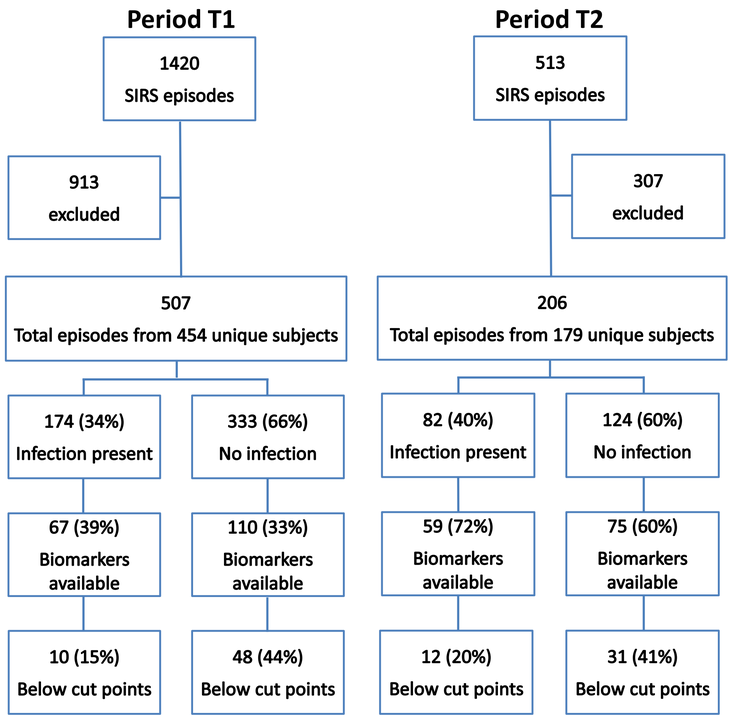

Figure 1. Flow diagram of entry into the OASIS II study.

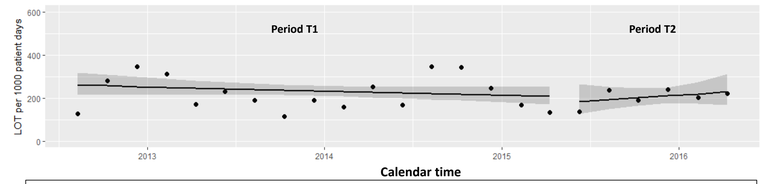

Figure 2. Length of therapy among patients without infections per two-month period. Modified Poisson regression analysis with adjustment for surgery, renal comorbidity, and biomarker values below cut points: Period T2 had a relative risk of 0.88 (95% CI: 0.69-1.12) compared to T1.

Table 2: Broad-spectrum antibiotic prescribing in relation to biomarker cut points among patients without infections.

	Period T1 LOT per 1000 patient-days	Period T2 LOT per 1000 patient-days	IRR (95% CI)
Above either cut point	241	273	1.13 (0.80, 1.60)
Below both cut points	197	104	**0.53 (0.30, 0.93)**
Biomarkers unavailable	239	215	0.90 (0.67, 1.21)
	DOT per 1000 patient days	**DOT per 1000 patient-days**	**IRR (95% CI)**
Above either cut point	371	450	1.21 (0.92, 1.59)
Below both cut points	301	130	**0.43 (0.26, 0.71)**
Biomarkers unavailable	326	384	0.84 (0.66, 1.07)

Key Results

- Broad-spectrum antibiotic prescribing did not change overall in patients without infections following implementation of an algorithm designed to identify patients at low-risk for bacterial infection in our PICU.
- Despite increased measurement of biomarkers during Period T2, few patients without identified bacterial infections (25%, n=31/124) met our criteria for low-risk (CRP < 4 mg/dL and PCT < 1 ng/mL).
- Broad-spectrum LOT and DOT significantly decreased among the subset of patients without infections who met our low-risk criteria.

Conclusions

- Biomarker-based algorithms can help to reduce unnecessary antibiotic use in low-risk patients.
- Biomarkers (CRP and PCT) are low in a minority of patients with SIRS in the PICU, even in the absence of identified bacterial infections.
- Future studies need to evaluate the cost effectiveness of biomarker-based algorithms to reduce broad-spectrum antibiotic use.

Acknowledgments

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