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Research Brief

Association of a blood culture utilization intervention on antibiotic use in a pediatric intensive care unit

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Blood cultures are essential for the evaluation of sepsis. However, they may sometimes be obtained inappropriately, leading to high false-positive rates, largely due to contamination.[1] As a quality improvement project, clinician decision-support tools for evaluating patients with fever or signs and symptoms of sepsis were implemented in April 2014 in our pediatric intensive care unit (PICU). This initiative resulted in a 46% decrease in blood culture obtainment[2] and has been replicated in other institutions.[3] It is important to evaluate antibiotic use as a balancing measure because a reduction in blood cultures could lead to an increase in antibiotic treatment days if clinicians continued empiric treatment in scenarios when blood culture results were not available. The objective of this study was to evaluate whether antibiotic use in the PICU changed in association with a reduction in blood culture utilization.

Methods

We conducted a retrospective observational study examining antibiotics administered to children admitted to the PICU at The Johns Hopkins Hospital during the 12 months before and during the implementation of a locally developed blood culture clinical practice guideline.[2] The antibiotic data reflect medication administered to patients while admitted to the PICU. Broad-spectrum antibiotics (BSA) commonly administered for the empiric treatment of sepsis were evaluated: cefepime, piperacillin-tazobactam, meropenem, imipenem-cilastatin, and vancomycin. The intervention primarily targeted hospital-onset events, for which ceftriaxone or fluoroquinolones were not typically prescribed. Antibiotic use was evaluated as (1) monthly antibiotic days of therapy (DOT) per 1,000 patient days (PD),[4] and (2) monthly number of antibiotic initiations per 1,000 PD. Initiations were defined as the start of a BSA with at least 48 hours elapsed from the last time the patient received a BSA.

The rate of antibiotic DOT per 1,000 PD and antibiotic initiations per 1,000 PD before and after the intervention were compared using a standard incident rate ratio (IRR) and by an interrupted time-series (ITS) model using log-transformed monthly antibiotic DOT and antibiotic initiations.[5] An existing preapproval antibiotic stewardship program restricted all the antibiotics evaluated, and there were no notable changes in antibiotic stewardship practices during the study period. The Johns Hopkins Institutional Review Board acknowledged this evaluation as part of a quality improvement project.

Results

In the year preceding implementation of the guideline, there were 11,196 PD, 6,255 antibiotic DOT and 701 initiations. The proportion of total antibiotic DOT contributed by each medication were as follows: cefepime (36%), vancomycin (31%), piperacillin-tazobactam (23%), meropenem (10%), and imipenem-cilastatin (0.6%). The distributions of antibiotics were similar in the preimplementation and postimplementation years. Compared to the preimplementation year, there were no changes in the overall antibiotic DOT per 1,000 PD (559 vs 556; IRR, 0.99; 95% CI, 0.96–1.03). In the ITS analysis (Fig. 1, panel A), the monthly rate of antibiotic DOT per 1,000 PD during the year preceding (IRR, 1.00; 95% CI, 0.98–1.02) and the year during implementation (IRR, 1.00; 95% CI, 0.97–1.02) were similar (P = .90).

No changes occurred in overall antibiotic initiations per 1,000 PD (63 vs 62; IRR, 0.98; 95% CI, 0.89–1.10) in the postimplementation year. Similarly, in the ITS analysis (Fig. 1, panel B), there was no change in the monthly rate of initiations during the year prior (IRR, 1.00; 95% CI, 0.99–1.02) or the year during implementation (IRR, 1.00; 95% CI, 0.98–1.02; P = .66).

Discussion

We examined broad-spectrum antibiotic use in the setting of a quality improvement project to optimize blood culture use. Despite a 46% decline in blood cultures following program implementation, there was no change in antibiotic use. A priori, there was concern that some clinicians who complied with the guidelines may have feared "missing" bacteremia and thus increased empiric antibiotic prescribing in scenarios when blood cultures were not obtained. Similarly, there was concern that clinicians would initiate empiric antibiotic therapy and, in the absence of blood culture results to follow, that they would not discontinue therapy after 48–72 hours. Our findings indicate that there was not a significant

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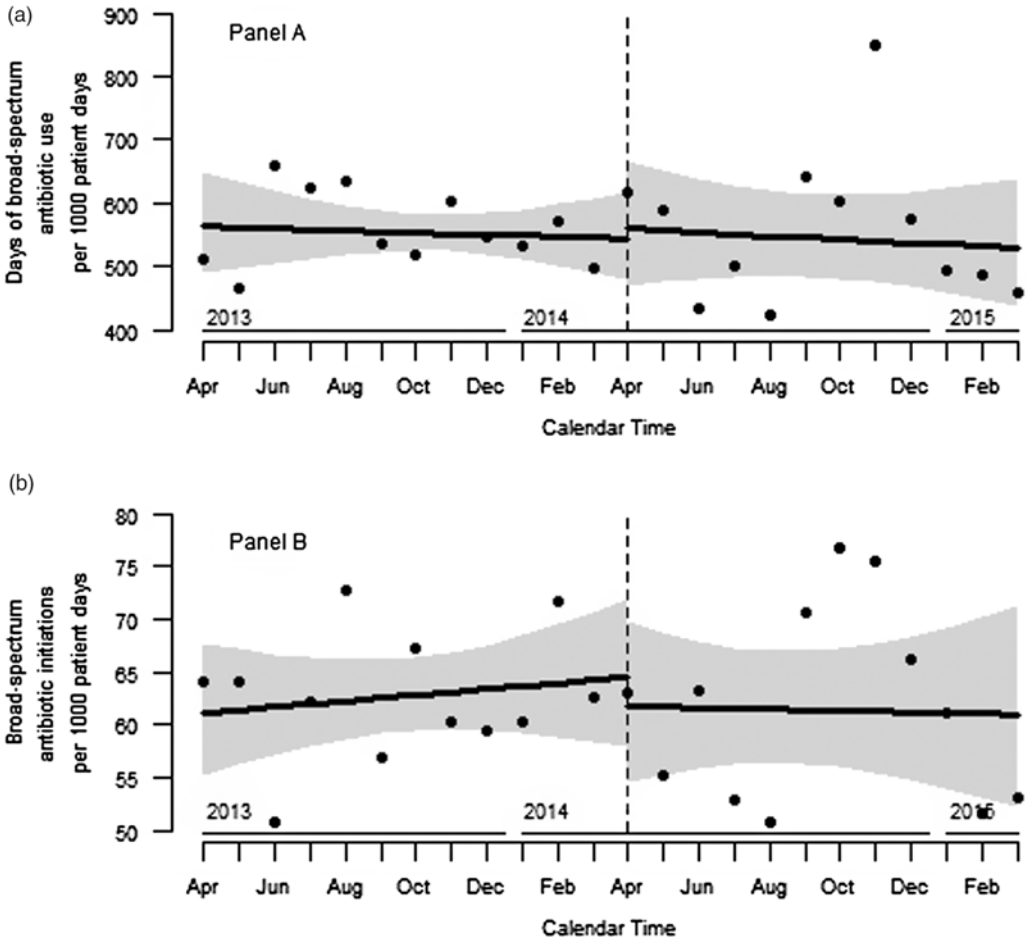

Fig. 1. Monthly broad-spectrum antibiotic days of therapy (panel A) and broad-spectrum antibiotic initiations (panel B) per 1,000 patient days in the pediatric intensive care unit. Antibiotic use depicted 12 months before and after implementation of a quality improvement initiative in April 2014 to optimize the use of blood cultures in the pediatric intensive care unit.

increase in antibiotic DOT with the reduction in blood culture obtainment.

Prior diagnostic stewardship interventions to improve urine culture testing have demonstrated a reduction in the frequency of urine cultures,[6,7] and reduced urine culture utilization was associated with reduced antibiotic use.[8,9] In contrast to these findings, we did not observe a decline in antibiotic DOT or initiations associated with a reduction in blood culture utilization. The reasons for this are unclear; however, it is possible that the reduction in blood cultures was primarily driven by decreasing the number of cultures obtained from each patient rather than the number of patients from whom blood cultures were obtained. For example, obtaining only a peripheral culture instead of peripheral and central-line cultures from the same patient, or obtaining initial blood cultures but not daily follow-up cultures could have contributed to the findings.

This study has several limitations. First, we used aggregate antibiotic data. As a result, we were unable to adjudicate indication or appropriateness of antibiotic treatment for individual patients. Perhaps there was a reduction of antibiotic use for the indication of ruling out bacteremia; however, this was coupled with an increase in the use of antibiotics for another indication leading to an overall equal rate of use. Alternatively, we may not have had the power to detect a small reduction in antibiotic use in this population given the variability in monthly use. Nevertheless, antibiotic use related to changes in blood culture practice remains an important balancing measure to evaluate. Additional larger, multicenter analyses are needed to better understand the association of improved blood culture use and antibiotic prescribing.

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High frequency of *Clostridium difficile* infections in Brazil: Results from a multicenter point-prevalence study

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Clostridium difficile is an important pathogen in healthcare facilities. Colonized or infected patients and spore-contaminated environments have been identified as sources for *C. difficile* infection (CDI). Patients generally develop CDI after exposure to broad-spectrum antibiotics.[1,2]

The incidence of CDI in Latin America is likely to be underestimated due to low clinical suspicion as well as limited availability (and low sensitivity) of diagnostic tools.[1,3] Here we report the results of a large survey conducted to determine the frequency of diarrhea and CDI in hospitalized patients in Brazil.

Methods

This point-prevalence study involved adult patients (aged ≥18 years) with diarrhea admitted to 8 university hospitals in Brazil. Hospitals were located in 3 Brazilian state capitals: São Paulo, Curitiba, and Porto Alegre.

The study was conducted on 2 distinct dates: March 8, 2017 (summer), and July 12, 2017 (winter). Clinical and demographic data were collected for each patient, including date of onset of current episode of diarrhea, underlying diseases, and antimicrobial use (up to 30 days prior to hospitalization). Patients were excluded if they had been hospitalized in emergency rooms, pediatric wards, and dialysis units. The study was approved by the local ethics committees of the participating hospitals.

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Stool samples were obtained from each enrolled patient. Samples were refrigerated at 4°C and sent to the reference laboratory within 24 hours (ie, the Molecular Biology Laboratory at Santa Casa de Misericordia de Porto Alegre). Only 1 fecal sample per patient was collected.

Culture for *C. difficile* was performed on fecal samples as follows. Samples were treated with absolute alcohol (1:1 proportion) at room temperature for 1 hour and subcultured on CM0601 *C. difficile* agar (Oxoid, Ontario, Canada), enriched with 7% blood horse, D-cycloserine and cefoxitin. The culture was incubated for 48 hours using an anaerobic generator (Genbox, bioMérieux SA, Marcy l'Etaile, France). Suspected colonies were identified at the species level by matrix-assisted laser desorption/ionization mass spectroscopy (MALDI-TOF/MS, Brucker Daltonics, Germany).

All fecal samples were investigated for the presence of toxin B (*tcdB*), binary toxin (*cdtA*), and deletion of 117 nucleotides on the *tcdC* gene using a commercial real-time polymerase chain reaction (PCR) kit (Xpert *C. difficile* test, Cepheid, Sunnyvale, CA) according to the manufacturer's recommendations.[4]

All patients with diarrhea and positive results for real-time PCR or culture plus MALDI-TOF were considered confirmed CDI cases. Statistical analyses were performed using JMP version 13.0.0 software (SAS Institute, Cary, NC).

Results

In the 2 days of study, we screened 6,374 patients and 153 presented with diarrhea. The point prevalence of diarrhea was 24.0 per 1,000 patient days (95% confidence interval [CI], 20.5–28.1).

Anaerobic culture was positive for 19 patients, 17 of whom had *C. difficile* confirmed by MALDI-TOF-MS. GeneXpert was

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