Yield of Repeat Blood Cultures beyond 48 Hours after Negative Initial Cultures in Patients Hospitalized on a Pediatric Hematology/Oncology Unit

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BACKGROUND

• Inpatient admissions are both common and costly for pediatric oncology patients.[1, 2]

• With mortality rates now as low as 0.6 - 3.0% in pediatric patients hospitalized for febrile neutropenia,[3-5] identifying patients that may safely have fewer blood cultures obtained and have shorter hospital admissions is appealing from both patient quality of life and cost-effectiveness perspectives.

• Pediatric-specific recommendations for febrile neutropenia are limited, with the International Pediatric Fever and Neutropenia Guideline Panel listing the "timing and necessity of repeated blood cultures for persistent fever" as a research gap in the field.[6]

• No consensus exists for the management of non-neutropenic fever.[7]

• It is common at our institution, and others,[8, 9] to obtain repeat blood cultures beyond 48 hours despite negative initial cultures in persistently-febrile hospitalized pediatric hematology/oncology patients, often with low yield and high cost.[8, 9]

• No studies have looked at blood culture utilization and the yield of repeat blood cultures after negative initial cultures in all hospitalized patients on a pediatric hematology/oncology unit, regardless of neutropenia status.

• The present study seeks to determine the yield of repeat blood cultures after 48 hours of negative initial cultures in hospitalized pediatric patients with cancer and to demonstrate the safety and cost-effectiveness of reducing the number of blood cultures obtained beyond 48 hours of initial presentation when all prior cultures have been negative.

MATERIALS & METHODS

• MedMined Incorporated Data Mining Surveillance database was utilized to review all blood cultures obtained on the pediatric hematology/oncology unit at Riley Hospital for Children between January 2015 and February 2021.

• Patients that had received a stem cell transplant, required a pediatric intensive care unit admission during the current hospitalization, or had bacteremia identified on a culture drawn within 48 hours of presentation were excluded.

• Blood cultures were followed for 15 days after presentation where day 0 was defined as the day in which the initial blood culture was obtained.

• Contaminants beyond 48 hours of negative initial cultures were excluded.

• All new positive blood cultures more than 48 hours after negative initial cultures prompted retrospective review of electronic medical records.

• Definitions:

  – Fever: single temperature of ≥ 38.0C [8, 9, 10]

  – Prolonged fever: lasting for at least 96 hours [10, 11]

  – Recurrent fever: new fever after a ≥ 72-hour defervescence period [11]

  – Neutropenia: ANC < 500/mm^3 [8, 10]

  – Hemodynamically unstable: vital sign or clinical exam changes, or other signs of septic shock that required fluid resuscitation or pressors [12, 13]

  – Blood culture sets: both peripheral and central blood cultures on day 0 and only central cultures on following days [14]

• Cost Analysis

  – Indiana University Health total cost for "routine venipuncture" and "blood culture" Current Procedural Terminology codes is $65.

  – Previously reported cost of pediatric, cancer-related, neutropenia or fever without a known source hospitalization is $3,051/day. [15]

RESULTS

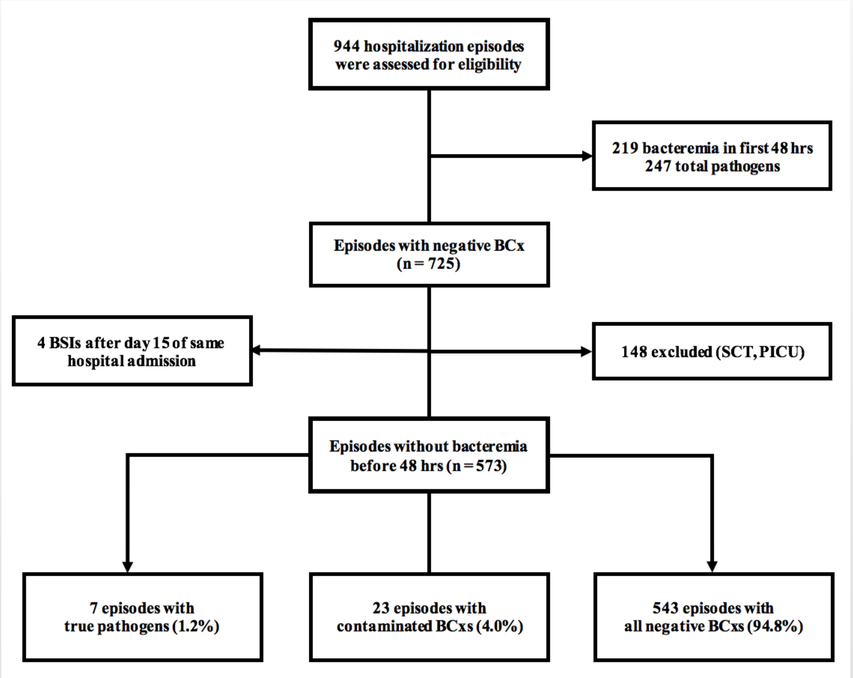
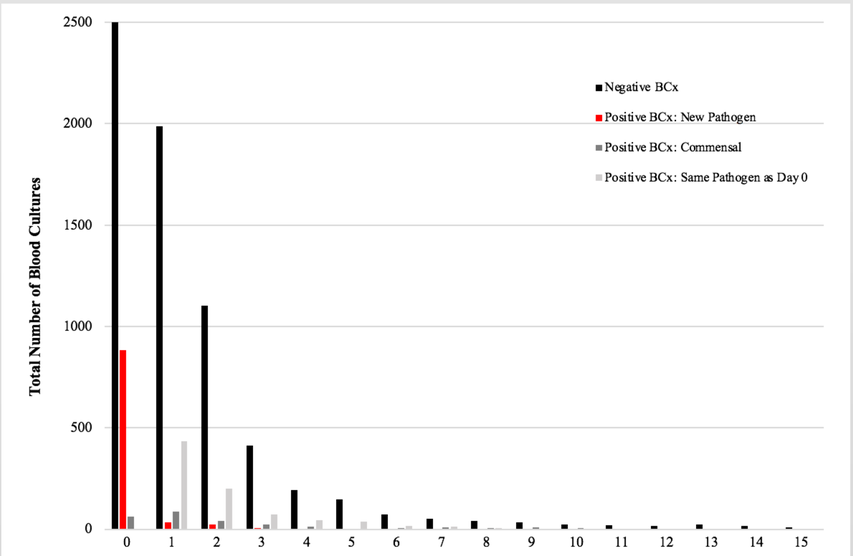


Figure 1. Study flowchart including the number of hospitalization episodes with and without positive blood cultures. BCx: blood culture, BSI: bloodstream infection, SCT: stem cell transplant, PICU: pediatric intensive care unit.



	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Negative BCx	2501	1989	1103	412	193	147	72	52	40	33	25	21	18	23	15	8
New Pathogen	882	34	25	7	3	2	4	3	4	3	4	0	0	4	2	0
Commensal	63	89	40	22	14	4	5	10	6	8	5	0	0	0	0	0
Same Pathogen as Day 0	N/A	435	201	72	44	37	18	12	6	4	0	0	0	0	0	0

Figure 2. Blood culture results by day of hospitalization episode where day 0 is the day that the first blood culture was obtained. "New pathogens" after day 0 represent pathogens cultured on the respective day but not grown on blood culture on day 0, and "new pathogens" beyond 48 hours (day 3) represent pathogens cultured on the respective day but not grown on blood culture before 48 hours (day 0, 1, or 2). BCx: blood culture.

New, true pathogen >48 hr	*Oncological diagnosis*	*Day of hospitalization episode*	*Fever pattern*	*Stable vs. unstable*	*Fever height*	*ANC*	*Abx at time of BCx*	*Action as result of new BCx*	*Additional dx/comment*	*Outcome*
Streptococcus mitis	AML	3	Recurrent	Stable	38.5	100	Cefepime	Added vancomycin	Mucositis	Alive
Bacillus species	ALL	10	Recurrent	Stable	38.6	0	Cefepime	Added vancomycin	Grew x1 day, but considered true	Alive
MRSA	NB	6	Recurrent	Unstable	39.5	0	Cefepime	Added vancomycin	PNA	Alive
E. coli	ALL	4	Prolonged	Unstable	39	100	Piperacillin-tazobactam	No change	Typhlitis	Alive
Candida albicans	AML	9	Recurrent	Unstable	38.7	200	Cefepime	Added micafungin	-	Alive
Staphylococcus epidermidis	RMS	13	Recurrent	Stable	38	1200	No abx	Added vancomycin	CoNS grew for 2 days then cleared	Alive
Enterococcus faecalis	NB	8	Recurrent	Stable	38.5	200	Cefepime	Switched to piperacillin-tazobactam	Diarrhea	Alive

Table 1. Patient and episode characteristics of the seven hospitalization episodes with new, true pathogens, or commensal organisms treated as true pathogens by the primary team, on repeat blood cultures beyond 48 hours when all cultures before 48 hours were negative. ANC: absolute neutrophil count per mm^3; abx: antibiotic, BCx: blood culture, dx: diagnosis, MRSA: methicillin resistant Staphylococcus *aureus*, E. coli: Escherichia *coli*, AML: acute myeloid leukemia, ALL: acute lymphocytic leukemia, NB: neuroblastoma, RMS: rhabdomyosarcoma, PNA: pneumonia, CoNS: coagulase-negative staphylococci.

RESULTS

• Of 573 included hospitalization episodes without bacteremia before 48 hours after presentation, only 1.2% were found to have a new pathogen >48 hours.

• 1,362 blood culture sets were collected beyond 48 hours (days 3 and later) in 792 patient hospitalizations (including the 219 episodes with bacteremia prior to 48 hours and the 573 episodes with all negative cultures before 48 hours)
  – 36 (2.6%) were positive for a new pathogen
  – 74 (5.4%) were contaminant cultures

• Of the seven patient hospitalizations found to have a new pathogen, or commensal organism treated as a pathogen, on a repeat blood culture beyond 48 hours where all cultures within the first 48 hours were negative:
  – New positive cultures were obtained between days 3 and 13
  – Organisms cultured were primarily gram-positive bacteria (71.4%)
  – Fever was recurrent in 6, prolonged in 1
  – Six of the patients were neutropenic
  – Six of the patients required antibiotic changes/additions
  – Two were commensals treated as pathogens

• Of the five hospitalization episodes in which new, true pathogens were found on blood cultures beyond 48 hours:
  – Three patients were hemodynamically unstable
  – Two patients had new clinical changes (mucositis, diarrhea)

• Of the 23 hospitalization episodes with new commensal organisms cultured beyond 48 hours where all cultures within the first 48 hours were negative:
  – The majority (14/23) were identified to be Staph epidermidis
  – Resulted in a total of 102 additional blood cultures being obtained and increased the total length of stay by 69 days

• The 1,133 negative (n=1,059) and contaminated (n=74) blood cultures obtained beyond 48 hours resulted in $73,645 in blood culture charges alone.

• The 23 patient hospitalization episodes in which a new commensal organism was grown on repeat blood culture beyond 48 hours with all previously negative cultures resulted in an increase in cost of $6,630 in repeat blood culture charges alone and a total cost of $210,519 associated with the increased length of stay.

DISCUSSION

• This is the largest study to date of repeat blood cultures after negative initial cultures in hospitalized patients on a pediatric hematology-oncology unit and the first report of the yield of repeat blood cultures after negative initial cultures in all hospitalized children with cancer, regardless of neutropenic status.

• The low yield of repeat blood cultures beyond 48 hours that was observed in this study is comparable to that reported in other recent pediatric studies investigating repeat blood cultures in patients with cancer and febrile neutropenia, even though these studies included all patients with negative cultures on day 1 rather than those with negative initial cultures through 48 hours as in the present study.[4, 8]

• This study adds to the existing body of evidence that repeat blood cultures beyond 48 hours are unnecessary with negative initial cultures in the context of hemodynamically and clinically stable patients.

• Most patients with positive blood cultures beyond 48 hours of negative initial cultures in this study had recurrent, rather than prolonged, fever which is consistent with other studies suggesting that increased duration of time between fevers increases the likelihood of a new pathogen growing on blood cultures.[10]

• There were no hemodynamically stable patients in this study with new, true pathogens on repeat blood cultures when fever recurred <72 hours from prior defervescence, so it is possible that repeat blood cultures are only needed in patients with a new fever after a 72-hour afebrile period, but this hypothesis requires additional studies to verify.

• Although the cost associated with additional blood cultures collected beyond 48 hours in this study was far less than has been previously reported in a similar study,[8] and the estimate of hospital charges for the increased length of stay relies on the assumption that no patient other than those with contaminated, rather than all negative, cultures beyond 48 hours had a prolonged admission, reducing the number of blood cultures obtained unnecessarily beyond 48 hours of negative cultures represents a significant cost savings.

• In conclusion, the yield of repeat blood cultures beyond 48 hours in hospitalized children with cancer with negative initial blood cultures is low, while the associated costs are high. Repeat blood cultures beyond 48 hours after negative initial cultures need not be obtained in febrile patients that are hemodynamically stable and without clinical changes.

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