**Diagnostic yield of initial and consecutive blood cultures in children with cancer and febrile neutropenia**

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**Key words:** blood cultures, diagnostic yield, febrile neutropenia, cancer, children

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**Summary:** In children with cancer and febrile neutropenia, the diagnostic yield of pre-antibiotic blood cultures is significantly higher than post-antibiotic cultures. In the absence of new fever or clinical instability, blood cultures beyond 48 hours of persistent fever have limited value.

**ABSTRACT**

**Background.** The timing and necessity of repeated blood cultures in children with cancer and febrile neutropenia (FN) is unknown. We evaluated the diagnostic yield of blood cultures collected pre- and post-empiric FN antibiotics.

**Methods.** Data collected prospectively from the Australian Predicting Infectious ComplicatioNs in Children with Cancer (PICNICC) study were used. Diagnostic yield was calculated as the number of FN episodes with a true blood stream infection (BSI) detected divided by the number of FN episodes that had a blood culture taken.

**Results.** A BSI was identified in 13% of 858 FN episodes. The diagnostic yield of pre-antibiotic blood cultures was higher than post-antibiotic cultures (12.3% versus 4.4%, p<0.001). Two thirds of the post-antibiotic BSIs were associated with a new episode of fever or clinical instability and only two new BSI were identified after 48 hours of empiric antibiotics and persistent fever. A contaminated blood culture was identified more frequently in post-antibiotic cultures.

**Conclusion.** In the absence of new fever or clinical instability, blood cultures beyond 48 hours of persistent fever have limited yield. Opportunity exists to optimise blood culture collection in this population and reduce the burden of unnecessary tests on patients, healthcare workers and hospitals.

**INTRODUCTION**

In children with cancer and febrile neutropenia (FN), bloodstream infection (BSI) is associated with increased mortality, underscoring the need for appropriate diagnostic investigation and early administration of broad-spectrum antibiotics.[1] Microbiological culture techniques are the current standard for identification of BSIs and, depending on the pathogen, may take up to 48-hours before a result is known. However, the timing and necessity of repeated blood cultures (BCs) for persistent fever in children with cancer and FN have not been robustly evaluated and are an important research gap.[2]

While paediatric FN guidelines recommend that at least two BC sets are collected prior to antibiotics, there is limited evidence to guide the frequency of collection beyond this timepoint.[2] In addition to increased demand upon hospital resources, unnecessary collection of BCs may contribute to iatrogenic anaemia in children or identification of false-positive common commensals (also known as a ‘contaminated BC’) that prompt avoidable antibiotic treatment.[3] The current Infectious Diseases Society of America (IDSA) recommendation is for BCs to be collected for a further two days in the setting of ongoing fever in patients with FN.[4]

Studies examining daily BCs in children with cancer and FN are all retrospective and vary in design and BSI definition, thereby limiting comparison.[5-9] One retrospective study demonstrated a low yield (1%) for BCs drawn after day 3 of neutropenia but the proportion of patients that remained febrile at this time was not reported.[5] A higher yield (11%) has been reported when repeated BCs are collected within the first 3 days of FN in patients that remain febrile, although it is unknown if contaminated BCs were excluded.[6] In children with FN and persistent fever for at least 24 hours the diagnostic yield of repeated BCs is between 1% and 9% in three small retrospective studies.[7-9] No study has specifically compared the yield of post-antibiotic BCs in the first 48 hours compared to beyond 48 hours.

The objectives of this analysis were to: (i) describe the type of bloodstream infections in a current-era paediatric population with FN, and (ii) evaluate the diagnostic yield of BCs collected for initial investigation of FN and after the commencement of empiric antibiotics.

**METHODS**

Data collected prospectively from the Australian Predicting Infectious ComplicatioNs in Children with Cancer (PICNICC) study were used. Eight tertiary paediatric cancer centres in Australia participated, which was open to recruitment between November 2016 and January 2018. Detailed study methods have previously been described.[10] Demographic, clinical and outcome data were collected for consecutive episodes of FN in children (aged <18yrs) with cancer or haematological malignancy. Fever was defined as a single tympanic temperature ≥38ºC and neutropenia as an absolute neutrophil count (ANC) <1000/mm3.Episodes were excluded if FN treatment commenced at a non-participating site, the patient had undergone an allogeneic hematopoietic stem cell transplant (HSCT) within the preceding three months or the episode occurred while in receipt of concurrent intravenous or oral antibiotics (excluding prophylaxis). Children were managed according to local FN guidelines with piperacillin-tazobactam or cefepime used as empiric FN therapy. Fluoroquinolone prophylaxis was not routinely used at any site.

The total number of all BC sets taken prior to empiric FN antibiotics (herein referred to as pre-antibiotic BCs) and the results of these were collected. For BC sets taken after the commencement of empiric FN antibiotics (herein referred to as post-antibiotics BCs), each day that ≥1 BC set was taken were collected rather than the total number of BCs taken.

**Definitions.** A BSI was defined as a recognized pathogen cultured from one or more BCs, or a common commensal cultured from two or more BCs drawn on separate occasions taken within 48 hours.[11] Common commensals were defined according to the National Healthcare Safety Network with the exclusion of bacteria associated with mucosal barrier injury.[12] A suspected ‘contaminated BC’ was defined as identification of a common commensal in one of two or more BCs drawn on separate occasions taken within 48 hours. A BC set was defined as either a single aerobic BC or an aerobic and anaerobic BC taken simultaneously.

A second fever episode was defined as a new fever ≥38ºC after a 48-hour afebrile period and occurring during the same index episode of neutropenia. Clinical instability was defined as severe sepsis or septic shock (as per Goldstein et al) [13] or admission to the intensive care unit for organ support.[11]

**Hospital blood culture policy.** Collection of two sets of BCs, from all lumens of CVAD where relevant, prior to the first dose of antibiotics was recommended practice at all eight study sites. Collection of peripheral BCs was not routinely recommended at any of the study sites.

Daily BCs were routinely recommended for at least the first 72-hours (irrespective of fever occurrence) at four sites and daily while febrile only at the remaining four sites. Two hospitals also recommended collection of a BC prior to the second dose of empiric antibiotic therapy for FN (i.e. prior to second dose of piperacillin-tazobactam). All sites routinely recommended repeat BCs in patients with a positive BC to document clearance or, for common commensal bacteria, confirm or exclude true infection.

**Analysis.** Continuous data were summarised as median and interquartile range. Mann–Whitney U test was used to estimate P-values for continuous data and Fisher’s exact test for categorical data. All tests were 2-tailed, and a P value <0.05 considered statistically significant.

Overall diagnostic yield was calculated as the number of FN episodes with a BSI divided by the number of FN episodes that had a BC taken and was presented separately for pre- and post-antibiotic BCs. For calculation of post antibiotic diagnostic yield, pathogens already identified on pre-antibiotic BCs were not included unless more than 14 days had elapsed since they were last identified. Diagnostic yield of post-antibiotic BCs was also calculated separately for patients who remained febrile and stratified to cultures taken in the first 48 hours and after the first 48 hours. Kaplan-Meier curves were constructed showing proportion of all positive BCs identified per hour of incubation.

**RESULTS**

In total, 858 episodes of FN occurring in 462 patients were included in the study. The median age of patients was 5.8 years (IQR 3.5-10.7 years) and 415 (48%) were female. There were 515 (60%) FN episodes in patients with hematological malignancy and 343 (40%) in patients with a solid tumour. A CVAD was *in situ* in 845episodes (99%).

A BSI was identified as the cause of initial fever in 111 FN episodes (13%). Of these, 108 (97.3%) were identified in pre-antibiotic BCs and 3 (2.7%) were identified in BCs taken within 48-hours of commencing empiric FN antibiotics. A second fever episode during the same period of neutropenia occurred in 150 episodes of which 15 (10%) episodes were associated with a new BSI.

***Type of bloodstream infections***

A total of 149 different pathogens were identified in 130 (15.2%) FN episodes (Table 1). The proportion of pathogens that were gram-negative was significantly higher in pre-antibiotic BCs compared to post-antibiotic BCs (54.5% versus 23.5%, p=0.002), in which gram-positive pathogens predominated. Polymicrobial BSI was identified in 32 (24.6%) FN episodes. The median time from BC draw to initial detection of a BSI with gram-negative or gram-positive bacteria was 19.5 hours (IQR 13.0-25.5 hours) and 17.7 hours (IQR 15.1-21.9 hours), respectively. The proportion of true BSIs identified within 24, 36 and 48 hours incubation was 73%, 89% and 94%, respectively (Figure 1)

Sixty four different common commensal bacteria causing contaminated BCs were identified in 56 FN episodes (27 pre-antibiotics, 37 post-antibiotics). Compared to BCs taken pre antibiotics, a contaminated BC was significantly more likely to occur in BCs that were taken post antibiotics (19% versus 26%, p=0.006). The median time from BC draw to initial detection of commensal bacteria causing a contaminated BC was 34.2 hours (IQR 21.8-53.5 hours).

Excluding the FN episodes that had a pathogen identified within 48 hours of a commensal or where antibiotic duration was unknown, there were 42 episodes with a contaminated BC that received antibiotics directed against the commensal bacteria. The median duration of this targeted antibiotic treatment administered was 9.5 days (IQR 6.0-11.2).

***Diagnostic yield of pre-antibiotic blood cultures***

A total of 1309 BC sets were taken for 820 FN episodes prior to commencement of empiric FN antibiotics. Of these, BCs were positive in 125 FN episodes (101 episodes with one or more true pathogens and 26 with a contaminated BC, including two with true pathogen and contaminated BC). Overall the diagnostic yield of the pre-antibiotic BCs was 12.3%.

The proportion of FN episodes where a contaminated BC was identified in one, two or three pre-antibiotic BCs sets was 1%, 4% and 19%, respectively (p<0.001) (Table 2). In four FN episodes where a commensal (coagulase negative staphylococci in all episodes) was identified on a single pre-antibiotic BC, an additional post-antibiotic BC was taken within 48 hours and prior to the commencement of a glycopeptide in all these episodes and all were negative.

In 38 FN episodes, no pre-antibiotic BC was collected. All of these had a BC collected within 48 hours of commencement of empiric FN antibiotics, with a pathogen identified in 3 episodes and contaminated BC isolated in 2 episodes.

***Diagnostic yield of post-antibiotic blood cultures***

There were 2424 post-antibiotic BC sets in 710 (82.8%) FN episodes. Of these, 86 BCs (3.5%) were positive in 75 (10.6%) FN episodes. In 31 FN episodes a new BSI with one or more pathogens was identified. In a further 24 FN episodes a contaminated BC with one or more common commensals was identified and in the remaining 20 the same pathogen as in the pre-antibiotic BC was re-identified. Overall the diagnostic yield of the post-antibiotic BCs was 4.4% which was significantly lower than the pre-antibiotic BC yield of 12.3% (p<0.001). The diagnostic yield was slightly higher in centres that only took BCs in febrile patients compared to centres that took daily BCs for the first 72 hours (3.6% versus 7.2%, p=0.07), although this did not achieve significance.

A new BSI or new contaminated BC was identified in 65 different post-antibiotic BCs taken in 55 FN episodes (Table 3). In nine BCs the corresponding clinical details were unknown, although all were taken more than 48 hours after the onset of a second fever episode. Excluding these positive BC episodes, the identification of a true BSI was significantly more likely to occur in the setting of a second fever episode as compared to the identification of a contaminated BC (63.3% versus 0, p<0.001). In the remaining 11 BSIs that did not correspond to an episode of new fever or clinical instability, all were identified during the primary febrile episode, with 81.8% from BCs taken within the first 48 hours compared to 18.2% taken after 48 hours of onset of fever (p=0.04).

***Diagnostic yield of post-antibiotic blood cultures in setting of persistent fever***

The median duration of fever in the entire cohort was 0.5 days (IQR 0.1-2.0 days). The initial fever persisted beyond 24 hours in 352 (41.0%) FN episodes and beyond 48 hours in 218 (25.4%) FN episodes. Of those patients that were febrile at 24 hours, 276 had a BC on Day 2 and two (0.7%) new BSIs were identified (plus 4 contaminated BCs). Of those episodes that were febrile at 48 hours, 165 had a BC taken on Day 3 and 2 (1.2%) new BSIs identified (plus 5 contaminated BCs) (Figure 2). Only 2 new BSI were identified after 48 hours in episodes with fever that persisted beyond this time (both were *Abiotrophia defectiva*). When BCs taken within the first 48 hours were compared with those taken beyond 48 hours, a new BSI was identified in 4/441 (0.9%) and 2/333 (0.6%), respectively (p=0.70).

Excluding episodes that had a positive pre-antibiotic BC or a second FN episode, there were 363 FN episodes that had resolution of initial fever within the first 24 hours. Despite this there were still at least 91 (25%) post-antibiotic BCs sets drawn from Day 3 onwards and no new pathogens identified.

**DISCUSSION**

This large, prospective multicentre study provides new insights into the diagnostic yield of pre- and post-empiric antibiotic BCs taken in children with cancer and FN. Not surprisingly, the diagnostic yield of the pre-antibiotic BCs was significantly higher than the yield of post-antibiotic BCs. Where a BSI was identified in post-antibiotic BCs, two thirds were associated with a second fever episode and only two episodes had a new BSI identified 48 hours after the initial fever presentation in the setting of persistent fever.

Overall, gram-positive bacteria were identified more frequently than gram-negative bacteria in keeping with earlier studies of children with cancer.[14] However, taking into consideration the timing of the BC (pre or post-empiric antibiotics) and following appropriate exclusion of contaminated BC , BSIs were more commonly due to gram-negative bacteria in BCs taken pre-antibiotics. In contrast, identification of a BSI due to a gram-positive pathogen was more common in BCs taken post-antibiotics and included bacteria not routinely covered by empiric FN antibiotic regimens.

The total number of BCs taken pre-antibiotics was less than the total number taken post-antibiotics. Despite this, the diagnostic yield of pre-antibiotic BCs was significantly higher than the post-antibiotics BCs (13.3% versus 4.4%). While the diagnostic yield did not appear to be influenced by the number of pre-antibiotic BCs, there was a significant increase in the proportion of contaminated BC identified when three or more pre-antibiotic BCs were taken as outlined in Table 2. These data suggest that drawing two pre-antibiotic BCs sets may strike the optimal balance between diagnostic yield and false positive results.

Regarding the post-antibiotic diagnostic yield, our rate of 4.4% is similar to previously described rates.[5, 8, 9] A higher rate was described in a study that only included patients with persistent fever beyond 96 hours (9.2%)[7] and in a study where the handling of potential contaminated BC bacteria was not clear (10.9%).[6] Although there were very few FN episodes that had a fever persisting beyond 96 hours in our cohort, only one new BSI episode was identified, translating to a diagnostic yield in this group of less than 2%.

When correlating clinical details with diagnostic yield, most true BSIs were identified either within the first 48 hours of initial fever onset or at the beginning of a second episode of fever. This is in keeping with a retrospective study of children with FN that found over half of post-antibiotic BSIs were associated with new onset clinical instability.[5] There were only two BSIs identified from BCs taken beyond the first 48 hours and included *A. defectiva* in two patients that remained febrile at days four and seven. In contrast, a contaminated BC organism was identified from 12 BC sets that were either taken beyond the first 48 hours of persistent fever or when there was not clear indication for BC to be taken (ie. no fever or clinical compromise). Notably, these patients were exposed to prolonged antibiotic treatment courses despite the common commensal bacteria only being identified in one of two or more BCs.

Although IDSA guidelines recommend daily BCs for up to 72 hours in patients with persistent fever, many patients in our observational study continued to have daily BCs taken in the absence of fever.[4] Given the high rate of contaminated BC identification and low diagnostic yield beyond 48 hours, we suggest that 72 hours may be excessive. A more pragmatic approach may be to ensure two, separate good-volume BC sets are taken pre-antibiotics with a repeat BC set at 24 and 48 hours in the setting of ongoing fever. Beyond this, repeat BCs should only be taken to confirm a positive culture result, document clearance pathogens or in the setting of a second fever or clinical instability (Table 4).

Applying this approach to our cohort of 858 FN episodes would result in missed identification of only two true BSIs, while avoiding 12 new contaminated BC results. A minimum of 2436 BC sets would be taken (including 2 sets day 1 and pre antibiotics; 352 sets day 2 and 218 sets day 3 for ongoing fever; and 150 sets for a second fever episode). This would result in a net saving of at least 1297 BC sets for our cohort. In Australia the allocated cost for one BC set is AUS $30.75 translating to a cost-saving of almost AUD $40,000 within our cohort.[15] As at least 1235 children with FN are treated per year in the eight Australian paediatric cancer centres included in this study, the broader economic impact is likely to be substantially higher.[10] Furthermore, it would align with the local and international ‘choosing wisely’ campaign to reduce the burden of unnecessary diagnostic tests on patients, healthcare workers and hospitals.[3, 16]

This is the largest study on the diagnostic yield of pre and post-antibiotic BCs in children with cancer and FN and the first time it has been prospectively examined. To ensure our data can reliably inform FN management protocols, we have presented data at the level of the FN episodes as well as the individual BCs and bacteria identified. Data on number of BC sets taken post-antibiotics is limited due to only one BC set being recorded per day and may therefore underreport the total taken. Despite this, there is still potential for cost, resource and procedural savings if the afore mentioned approach is taken. Our study also did not evaluate the volume of blood in each BC bottle, with an adequate volume being shown to be an important factor in increasing diagnostic yield.[17-19]

Our study highlights potential for optimising BC collection protocols for children with cancer and FN. Given the diagnostic yield is highest in BCs taken pre-antibiotics, education and attention should be focused on ensuring two sets are taken in all FN episodes. Restricting the total number of BCs taken post-antibiotics to avoid routine, daily BCs in otherwise well and afebrile patients would dramatically reduce the total number of BCs and the costs associated with collection, processing and reporting.

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**CONFLICTS OF INTEREST**

There are no relevant conflicts of interest to declare.

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**FIGURE LEGENDS**

**Figure 1.** Kaplan-Meier curve showing percentage of all positive pre-antibiotic BCs (y-axis) identified per hour of incubation (x-axis).

**Figure 2.** Results of BCs taken in episodes of febrile neutropenia with persistent fever

**Table 1.** Type of bloodstream infections in paediatric patients with febrile neutropenia

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Pre-antibiotic period** | **Post-antibiotic period** | **Overall** |
| **Gram positive organisms** | **50** | **26** | **76** |
|  *Bacillus* spp. | 1 | 2 | 3 |
|  coagulase-negative Staphylococcus spp. | 8 | 3 | 11 |
|  *Clostridium* spp. | 0 | 3 | 3 |
|  *Enterococcus* spp.a | 3 | 5 | 8 |
|  Nutritionally-variant Streptococci | 1 | 3 | 4 |
|  *Paenibacillus* spp. | 0 | 1 | 1 |
|  *Staphylococcus aureus*b | 9 | 2 | 11 |
|  viridans Streptococcus spp.c | 27 | 7 | 34 |
|  *Streptococcus pneumoniae* | 1 | 0 | 1 |
| **Gram negative organisms** | **60** | **8** | **68** |
|  *Acinetobacter baumannii* | 1 | 0 | 1 |
|  *Capnocytophaga sputigena* | 3 | 0 | 3 |
|  *Enterobacter cloacae* | 5 | 1 | 6 |
|  *Escherichia coli* | 17 | 2 | 19 |
|  *Escherichia fergusonii* | 1 | 0 | 1 |
|  *Fusobacterium nucleatum* | 1 | 0 | 1 |
|  *Klebsiella* spp. | 13 | 1 | 14 |
|  *Moraxella* spp. | 1 | 2 | 3 |
|  *Neisseria* spp. | 5 | 0 | 5 |
|  *Pseudomonas* spp. | 10 | 2 | 12 |
|  *Sphingomonas paucimobilis* | 1 | 0 | 1 |
|  *Stenotrophomonas maltophilia* | 1 | 0 | 1 |
|  *Elizabethkingia* spp. | 1 | 0 | 1 |
| **Fungal organisms** | **3** | **2** | **5** |
|  *Candida* spp. | 3 | 2 | 5 |
| **TOTAL** | **113** | **36** | **149** |

avancomycin-resistant *Enterococcus* isolates identified in 2/8 (25%) instances;

bmethicillin-resistant *Staphylococcus aureus* identified in 3/11 (27.3%) instances;

cpenicillin-resistant *Streptococcus* spp. identified in 2/34 (5.9%) instances;

**Table 2.** Diagnostic yield according to frequency of collection of pre-antibiotic blood cultures in patients with febrile neutropenia: bloodstream infections and contaminated blood cultures

|  |  |
| --- | --- |
|  | **Number of pre-antibiotic blood cultures collected** |
|  | **One** | **Two** | **Three** |
| Total number of patient episodes | 357 | 437 | 26 |
| Number bloodstream infections (% of total)  | 37a (10.4%) | 62b (14.2%) | 2 (7.7%) |
| Number. contaminated blood cultures (% of total) | 5c (1.4%) | 16d (3.7%) | 5 (19.2%) |

apolymicrobial in 5 instances; bpolymicrobial in 9 instances; cpolymicrobial in one instance; dpolymicrobial in 2 instances

**Table 3.** Clinical characteristics of neutropenic paediatric patients with positive blood cultures following commencement of empiric antibiotic therapy

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Bloodstream infection** | **Contaminated blood culture** | ***p*-value** |
| Total number positive blood cultures | 30a | 26b | - |
| Ongoing initial febrile episode [≤48h], n (% total positive) | 9 (30.0%) | 14 (53.8%) | 0.103 |
| Ongoing initial febrile episode [>48h], n (% total positive) | 2 (6.7%)c | 7 (26.9%) | 0.066 |
| Second fever episode, n (% total positive) | 19 (63.3%) | 0 (0%) | 0.000 |
| No documented indication for collection of blood culture | 0 (0%) | 5 (19.2%) | 0.017 |

a clinical details unknown in 4 and 1 blood culture set had 3 pathogens (all 4 unknown blood cultures were taken >48h after onset 2nd fever); bclinical details unknown in 5 and 4 blood cultures had a pathogen and contaminant and 1 blood culture had a pathogen and 2 contaminants (all 5 blood cultures were classified as true). All 5 blood cultures were taken >48h after onset of 2nd fever; c*Abiotrophia defectiva* in 2 patient episodes and both remained febrile at Days 4 and 7.

**Table 4.** Suggested approach to blood culture collection for paediatric patients with FN

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| **General information*** A blood culture set consists of one catheter access draw inoculated into an aerobic BC bottle and an anaerobic BC bottle
* The minimum and maximum blood volume recommendations should be adhered to and taking into consideration the patients age and weight
* Peripheral blood cultures should be taken in accordance with local hospital policies

**(a) Pre antibiotic blood cultures*** A minimum of 2 blood culture sets should be taken prior to the first antibiotic dose (but do not delay antibiotics)
* For patients with a CVC, a blood culture set should be taken from all lumens
* Always label the blood culture bottle with site from which blood has been taken including specific CVC lumen

**(b) Post antibiotic blood cultures*** Afebrile and clinical stable – a repeat blood culture set is not required
* Ongoing fever or clinical instability – repeat 1 blood culture set on Day 2 (+/- Day 3 if fever persists)
* Any of: (i) new onset fever (after >48h afebrile) or clinical instability; (ii) change to antibiotics; or (iii) to confirm/exclude positive BC result – repeat step (a)
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