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Note

Utility of follow-up blood cultures for Gram-negative rod bacteremia in children

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ABSTRACT

Persistent Gram-negative rod (GNR) bacteremia is uncommon under appropriate antibiotic therapy. A recent study showed that follow-up blood cultures (FUBCs) to confirm clearance 24–48 h after initiation of antibiotics, added little value in the management of GNR bacteremia in adults. However, the utility of FUBC in children is still unknown. We retrospectively reviewed the microbiology database to identify children aged <18 years with GNR bacteremia. Clinical information including gender, age, underlying diseases, presence of central venous line (CVC), source of bacteremia, and organisms was extracted from medical records. FUBCs for 99 episodes of GNR bacteremia in children became positive in 21%, which led to intervention in 57% of the episodes. In multivariate analysis between FUBC positive (n = 21) and negative (n = 78) groups, presence of CVC (n = 18, 86% vs n = 38, 49%, $P = 0.001$) and resistance to empirical antibiotics (n = 3, 14% vs n = 4, 5%, $P = 0.04$) were independently associated with positive FUBCs. Interestingly, no positive FUBC was observed in cases due to UTI (n = 13). Contrary to findings in adults, FUBC may still be useful in the management of GNR bacteremia in children.

Follow-up blood cultures (FUBCs) are generally obtained after an initial positive blood culture to exclude persistent bacteremia [1,2]; however, the overall rate of persistent bacteremia in adults is only 6.6%–14% [1,3,4]. Gram-positive cocci (GPC), such as *Staphylococcus aureus*, are more prone to cause persistent bacteremia and FUBCs are recommended [2,3,5]. On the other hand, Gram-negative rod (GNR) bacteremia is commonly transient and often resolves after the initiation of treatment [1,3]. A recent study has shown that FUBCs added little value to the management of GNR bacteremia in adults [1]. Unnecessary FUBCs lead to increased healthcare costs and longer hospital stays and thus should be avoided [6]. The etiology of bacteremia and underlying conditions are different between adults and children; however, there have apparently been no reports on FUBCs for GNR bacteremia among children. The aim of this study was to investigate the value of FUBCs and identify risk factors for persistent GNR bacteremia among children.

This retrospective observational study was conducted at a tertiary care children's hospital with 490 beds in Tokyo, Japan, which includes a pediatric medical/surgical ward, transplant center, children's cancer center, pediatric intensive care unit, neonatal intensive care unit, and an obstetrical ward. We reviewed all records of positive blood cultures which were taken between May 1, 2014 and October 30, 2017. Patients eligible for the study were <18 years of age. We excluded the episodes of non-GNR bacteremia, polymicrobial bacteremia, FUBCs taken within 24 h from the initial blood culture and antimicrobial administration delayed beyond 48 h from the initial positive blood culture.

We extracted the following information from the medical records: demographic data (age, sex), bacteria detected from blood culture and susceptibility to antibiotics, source of bacteremia, underlying diseases (post solid organ transplantation, malignancy, urological anomalies, and others), presence of a central venous catheter (CVC), and antimicrobials prescribed. We reviewed clinical charts of patients with positive FUBCs to investigate the presence of treatment modification according to results of FUBCs.

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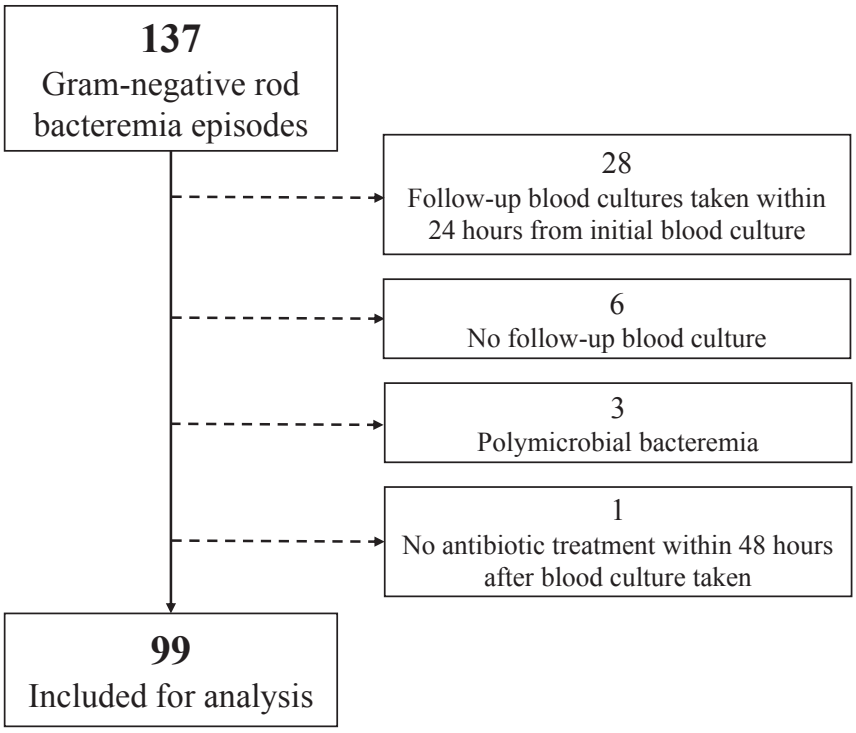

Fig. 1. Data collection flow.

GNR isolated from at least one positive blood culture was considered a true pathogen. Persistent bacteremia was defined as isolation of the same organism from blood samples drawn at least 24 h apart during the same infectious episode according to a previous study [1]. Infectious episodes were counted separately when an organism different from the previous episode was isolated or the same organism was positive more than 30 days after the previous episode. We excluded episodes without FUBCs from further analyses. We defined the source of bacteremia according to the Center for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) surveillance definition of health care-associated infection [7].

Patient characteristics were compared between positive and negative FUBC groups. Categorical variables were analyzed using the Fisher exact test and continuous variables were analyzed by the Mann-Whitney *U* test. Odds ratios (OR) and 95% confidential intervals (95%CI) were estimated by multivariate logistic regression analysis. Among all variables existing in the dataset, variables that were considered clinically significant, such as age, sex, underlying diseases, presence of a CVC, and resistance to empirical antibiotics, were added as explanatory variables. A two-sided $P < 0.05$ was considered statistically significant. Since this study was exploratory, we did not adjust the multiplicity of the statistical tests. All analyses were performed by the SPSS 20.0 software package (SPSS, Inc., Chicago, IL) and SAS software, version 9.4 (SAS Institute Inc.). This study was approved by the ethics committee at the National Center for Child Health and Development (NCCHD-1746).

One hundred thirty-seven GNR bacteremia episodes were identified. Of these, episodes without FUBCs (n = 6) or episodes with FUBCs taken within 24 h from the initial blood culture (n = 28) were excluded. One hundred three (75.2%) had one or more FUBCs that were taken at least 24 h after the initial blood culture. Three episodes of polymicrobial bacteremia, and one episode where antimicrobial administration was delayed beyond 48 h from the initial positive blood culture, were excluded from the analysis (Fig. 1). Demographic data of the 99 episodes analyzed are presented in Table 1. Median age was 2 years and 59% were male. More than half (57%) of the patients had CVC placement. The pathogens and the source of bacteremia are presented in Supplemental Table. The most common pathogens were *Klebsiella* spp. (n = 29), followed by *Escherichia coli* (n = 26). In 52 cases, the source of infection was unknown.

Of the 99 episodes, 21 (21.2%) FUBCs were positive. The differences between positive and negative FUBC groups are shown in Table 2. In univariate analysis, age (median 0.0 vs 2.5 years, $P = 0.02$) and presence of a CVC (85.7% [n = 18] vs 48.7% [n = 38], $P = 0.006$) were significantly associated with positive FUBCs. Presence of CVC was independently associated with positive FUBCs in logistic regression analysis (CVC: OR 117.33 [95%CI: 3.04–98.62], $P = 0.001$). Resistance to empirical antibiotics was also associated with positive FUBCs (OR 9.09 [95%CI: 1.07–77.30], $P = 0.04$) in multivariate analysis. No positive FUBCs were observed in cases due to urinary tract infection (UTI) (n = 13). Positive FUBCs led to intervention in 12/21 (57%) episodes, which included change in

Table 1
Patient characteristics.

Variables	Values
Total number of episodes[a]	99
Median age, years (IQR)	2 (0–6.5)
Sex, male (%)	58 (58.6%)
Underlying diseases	
Post organ transplantation	21 (21.2%)
Malignant neoplasm	17 (17.2%)
Anomalies of the kidney and urinary tract	15 (15.2%)
Presence of a central venous catheter[b]	56 (56.6%)

IQR, interquartile range.
[a] Six, one, and one patient(s) had two, three, and four separate episodes, respectively.
[b] Includes peripherally inserted central venous catheters.

Table 2
Differences among episodes associated with positive or negative follow-up blood cultures.[a]

Variables	Positive	Negative	OR (95%CI)[b]	*P* value[b]	OR (95%CI)[c]	*P* value[c]
	(n = 21)	(n = 78)	Unadjusted		Adjusted	
Median age, years (IQR)	0.0 (0–2)	2.5 (0–8)	0.82 (0.70–0.97)	0.02	0.80 (0.63–1.00)	0.05
Sex, male (%)	12 (57.1%)	46 (59.0%)	1.08 (0.41–2.86)	0.88	1.21 (0.35–4.19)	0.76
Source of bacteremia[d]						
Catheter-related bloodstream infection	10 (47.6%)	14 (17.9%)				
Urinary tract infection	0 (0.0%)	13 (16.7%)				
Gastrointestinal system infection	0 (0.0%)	4 (5.1%)				
Intra-abdominal infection	1 (4.8%)	2 (2.6%)				
Central nervous system infection	1 (4.8%)	0 (0.0%)				
Lower respiratory infection or pneumonia	0 (0.0%)	1 (1.3%)				
Skin and soft tissue infection	0 (0.0%)	1 (1.3%)				
Unknown	9 (42.9%)	43 (55.1%)				
Underlying diseases						
Post organ transplantation	5 (23.8%)	16 (20.5%)	1.21 (0.39–3.80)	0.74	4.20 (0.69–25.69)	0.12
Malignant neoplasm	2 (9.5%)	15 (19.2%)	0.44 (0.09–2.11)	0.31	0.24 (0.03–1.70)	0.15
Anomalies of the kidney and urinary tract	3 (14.3%)	12 (15.4%)	0.92 (0.23–3.60)	0.90	1.82 (0.32–10.37)	0.50
Gastrointestinal disorders	6 (28.6%)	20 (25.6%)	1.16 (0.37–3.40)	0.79	0.47 (0.11–2.07)	0.32
Presence of a central venous catheter	18 (85.7%)	38 (48.7%)	6.32 (1.72–23.18)	0.006	17.33 (3.04–98.62)	0.001
Resistance to empirical antibiotics	3 (14.3%)	4 (5.1%)	3.08 (0.63–15.02)	0.16	9.09 (1.07–77.30)	0.04

IQR, interquartile range.
[a] Unadjusted and adjusted ORs are presented except for source of bacteremia.
[b] *P* value from the Fisher's exact test or Mann-Whitney nonparametric test; 95% confidence intervals are based on logistic regression.
[c] *P* value and 95% confidence intervals from multiple logistic regression.
[d] *P* value and 95% confidence interval could not be estimated because of the occurrence of 0 cells.

choice and/or dose of antibiotics (n = 5), removal of medical devices such as catheters (n = 5), or both (n = 2).

In our study, 21% of FUBCs for GNR bacteremia were positive. Presence of a CVC, and resistance to empirical antibiotics were significantly associated with positive FUBCs. No positive FUBCs were observed in UTI cases. Positive FUBCs led to additional clinical intervention in more than half of the patients.

Risk factors for positive FUBCs have been investigated in adult patients. An endovascular source has been reported as a risk factor for positive FUBCs among adults [1,3]. Canzoneri et al. reported that 62% of patients whose FUBCs were positive had a CVC [1]. Our study showed similar results and suggests that FUBCs should be obtained for pediatric patients with a CVC. In contrast, the probability of positive FUBCs has been reported to significantly decrease when UTI was the cause of bacteremia among adults [1,3]. Only 2.8%–5.9% of UTI cases showed positive FUBCs in those studies [1,3]; however, UTI with renal abscess appeared to be a risk factor for positive FUBCs [8]. In addition, intra-abdominal infection has been reported as a risk factor for persistent *Klebsiella pneumoniae* bacteremia [4]. Therefore, it is important to exclude the presence of renal or intra-abdominal abscess for patients with GNR bacteremia. In our study, no UTI cases showed positive FUBCs; however, the number of the patients was small and a larger study is needed to assess the value of FUBCs in the management of GNR bacteremia in children with urosepsis.

Positive FUBC results led to interventions in more than half of the episodes, which included medical device removal and/or optimization of antibiotic regimen. Delayed initiation of appropriate antibiotics in bacteremic patients has been associated with poor prognosis [9]. In addition, early removal of CVCs is recommended for preventing catheter-related bloodstream infections due to GNR [10]. Thus, FUBCs may promote optimal treatment of GNR bacteremia, particularly in pediatric patients with CVCs.

Our study has some limitations. First, the timing of obtaining FUBCs was different for each case, which may have influenced the FUBC results. Second, FUBCs were not obtained in 24.8% of our cohort, which may represent selection bias. Finally, the analysis of risk factors for positive FUBCs of GNR bacteremia among children was limited by the low occurrence of the event.

In conclusion, 21% of FUBCs for GNR bacteremia were positive among children in which presence of a CVC and resistance to empirical antibiotics were risks for positive FUBCs. Larger studies are needed to more firmly demonstrate that FUBCs add little value to the management of GNR bacteremia in children with urosepsis.

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Authorship statement

All authors meet the ICMJE authorship criteria. All authors do not have any potential, perceived, or real conflicts of interest relevant to this manuscript.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.04.014.

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