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Major article

Breakthrough bacteremia in the neonatal intensive care unit: Incidence, risk factors, and attributable mortality

Ming-Horng Tsai MD [a,b,c], Shih-Ming Chu MD [b,d], Jen-Fu Hsu MD [b,d], Reyin Lien MD [b,d], Hsuan-Rong Huang MD [b,d], Ming-Chou Chiang MD [b,d], Ren-Huei Fu MD, PhD [b,d], Chiang-Wen Lee MD, PhD [c,e], Yhu-Chering Huang MD, PhD [b,f,*]

[a] Division of Neonatology and Pediatric Hematology/Oncology, Department of Pediatrics, Chang Gung Memorial Hospital, Yunlin, Taiwan
[b] College of Medicine, Chang Gung University, Taoyuan, Taiwan
[c] Research Center for Industry of Human Ecology, Chang Gung University of Science and Technology, Taoyuan, Taiwan
[d] Division of Pediatric Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[e] Division of Basic Medical Sciences, Department of Nursing, Chronic Diseases and Health Promotion Research Center, Chang Gung University of Science and Technology, Chiayi, Taiwan
[f] Division of Pediatric Infectious Disease, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan

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Background: An episode of breakthrough bacteremia, which was defined as positive blood cultures despite appropriate antibiotic therapy, imposes a treatment challenge in the neonatal intensive care unit (NICU).

Methods: All episodes of breakthrough bacteremia from a tertiary level NICU in Taiwan between 2004 and 2011 were analyzed and compared with nonbreakthrough bacteremia.

Results: Breakthrough bacteremia was identified in 7.6% (72/942) of neonatal bacteremia, and 43 (59.7%) occurred as recurrent episodes. Gram-negative organisms (41.7%) and fungi (15.3%) accounted for more than half of all microorganisms in breakthrough bacteremia. Compared with nonbreakthrough bacteremia, breakthrough bacteremia was significantly associated with more severe disease, was more likely to require aggressive therapies, and had a higher rate of infectious complications. Previous use of broad-spectrum antibiotics (odds ratio [OR], 7.54; $P < .001$) and particular microbial etiologies (*Pseudomonas aeruginosa*: OR, 4.40; $P = .025$; fungi: OR, 2.70; $P = .013$) were independent risk factors for developing breakthrough bacteremia. The crude sepsis-attributable mortality rate was greater in breakthrough bacteremia episodes (16.7% vs 6.4%; $P = .004$), and this condition was independently associated with an increased risk of death (OR, 2.14; 95% confidence interval, 1.04-4.40; $P = .040$).

Conclusion: Breakthrough bacteremia is not uncommon (7.6% of all bacteremia) in NICUs and represents a more severe form of neonatal bacteremia that is independently associated with an increased risk of death.

An episode of breakthrough bacteremia, defined as the growth of a microorganism in the blood cultures while receiving in vitro susceptible antibiotics, often imposes difficulties on therapeutic strategies in clinical practice.[1,2] Breakthrough bacteremia is different from recurrent bacteremia, which is regarded as a new-onset bacteremia after a complete course of antimicrobial therapy for a previous one and resolution of clinical symptoms.[3,4] Several predisposing factors, including an inadequate therapeutic level of an active drug,[5] particular circumstances of immunodeficiency,[6,7] some kinds of serious underlying conditions,[2] or emergence of selected resistant strains after previous antibiotic exposure,[8,9] may account for the occurrence of breakthrough bacteremia.

Breakthrough bacteremia has been correlated with an adverse outcome, including an independent predictor of death[2] and focal suppurative complications.[10,11] In the neonatal setting, there have been no reports regarding breakthrough bacteremia; however, there were several reports regarding persistent bacteremia, mostly

* Address correspondence to Yhu-Chering Huang, MD, PhD, Division of Pediatric Infection Disease, Department of Pediatrics, Chang Gung Memorial Hospital, 5, Fu-Shing St, Kwei-Shan, Taoyuan 333, Taiwan.
E-mail address: ychuang@adm.cgmh.org.tw (Y.-C. Huang).

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Table 1
Comparison of demographic characteristics between breakthrough and nonbreakthrough bacteremia in infants hospitalized in the neonatal intensive care unit

Characteristics	Breakthrough bacteremia (72 episodes)	Nonbreakthrough bacteremia (870 episodes)	*P* value
Birth weight (g)	1,095.0 (779.5-2,037.5)	1,285.5 (900.0-1,976.3)	.09
Gestational age (weeks)	28.0 (26.3-34.8)	30.0 (27.0-34.0)	.22
Sex (boy/girl)	33 (45.8)/39 (54.2)	467 (53.7)/403 (46.3)	.22
Community acquired/nosocomial*	0 (0)/72 (100)	11 (1.3)/859 (98.7)	1.00
Days of life at onset of bacteremia	37.5 (20.3-78.8)	27.0 (17.0-50.3)	.007
Underlying chronic conditions			
Congenital anomalies†	4 (5.6)	51 (5.9)	.92
Neurologic comorbidity, congenital or acquired	14 (19.4)	111 (12.8)	.15
Cardiovascular			
Complicated congenital heart disease	5 (6.9)	36 (4.1)	.23
Acyanotic heart disease with heart failure	2 (2.8)	16 (1.8)	.58
Respiratory			
Bronchopulmonary dysplasia	32 (44.4)	335 (38.5)	.32
Pulmonary hypertension and cor pulmonale	3 (4.2)	28 (3.2)	.67
Renal‡	6 (8.3)	32 (3.7)	.06
GI			
Congenital GI pathology	6 (8.3)	52 (6.0)	.44
Sequelae after operation of GI pathology§	7 (9.7)	30 (3.4)	.018
Previous treatment (within 1 month before bacteremia)			
Surgery	3 (4.2)	73 (8.4)	.61
Use of broad-spectrum antibiotics‖	57 (79.2)	261 (30.0)	<.001
Use of therapeutic antibiotics (duration >5 days)	61 (84.7)	662 (76.1)	.11
Use of corticosteroid	8 (11.1)	36 (4.1)	.015
Procedure or medical devices at onset of bacteremia			
On high-frequency oscillator ventilator	8 (11.1)	51 (5.9)	.12
Intubation with mechanical ventilator	31 (43.1)	285 (32.8)	.09
Presence of central venous catheter	63 (87.5)	708 (81.4)	.26
Use of TPN and intrafat	56 (77.8)	647 (74.4)	.58
Sequence of episodes of bacteremia			<.001
First episode	29 (40.3)	685 (78.7)	
Recurrent episode	43 (59.7)	185 (21.3)	

NOTE. Values are n (%), median (IQR), or as otherwise indicated.
GI, gastrointestinal; *IQR*, interquartile range; *TPN*, total parenteral nutrition.
*An episode of bacteremia detected in a neonate who had been discharged from the hospital and admitted because of young infant fever was considered to be community acquired.
†Included all documented and undocumented syndromes, chromosome anomalies, genetic or metabolic disorder, but it did not include simple cleft palate or polydactyly.
‡Including congenital nephrotic syndrome, renal failure requiring hemodialysis, and IgA nephropathy.
§Including short bowel syndrome, GI pseudo-obstruction, adhesion ileus, and chronic malnutrition.
‖Including vancomycin, teicoplanin, third-generation cephalosporin, cefepime, or carbapenem, which were used for >72-hour period.

focused on coagulase-negative staphylococci (CoNS).[12-17] We therefore conducted a study on neonatal breakthrough bacteremia to better understand the clinical significance and outcomes and provide a reference for future management in neonatal intensive care unit (NICU) clinical practice.

PATIENTS AND METHODS

Subjects and setting

All neonates with late-onset (defined as >3 days of age) sepsis and breakthrough bacteremia who were admitted to the NICU of Chang Gung Memorial Hospital (CGMH) between January 1, 2004, and December 31, 2011, were identified by retrospective review of a prospectively collected database. Our NICU database was recorded by a full-time nurse specialist who followed-up on neonates from birth or admission, if transferred from another hospital, until discharge or death over the last 10 years. The attending physicians cross-checked the database with microbiology service to verify the data before the start of the study. The NICU of CGMH, a university-affiliated medical center, has a capacity of 49 beds equipped with a mechanical ventilator, has 28 beds with special care nurseries, and provides broad medical and intensive care in Northern Taiwan. Data from patients with breakthrough bacteremia were compared with data from patients with nonbreakthrough bacteremia. This study was reviewed and approved by the institutional review board of CGMH.

Microbiology

In our NICU, blood cultures were drawn from patients with suspected sepsis at the discretion of the attending physicians or residents on duty. Blood sampling was obtained through peripheral veins (never through central venous catheters [CVCs]), and the blood culture system used was BACTEC 9240 (BD - Canada, Mississauga, ON, Canada). Polymicrobial bacteremia was defined as ≥2 microorganisms identified from the same blood culture set; all of them were considered to be significant. Isolates were identified using standard microbiologic methods. Clinical and Laboratory Standards Institute criteria were used to define susceptibility or resistance to antimicrobial agents.[18]

In our NICU, empirical antibiotics for coverage of both gram-positive and gram-negative organisms were usually prescribed at the onset of clinical sepsis. Modification of antimicrobial regimens would be decided by the attending physicians in charge, according to results and antibiotic susceptibility patterns of blood cultures. All therapeutic antimicrobial regimens were administrated through intravenous routes, and the dosages, according to the standard guidelines, were confirmed by both the attending physicians and pharmacists.

Definition

An episode of bacteremia was considered to be significant depending on any bacterium isolated from at least 1 blood culture,