



Antimicrobial Stewardship Opportunities in Patients with Bacteremia Not Identified by BioFire FilmArray

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ABSTRACT A subset of bacteremia cases are caused by organisms not detected by a rapid-diagnostics platform, BioFire blood culture identification (BCID), with unknown clinical characteristics and outcomes. Patients with ≥ 1 positive blood culture over a 15-month period were grouped by negative (NB-PC) versus positive (PB-PC) BioFire BCID results and compared with respect to demographics, infection characteristics, antibiotic therapy, and outcomes (length of hospital stay [LOS] and in-hospital mortality). Six percent of 1,044 positive blood cultures were NB-PC. The overall mean age was 65 ± 22 years, 54% of the patients were male, and most were admitted from home; fewer NB-PC had diabetes (19% versus 31%, $P = 0.0469$), although the intensive care unit admission data were similar. Anaerobes were identified in 57% of the bacteremia cases from the NB-PC group by conventional methods: *Bacteroides* spp. (30%), *Clostridium* (11%), and *Fusobacterium* spp. (8%). Final identification of the NB-PC pathogen was delayed by 2 days ($P < 0.01$) versus the PB-PC group. The sources of bacteremia were more frequently unknown for the NB-PC group (32% versus 11%, $P < 0.01$) and of pelvic origin (5% versus 0.1%, $P < 0.01$) compared to urine (31% versus 9%, $P < 0.01$) for the PB-PC patients. Fewer NB-PC patients received effective treatment before (68% versus 84%, $P = 0.017$) and after BCID results (82% versus 96%, $P = 0.0048$). The median LOS was similar (7 days), but more NB-PC patients died from infection (26% versus 8%, $P < 0.01$). Our findings affirm the need for the inclusion of anaerobes in BioFire BCID or other rapid diagnostic platforms to facilitate the prompt initiation of effective therapy for bacteremia.

KEYWORDS antimicrobial stewardship, bloodstream infections, diagnostics, rapid tests

Sepsis affects more than 1.5 million people each year in the United States and is associated with significant morbidity and mortality (1). Rapid and accurate identification of the causative pathogen from a positive blood culture and prompt selection of appropriate antimicrobial therapy are critical for treatment success of sepsis due to bacteremia (2, 3). Delays in treatment and utilization of inappropriate antimicrobials can lead to increases in mortality, length of stay, health care costs, and antimicrobial resistance (3–6). Treatment of sepsis is complicated by the continuing increase in antibiotic resistance. Excess mortality attributable to inadequate antimicrobial therapy ranges from 10 to 40% (7, 8).

In a patient with suspected bacteremia, a blood sample is typically obtained to inoculate blood culture bottles for aerobic and anaerobic growth in an automated blood culture instrument by conventional methods. After an average 18 h of incubation at our institution, when growth is detected by the instrument, identification and

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antibiotic susceptibility testing will follow, which generally requires 2 or more additional days to obtain results. The recent availability of a rapid diagnostics platform has shortened the time to detection of bacterial pathogens from blood by 24 h compared to conventional methods (9). Specifically, the BioFire BCID is a two-stage, multiplexed, nested PCR test that provides results in 65 min (times vary from 1.7 to 2.5 h depending on microbiology laboratory workflow). It is designed to detect simultaneously 24 pathogens (8 Gram-positive and 11 Gram-negative aerobes and 5 *Candida* species) and three antimicrobial resistance genes (*mecA*, *vanA* or *vanB*, and *bla*_{KPC}).

Published studies have reported off-panel BioFire BCID organisms (i.e., positive bacteremia is detected by conventional methods, but the organism is not found on the BioFire BCID panel and hence yields a negative result so the organism detected is considered an off-panel BioFire BCID organism) as the cause of up to 18% of bacteremia (Table 1) (10–12). Off-panel BioFire BCID organisms identified in those studies using parallel blood culture workup by conventional methods included *Bacillus* spp. (but not *B. anthracis*), *Micrococcus* spp., and *Corynebacterium* spp., which were generally considered contaminants from normal skin flora (Table 1). Analysis from these studies primarily focused on clinical outcomes of patients from pathogens identified by rapid diagnostics. Therefore, it is not clear how negative BioFire BCID results impact outcomes of patients with culture-positive bacteremia determined by conventional methods. Therefore, the goal of this study is to call attention to this subset of patients to clinicians who routinely rely on BioFire BCID in identifying patients with bacteremia. The objectives of this study are to describe the pathogens identified and compare the clinical characteristics, management, and outcome of this subset of patients to those with bacteremia caused by pathogens readily identified by BioFire BCID.

MATERIALS AND METHODS

This was a retrospective study conducted over a 15-month period (2/2016 to 4/2017) at a 625-bed community teaching hospital. The study was approved by the Institutional Review Board; informed consent was waived, since only existing clinical data were collected for routine clinical purposes. All hospitalized patients plus those discharged from the emergency department were included if they had at least one positive blood culture identified by conventional methods and a BioFire BCID result. Exclusion criteria included comfort care only, deceased prior to BioFire BCID result, discharged prior to BioFire BCID, or outpatient, and we only included the first positive bacteremia per patient. Our microbiology laboratory used the BD Bactec FX blood culture system (BD Diagnostics, Sparks, MD). Upon detection of growth from the blood culture bottle, a Gram stain was performed, and the specimen was assayed by BioFire BCID. In addition, standard phenotypic identification procedures using Phoenix (BD) according to the manufacturer's instructions for organism identification and antibiotic susceptibility testing were initiated. The standard automated phenotypic identification procedure was used as the reference method to evaluate performance of BioFire BCID. Additional manual techniques were performed according to our institution's protocols, which conformed to the standards of the Clinical and Laboratory Standards Institute.

Within 2 h after growth was detected from the blood culture by the automated blood culture system, BioFire BCID testing according to the manufacturer's instructions was initiated. The BioFire BCID instrument automatically performed nucleic acid extraction, multiplexed nested PCR, and product melt analysis, with results obtained in 65 min. BioFire BCID results were displayed only if the two internal pouch controls for the run were valid. All target sequences are longer than 200 bp and are proprietary, developed by BioFire BCID for the FilmArray system. rRNA was not used as a target in the BioFire BCID assay (13, 14). Antibiotic resistance genes were reported as detected by BioFire BCID only if an organism known to carry that gene was also detected: *mecA* for *Staphylococcus* spp.; *vanA/B* for *Enterococcus* spp.; and *bla*_{KPC} for *A. baumannii*, *P. aeruginosa*, or a member of the *Enterobacteriaceae* family (9). BioFire BCID results were compared to those from the reference method to determine true or false positives and negatives. Similarly, results of antibiotic susceptibility testing of the isolated pathogens by the phenotypic technique were used for comparison with BioFire BCID resistance gene detection. Of note, susceptibility for anaerobic bacteria was presumed based on published literature since testing was not performed at our facility.

All patients with a positive blood culture determined by the reference method were grouped based on whether they had a positive BioFire BCID (PB-PC) or negative BioFire BCID (NB-PC) result. If the BioFire BCID was able to identify any genus and/or species, these were included in the PB-PC cohort. If the BioFire BCID did not detect any organism despite the pathogen being on the panel and the organism was identified by conventional methods, these were included in the NB-PC cohort. Patient charts were reviewed for demographics, infection characteristics, time to effective therapy, and outcomes, including length of hospital stay (LOS) and in-hospital mortality between those with NB-PC and PB-PC results. Patients from whom growth of organism(s) in blood was deemed a contaminant were excluded from comparison between NB-PC and PB-PC on antibiotic therapy and outcomes. Concurrent infection is

TABLE 1 Off-panel organisms identified by conventional methods but not BioFire BCID from previous studies and present study^a

Microorganisms not included in the BioFire BCID panel	No. of isolates reported	
	From prior studies	In this study
Aerobic bacteria		
Gram-positive bacilli		
<i>Corynebacterium jeikeium</i>	1	0
<i>Corynebacterium</i> spp./diphtheroids	55	5
<i>Mycobacterium fortuitum</i> complex	1	0
<i>Paenibacillus</i> spp. (facultative anaerobe)	1	0
Gram-positive cocci		
<i>Abiotrophia</i> or <i>Granulicatella</i> spp.	8	0
<i>Aerococcus</i> spp.	3	1
<i>Aeromonas</i> spp.	0	1
Coagulase-negative staphylococcus	0	7
<i>Micrococcus</i> spp.	30	2
<i>Staphylococcus capitis</i>	0	2
<i>Staphylococcus pettenkoferi</i>	16	0
<i>Streptococcus</i> , viridans group	0	4
Gram-positive coccobacilli		
<i>Rhodococcus</i> spp.	1	0
<i>Rothia</i> (<i>Stomatococcus</i>) <i>mucilaginosus</i> (facultative anaerobe)	4	0
<i>Stomatococcus</i> spp.	1	0
Gram-negative bacilli		
<i>Achromobacter xylosoxidans</i>	1	0
<i>Aeromonas sobria</i>	1	0
<i>Bacillus cereus</i> (facultatively anaerobic)	19	0
<i>Bacillus</i> spp.	18	2
<i>Brevundimonas</i> spp.	2	0
<i>Burkholderia cepacia</i> complex	2	0
<i>Chryseobacterium luteola</i>	1	0
<i>Chryseobacterium meningosepticum</i>	1	0
<i>Falvobacterium</i> spp. (facultative anaerobe)	1	0
<i>Haemophilus parainfluenzae</i> I	0	1
<i>Morganella morganii</i>	0	1
<i>Providencia stuartii</i>	0	1
<i>Pseudomonas</i> spp. (facultative anaerobe)	5	1
<i>Pseudomonas stutzeri</i> (facultative anaerobe)	1	0
<i>Raoultella ornithinolytica</i>	4	0
<i>Raoultella planticola</i>	1	0
<i>Rhizobium radiobacter</i>	1	0
<i>Sphingomonas mucosissima</i>	1	0
<i>Stenotrophomonas maltophilia</i>	11	0
<i>Weeksella virosa</i>	1	0
Gram-negative coccobacilli		
<i>Acinetobacter lwoffii</i>	1	0
<i>Acinetobacter</i> spp. (not <i>A. baumannii</i>)	1	0
<i>Brevibacterium</i>	2	0
<i>Moraxella</i> spp.	2	0
Gram-negative diplococci		
<i>Moraxella catarrhalis</i>	1	0
<i>Neisseria</i> spp.	2	2
Anaerobic bacteria		
Gram-positive bacilli		
<i>Actinomyces odontolyticus</i>	2	0
<i>Actinomyces</i> spp.	1	0
<i>Clostridium citroniae</i>	0	1
<i>Clostridium clostridioforme</i>	0	1
<i>Clostridium tertium</i>	0	1
<i>Eggerthella lenta</i>	1	1
<i>Lactobacillus</i> spp. (facultative anaerobe)	4	5
<i>Propionibacterium</i> spp.	9	1

(Continued on next page)

TABLE 1 (Continued)

Microorganisms not included in the BioFire BCID panel	No. of isolates reported	
	From prior studies	In this study
Gram-positive cocci		
<i>Gemella</i> spp. (facultative anaerobe)	1	0
<i>Kocuria kristinae</i> (facultative anaerobe)	1	0
<i>Micromonas micros</i>	0	1
<i>Parvimonas micra</i>	1	0
<i>Pediococcus pentosaceus</i>	0	1
<i>Peptococcus</i> spp.	1	0
<i>Peptoniphilus</i> spp.	2	2
Gram-positive coccobacilli		
<i>Weissella confusa</i>	0	1
Gram-negative bacilli		
<i>Bacteroides fragilis</i> group	2	7
<i>Bacteroides thetaiotaomicron</i>	0	2
<i>Bacteroides vulgatus</i>	0	2
<i>Capnocytophaga canimorsus</i> (facultative anaerobe)	1	1
<i>Capnocytophaga</i> spp. (facultative anaerobe)	1	0
<i>Chryseobacterium indologenes</i> (facultative anaerobe)	1	0
<i>Desulfovibrio desulfuricans</i>	0	2
<i>Eikenella corrodens</i> (facultative anaerobe)	0	1
<i>Fusobacterium</i>	1	3
<i>Parabacteroides distasonis</i>	0	1
<i>Pedobacter</i> spp.	0	1
<i>Prevotella buccae</i>	1	0
Gram-negative cocci		
<i>Veillonella</i>	1	0
Gram-negative coccobacilli		
<i>Pasteurella</i> spp.	1	0
<i>Pasteurella stomatis</i>	1	0
Yeast		
<i>Candida kefyr</i>	1	0
<i>Cryptococcus neoformans</i>	2	0
<i>Rhodotorula rubra</i>	1	0
Mold		
<i>Fusarium</i> spp.	1	0

^aPrevious studies refer to references 10, 11, and 12. The conventional methods included culture-based ID methods, followed by Microscan WalkAway 96 system (Siemens Healthcare, Malvern, PA) (10), RapID ANA (Remel) (10), Bruker MALDI-TOF MS (Bruker Daltonics, Bremen, Germany) (11), Vitek2 XL (bioMérieux, Marcy l'Etoile, France), MicroScan WalkAway (Siemens Medical Solutions, Deerfield, IL) (12), Vitek 2 (bioMérieux, Durham, NC) (12), and Phoenix (BD Diagnostics, Sparks, MD). For discrepant results, PCR and sequence analysis was conducted using portions of the 16S rRNA and *rpoB* genes, and BLAST analysis of the 16S rRNA and *rpoB* genes was performed against the National Center for Biotechnology Information GenBank database (NCBI, Washington, DC).

defined as another infection in addition to the primary source of bacteremia (e.g., patient with *Escherichia coli* bacteremia secondary to urinary tract infection plus concurrent MRSA pneumonia). Comorbid conditions included those from Elixhauser comorbidities (15). The Elixhauser comorbidity index is used to categorize comorbidities of patients based on International Classification of Diseases diagnosis codes found in administrative data. Each comorbidity category is dichotomous. The Elixhauser comorbidity index can be used to predict hospital resource use and in-hospital mortality. A sepsis-related organ failure assessment (SOFA) for those admitted to the intensive care unit (ICU) or a quick SOFA (qSOFA) score for those not admitted to the ICU was calculated for each patient within 24 h of positive blood culture collection. Effective therapy was defined as antimicrobial regimens containing at least one agent with *in vitro* activity against the isolated pathogen (presumed activity in the case of anaerobes). All data were recorded on a structured data collection form and managed using Microsoft Excel 2013. Blood contamination was determined by the attending physician based on clinical presentation and the number of blood culture sets that grew the same organism (i.e., only one positive of two or more blood cultures without any signs or symptoms of an infection).

Data analysis. The Student *t* test or Wilcoxon-Mann-Whitney, Fisher exact, or chi-square tests were used to analyze continuous or categorical variables, where appropriate, using Prism 4.0 (GraphPad Software, San Diego, CA). A *P* value of ≤ 0.5 was considered statistically significant.

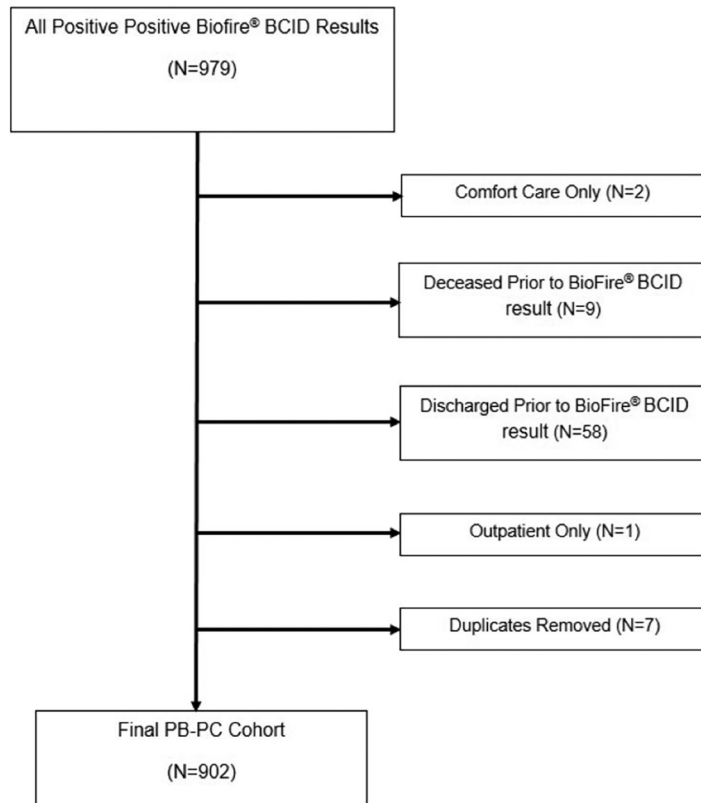


FIG 1 Positive Biofire BCID (PB-PC) cohort inclusion and exclusion flowchart.

RESULTS

Among the 1,044 positive blood cultures, 63 (6%) were reported negative by BioFire BCID (NB-PC). Of the 979 BioFire BCID test results with on-panel organisms, there were 13 false negatives, 9 false positives, and 12 misidentified (i.e., they did not match the organism finalized by culture). After excluding patients on comfort care only ($n = 2$), deceased prior to BioFire BCID result ($n = 9$), discharged prior to BioFire BCID ($n = 58$), or outpatient ($n = 1$) and after only including the first positive bacteremia per patient, there were 902 patients in the PB-PC cohort (Fig. 1). After only including first positive bacteremia per patient from the NB-PC cohort, there were 63 patients. Patients who were deemed to have contaminants in their blood were considered sick enough on presentation to have blood cultures ordered initially to rule out infection; these patients were kept in the analysis of baseline characteristics. The overall mean age of the study cohort was 65 ± 22 years, and 54% were male, values which were similar between the two groups. The majority (76%) were admitted from home (Table 2). Compared to the PB-PC cohort, a lower proportion of patients with NB-PC had diabetes (19% versus 31%, $P = 0.0469$). Clinical presentation was similar between groups in terms of ICU admission (17%) and SOFA and qSOFA scores (medians of 9 and 1, respectively) (Table 2). Among the NB-PC ($n = 63$) and PB-PC ($n = 902$) cohorts, diagnosis at the time of blood culture collection, of which most (89%) were diagnosed at time of admission, included the following in descending order: sepsis (21% versus 30%, $P = 0.1523$), urinary tract infection (UTI; 25% versus 29%, $P = 0.5689$), pneumonia (17% versus 21%, $P = 0.6305$), acute bacterial skin and skin structure infection (13% versus 3%, $P = 0.0773$), systemic inflammatory response syndrome of unclear etiology (13% versus 11%, $P = 0.6805$), septic shock (5% versus 6%, $P = 0.7917$), and intra-abdominal infection (5% versus 3%, $P = 0.4133$) (Table 2).

Fifty-nine percent (37/63) of NB-PC were identified by conventional methods as anaerobes (Table 3): *Bacteroides* (30%), *Clostridium* (11%), and *Fusobacterium* (8%)

TABLE 2 Patient characteristics of PB-PC versus NB-PC

Characteristics	PB-PC (n = 902)	NB-PC (n = 63)	P
Demographics			
Age (mean ± SD), yr	65 ± 22	64 ± 25	0.9936
Pediatric (<18 yr)	46 (5)	4 (6)	0.5612
Neonate (<4 wk)	14 (2)	2 (3)	0.2810
Male, no. (%)	488 (54)	36 (55)	0.6956
BMI (mean ± SD), kg/m ²	27.8 ± 0.7	25.4 ± 0.8	0.392
Residence prior to admission, no. (%)			
Home	697 (77)	48 (74)	0.8766
Skilled nursing or long-term care facility	149 (17)	14 (22)	0.2280
Outside hospital	20 (2)	0 (0)	0.6353
Homeless	22 (2)	0 (0)	0.3913
Past medical history, no. (%)			
Prior hospitalization within 30 days	70 (8)	9 (14)	0.0904
Past bacteremia ^a	41 (5)	0 (0)	0.1040
Comorbidity condition, no. (%)			
≥3 comorbidities	551 (61)	30 (47)	0.0134
Neurologic disease ^b	171 (19)	16 (25)	0.2469
Cardiovascular disease ^c	544 (60)	35 (55)	0.5065
Pulmonary disease ^d	153 (17)	5 (8)	0.0763
Renal insufficiency ^e	149 (17)	8 (13)	0.4855
Liver disease	68 (8)	4 (6)	1.0000
Diabetes	283 (31)	12 (19)	0.0469
Ulcerative colitis/Crohn's disease	6 (0.7)	2 (3)	0.0910
Malignancy	176 (20)	13 (20)	0.8695
Received chemotherapy within 90 days	39 (4)	2 (3)	1.0000
HIV/AIDS	10 (1)	1 (2)	0.5261
Admission characteristics			
ICU at time of BioFire result, no. (%)	151 (17)	12 (19)	0.6041
Median SOFA ^f score (IQR) at time of blood culture collection, n	9 (6–12), 175	7 (7–9.5), 7	0.8307
Median qSOFA ^g score (IQR) at time of blood culture collection, n	1 (1–2), 711	1 (1–2), 26	0.5312
Diagnosis at time of blood culture collection			
Sepsis	271 (30)	13 (21)	0.1523
UTI	262 (29)	16 (25)	0.5689
Pneumonia	189 (21)	11 (17)	0.6305
Acute bacterial skin and skin structure infections	27 (3)	8 (13)	0.0773
Systemic inflammatory response syndrome of unclear etiology	99 (11)	8 (13)	0.6805
Septic shock	54 (6)	3 (5)	0.7917
Intra-abdominal infection	27 (3)	3 (5)	0.4133

^aThe median (minimum, maximum) time period for past bacteremia for the PB-PC cohort was 172 days (24 days, 8.5 years).

^bCerebral vascular accident, seizure disorder, encephalopathy, Parkinson's disease, and Alzheimer's disease.

^cCardiac arrhythmia, hypertension, hyperlipidemia, dyslipidemia, hypercholesteremia, coronary artery disease, congestive heart failure, and prior myocardial infarction.

^dChronic obstructive pulmonary disease, asthma, tracheostomy or vent dependent secondary to respiratory failure, and pulmonary circulation disorder.

^eEnd-stage renal disease or requiring hemodialysis.

^fSepsis-related organ failure assessment score for those admitted to the ICU calculated within 24 h of positive blood culture collection time. IQR, interquartile range.

^gQuick sepsis-related organ failure assessment score for those not admitted to the ICU calculated within 24 h of positive blood culture collection time.

species (Fig. 2). Among the aerobic organisms, most were coagulase-negative staphylococci (CoNS; 41%), *Streptococcus viridans* group (18%), and *Corynebacterium* spp. (18%) (Fig. 3). Among those not detected by BioFire BCID but identified by conventional methods via the RapID ANA II system from Thermo Fisher as anaerobes, 11% (4/37) were polymicrobial, with the following being the primary source of bacteremia: intra-abdominal infection ($n = 1$), acute bacterial skin and skin structure infection with abscess ($n = 1$), tubo-ovarian abscess ($n = 1$), and unknown ($n = 1$). Nearly one-third of the NB-PC results (20/63) were considered contaminants per study definition. The majority of the contaminants identified were CoNS (32%, 7/20), *Corynebacterium* species (18%, 4/20), and *Micrococcus* species (9%, 2/20). The NB-PC cohort had significantly more unknown sources of bacteremia (35%, 12/34 versus 10%, 67/646, $P = 0.0002$) and of pelvic origin (6%, 2/34 versus 0.2%, 1/646, $P = 0.0071$), whereas most sources among

TABLE 3 Individual outcomes from NB-PC cohort with organism, primary source of bacteremia and associated empiric therapy after BioFire BCID result^a

Cohort	Organism identified by conventional methods	Primary source of bacteremia	Empiric therapy after BioFire BCID result and before final cultures and susceptibilities	Outcome
1	<i>Aerococcus urinae</i>	Unknown	VAN	Survived
2	<i>Aeromonas</i> spp.	Unknown	TZP	Survived
3	<i>Anaerococcus prevotii</i>	Unknown	TZP+LZD	Died
4	<i>Anaerococcus tetradius</i>	Unknown	CIP+CRO	Survived
5	<i>Bacillus coagulans</i>	Unknown	ATM	Survived
6	<i>Bacteroides fragilis</i>	Intra-abdominal infection	TZP+VAN+MTZ	Died
7	<i>Bacteroides fragilis</i>	Intra-abdominal abscess status, after colonic perforation	MTZ+MIC+TZP+VAN	Survived
8	<i>Bacteroides fragilis</i>	Stage IV sacral decubitus ulcer	TZP+VAN	Survived
9	<i>Bacteroides fragilis</i>	Unknown	CRO	Survived
10	<i>Bacteroides fragilis</i>	Unknown	MTZ+TZP	Survived
11	<i>Bacteroides fragilis</i>	Intra-abdominal infection	TZP	Died
12	<i>Bacteroides vulgatus</i>	Postpartum endometritis	CRO+GM+MTZ	Survived
13	<i>Bacteroides thetaiotaomicron</i>	Unknown	TZP+VAN	Died
14	<i>Bacteroides thetaiotaomicron</i>	Intra-abdominal infection with fecal contamination	MTZ+TZP+VAN	Died
15	<i>Clostridium citroniae</i>	Pelvic mass vs necrotic tumor vs septic pelvic vein thrombophlebitis	MEM+MTZ+VAN	Survived
16	<i>Clostridium clostridioforme</i>	Intra-abdominal infection	VAN+MTZ+FEP	Died
17	<i>Corynebacterium amycolatum/freneyi</i>	Aspiration pneumonia	ATM+MTZ+AZM	Survived
18	<i>Desulfovibrio desulfuricans</i>	Acute appendicitis	MTZ+MEM	Survived
19	<i>Fusobacterium</i> spp.	Shoulder wound infection with prosthesis	CRO+VAN	Survived
20	Gram-negative bacillus, unidentified nonfermenter	Unknown	TZP	Died
21	<i>Haemophilus parainfluenzae</i> I	Bronchitis	TZP	Survived
22	<i>Morganella morganii</i>	UTI	CRO	Survived
23	<i>Neisseria mucosa</i>	Unknown	TZP	Survived
24	<i>Neisseria</i> spp. (saprophytic)	Spontaneous bacterial peritonitis	CRO	Survived
25	<i>Parabacteroides distasonis</i>	Perforated diverticulitis	ATM+MTZ	Survived
26	<i>Pediococcus pentosaceus</i>	Abdominal abscess	TZP+VAN	Survived
27	<i>Peptoniphilus asaccharolyticus</i> , <i>Micromonas micros</i>	Tube-ovarian abscess	SAM+CLI	Survived
28	<i>Providencia stuartii</i>	UTI	CRO	Survived
29	<i>Pseudomonas</i> spp.	Unknown	MTZ+MEM+CIP	Died
30	<i>Staphylococcus capitis</i>	Unknown	TZP+VAN	Died
31	<i>Staphylococcus capitis</i>	Hemodialysis catheter	VAN	Survived
32	<i>Streptococcus</i> , viridans group	UTI	VAN+CRO	Survived
33	<i>Streptococcus</i> , viridans group	Endocarditis	AZM+VAN+TZP	Survived
34	<i>Streptococcus</i> , viridans group; <i>Lactobacillus</i> spp.; gamma <i>Streptococcus</i> , not group D	Gastric tube site infection with abdominal abscess	TZP+VAN	Survived

^aExcluding contaminants and patients discharged or expired prior to BioFire BCID result. TZP, piperacillin-tazobactam; ATM, aztreonam; VAN, vancomycin; CRO, ceftriaxone; MTZ, metronidazole; MEM, meropenem; CIP, ciprofloxacin; SAM, ampicillin-sulbactam; CLI, clindamycin; LZD, linezolid; GM, gentamicin; MIC, micafungin; AZM, azithromycin; FEP, cefepime; DOX, doxycycline.

the PB-PC cohort were from a UTI or pyelonephritis (31%, 203/646 versus 9%, 3/34, $P = 0.0037$). Of note, among the NB-PC cohort with true infection, patients with an unknown source of bacteremia had significantly more neurologic diseases (i.e., dementia, developmental delay, and cerebrovascular accident) compared to those with a known source of infection (7/14 versus 2/29).

Excluding those with blood contaminants ($n = 20$) and those discharged ($n = 8$) or expired ($n = 1$) prior to BioFire BCID result, a comparison between NB-PC and PB-PC cohorts indicated that a lower proportion of NB-PC patients received effective empirical treatment both before (23/34 [68%] versus 545/646 [84%], $P = 0.0166$) and after BioFire BCID results (28/34 [82%] versus 618/646 [96%], $P = 0.0048$). In addition, the NB-PC group had significantly delayed times to result for Gram stain (47 ± 3 h versus 22 ± 0.4 h, $P < 0.0001$), BioFire BCID (48 ± 5 h versus 26 ± 0.5 h, $P < 0.0001$), and final culture and susceptibilities (125 ± 9 h versus 79 ± 1 h, $P < 0.0001$, respectively). Among those with confirmed infection, time to receipt of effective therapy was twice as long among the NB-PC cohort ($n = 34$) compared to those with PB-PC ($n = 639$) results, with a trend toward statistical significance (24.8 ± 32.6 h versus 12.4 ± 18.6 h, $P = 0.069$). In

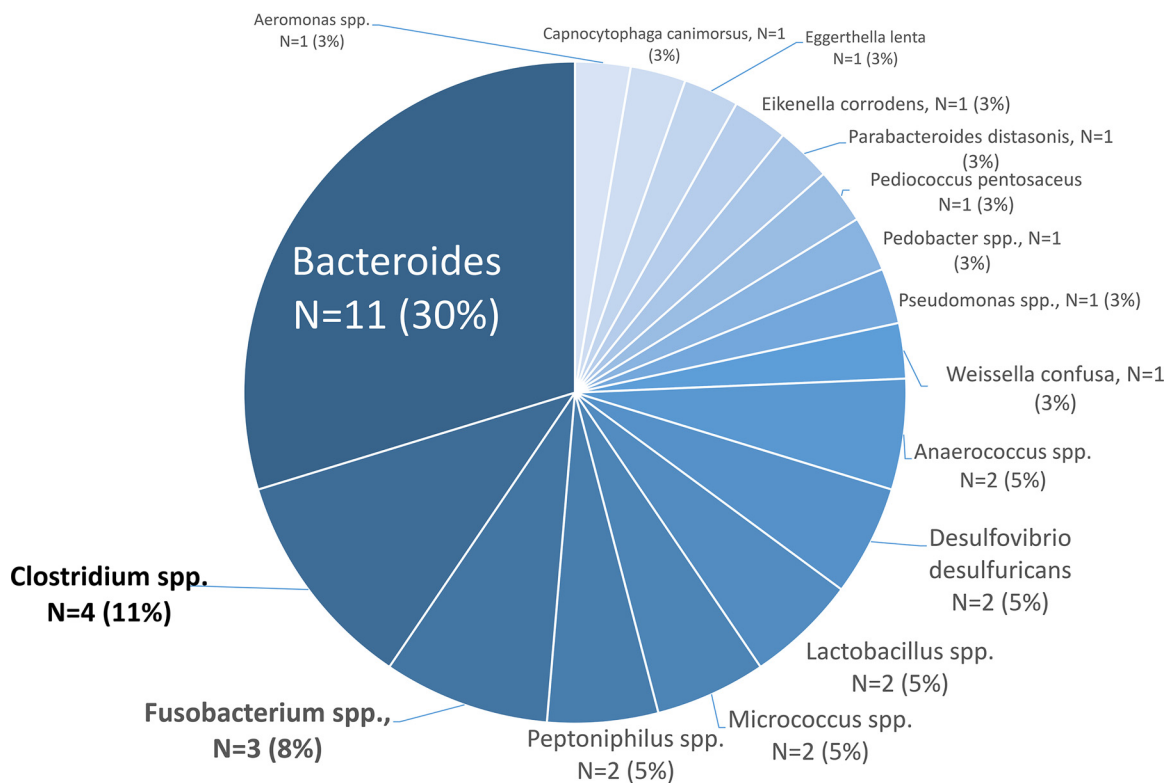


FIG 2 Anaerobic organisms identified by Phoenix BD diagnostics from NB-PC cohort.

particular, the time to effective therapy in the NB-PC cohort was significantly longer for those with anaerobic versus aerobic bacteremia (27.9 ± 1.6 h versus 16.4 ± 1.1 h, $P = 0.049$). More than half (60%) of the patients infected with anaerobic NB-PC bacteremia ($n = 20$) received active empirical therapy prior to the BioFire BCID result. Empiric therapy prescribed to those with anaerobic NB-PC bacteremia ($n = 20$) was mostly combination therapy (80%, 16/20) (Table 4). Prior to BioFire BCID results, 11 patients did not receive effective empirical therapy, and the majority (8/11) were anaerobic organisms (Table 4). Infectious sources for these anaerobes were mostly unknown ($n = 4$); otherwise, known sources were perforated diverticulitis ($n = 1$), abdominal abscess ($n = 1$), tuboovarian abscess ($n = 1$), and skin soft tissue infection in the pelvic area ($n = 1$). The three aerobic organisms identified were *S. capitis* (from hemodialysis catheter), saprophytic *Neisseria* spp. (from spontaneous bacterial peritonitis), and an unidentified Gram-negative bacillus nonfermenter (from an unknown source) and were treated empirically with piperacillin-tazobactam plus vancomycin ($n = 1$) or no antibiotics ($n = 2$). Bacteremia plus concurrent infections included (i) pneumonia ($n = 2$), plus UTI ($n = 3$) or intra-abdominal infection ($n = 1$) and (ii) UTI ($n = 1$) plus sacral decubitus ulcers and pneumonia ($n = 1$).

The length of hospital stay was similar (median, 7 days) between study groups, but more NB-PC patients died from infection compared to the PB-PC group (26% [9/34] versus 8% [50/646]; $P = 0.0014$; odds ratio = 4.291, 95% confidence interval = 1.9 to 9.694). Of the nine NB-PC patients who died, six developed septic shock, and three developed sepsis. Among the NB-PC cohort, more anaerobic organisms were identified among those who died compared to survivors (8/9 [89%] versus 48% [12/25], $P = 0.05$). In the NB-PC cohort, there appears to be a trend toward longer time to effective treatment among anaerobic compared to aerobic bacteremia (median, 9.7 versus 3.1 h; $P = 0.6479$), higher mortality (6/18 [33%] versus 3/16 [19%], $P = 0.4479$), and longer length of stay (median, 12 versus 7 days; $P = 0.3717$) (Table 5).

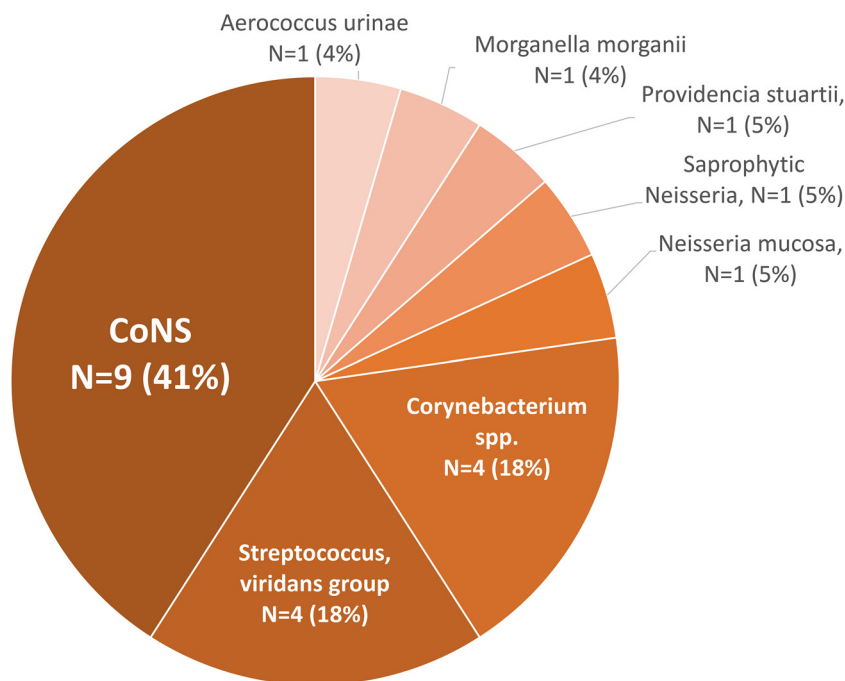


FIG 3 Aerobic organisms identified by Phoenix BD diagnostics from NB-PC cohort.

DISCUSSION

In this study, we intended to bring attention to the subset of patients with negative BioFire BCID results to clinicians who routinely rely on rapid diagnostics in identifying patients with bacteremia. We identified off-panel organisms and compared the clinical characteristics, management, and outcome of this subset of patients to those with bacteremia caused by pathogens readily identified by BioFire BCID.

There is no published data to our knowledge regarding the outcomes of patients with bacteremia due to off-panel organisms. Altun et al. (11) found 7.8% (13/167) of

TABLE 4 Empiric antimicrobial therapy for anaerobic bacteremia NB-PC cohort^a

Empiric antimicrobial therapy		
Prior to BioFire BCID	After BioFire BCID and before final cultures and susceptibility determinations	Organism (no. of isolates) identified by conventional methods
Monotherapy		
TZP	TZP	<i>Bacteroides fragilis</i>
None	TZP	<i>Aeromonas</i> spp.
ATM	ATM	<i>Bacillus coagulans</i>
VAN+azithromycin	CRO	<i>Bacteroides fragilis</i>
Combination therapy		
TZP regimen	TZP regimen	<i>Bacteroides thetaiotaomicron</i> (1), <i>Bacteroides fragilis</i> (1), <i>Anaerococcus prevotii</i> (1), <i>Pediococcus pentosaceus</i> (1)
TZP+MTZ regimen	TZP+MTZ regimen	<i>Bacteroides fragilis</i> (3), <i>Bacteroides thetaiotaomicron</i> (1)
MEM+MTZ	MEM+MTZ	<i>Desulfovibrio desulfuricans</i> (1)
CIP	MEM+MTZ regimen	<i>Clostridium citroniae</i> (1)
Sulfamethoxazole-trimethoprim	MTZ regimen	<i>Parabacteroides distasonis</i> (1)
CRO+MTZ	MTZ regimen	<i>Bacteroides vulgatus</i> (1)
MTZ+VAN regimen	MTZ+VAN regimen	<i>Clostridium clostridioforme</i> (1)
None	SAM+clindamycin regimen	<i>Peptoniphilus asaccharolyticus</i> (1)
MEM regimen	CRO+VAN	<i>Fusobacterium</i> spp. (1)
None	CRO+CIP	<i>Anaerococcus tetradius</i> (1)

^aTZP, piperacillin-tazobactam; ATM, aztreonam; VAN, vancomycin; CRO, ceftriaxone; MTZ, metronidazole; MEM, meropenem; CIP, ciprofloxacin; SAM, ampicillin-sulbactam.

TABLE 5 Time to effective therapy and length of stay and mortality outcomes among NB-PC cohort between aerobic and anaerobic bacteremia

NB-PC group	Finding (IQR)		P
	Aerobe (n = 16)	Anaerobe (n = 18)	
Median time (h) to effective treatment	3.1 (1–38.6)	9.7 (5–35.1)	0.6479
Mortality, no. (%)	3 (19)	6 (33)	0.4479
Median LOS (days)	7 (4–8)	12 (4–20)	0.3717
Median time (h) to final identification	129 (86–196)	228 (121–296)	0.0199

organisms identified by conventional methods were off-panel organisms on the BioFire BCID and included *Micrococcus* (n = 3), *Corynebacterium* (n = 2), *Peptoniphilus* (n = 2), *Gemella* spp. (n = 1), *Bacteroides fragilis* (n = 1), *Capnocytophaga canimorsus* (n = 1), *Eggerthella lenta* (n = 1), *Parvimonas micra* (n = 1), and *Lactobacillus* spp. (n = 1). Salimnia et al. (12) reported 11.9% (186/1,568) off-panel organisms that mostly included *Corynebacterium* (n = 48), *Micrococcus* (n = 27), *Acinetobacter* spp. (excluding *baumannii*, n = 23), *Bacillus cereus* (n = 19), *Staphylococcus pettenkoferi* (n = 16), and *Bacillus* spp. (n = 14). Southern et al. (10) reported the highest number of off-panel organisms (17.8%, 27/152), which included organisms such as *Propionibacterium* (n = 8), *Corynebacterium* (n = 5), *Bacillus* spp. (n = 4), and *Bacteroides fragilis* (n = 1). The sources of these off-panel organisms were not reported. Organisms that always or nearly always ($\geq 90\%$) represent true infection when isolated from blood cultures include *B. fragilis* (3, 16, 17). Unfortunately, *Bacteroides* spp. identified by conventional methods in our NB-PC cohort are not readily identified from blood cultures when using rapid diagnostic platforms.

In our study, only 6% of organisms could not be identified by BioFire BCID since they were not found on the panel. The spectrum of causative pathogens and the sources of infection for the NB-PC group in our study corresponded to that reported in the literature (18–20). In our study, the organisms from the NB-PC cohort that were determined to be true pathogens were mostly *Bacteroides* spp., followed by *Clostridium* and *Fusobacterium* spp. Nearly one-third of our patients with anaerobic bacteremia had an unknown source of infection, suggesting uncommon foci as possible sources. The gastrointestinal tract was previously reported as the principal source of *B. fragilis* group and clostridial bacteremia, while the female genital tract served as the principal source of *Peptostreptococcus* and *Fusobacterium* bacteremia, which is consistent with our findings (21, 22). Nearly one-third of NB-PC results were considered contaminants per study definition. The majority of the contaminants identified were CoNS (32%), *Corynebacterium* spp. (18%), and *Micrococcus* spp. (9%), which is similar to the findings in another study, where 48.9% of the off-panel organisms were regarded as skin contaminants such as corynebacteria/diphtheroids (45%), bacilli (30%), and micrococci (25%) (12). Patients deemed to have contamination had discontinuation of antibiotic therapy and thus were excluded from our outcome analysis.

Even though anaerobic bacteremia is rare (0.5 to 11.8% of all positive cultures), mortality remains high, from 25% up to 44% (23). Overall mortality among our NB-PC cohort was 26% (9/34), which included aerobic and anaerobic bacteremia. Among those with only anaerobic bacteremia, mortality was 25% (7/28). We were not able to assess *in vitro* activity of antimicrobial agents against anaerobic organisms since susceptibility testing was not routinely performed at our institution. However, considering the relatively low rates of resistance to commonly prescribed antimicrobial agents with anaerobic activity such as metronidazole, carbapenems, and piperacillin-tazobactam, therapy was presumed to be appropriate if the patient received any of these agents for anaerobic bacteremia.

Excluding contaminants and patients discharged or expired prior to BioFire BCID result, 32% of the NB-PC cohort did not receive effective empirical therapy (Table 4). This discrepancy continued even after BioFire BCID resulted. None of these patients expired during hospitalization. The patient with the unidentified nonfermenter Gram-negative bacilli died during admission.

Among those who died, a significantly higher proportion had concurrent infections (8/9 [89%] versus 7/25 [28%], $P = 0.0042$). In addition, a trend toward more piperacillin-tazobactam administration (6/9 [67%] versus 7/25 [25%], $P = 0.0565$) and more anaerobic bacteremia (8/9 [89%] versus 12/25 [48%], $P = 0.0504$) was observed among those who died compared to those who survived in the NB-PC group. The decision to broaden antibiotics to include anaerobic coverage tends to take longer since these blood cultures turned positive later (24). Nonetheless, even among those not identified by BioFire BCID, effective empirical antibiotics were usually started before bacteremia was detected. Delayed time to BioFire BCID and final susceptibility is likely multifactorial but largely driven primarily by the longer time required for anaerobic growth. There are rapid diagnostic platforms available that are able to detect directly from blood at an inoculum as low as 1 CFU/ml by magnetic resonance and PCR technology, such as T2 Biosystems, and can therefore potentially meet the need for detecting anaerobic bacteremia earlier than current methods when growth to reach sufficient inoculum for detection is not required. The higher proportion of anaerobic bacteremia and concurrent infections, along with a significant delay in starting active anaerobic coverage, likely contributes to the higher mortality observed in the NB-PC group compared to the PB-PC group.

Conclusion. Despite a similar clinical presentation and fewer comorbidities, increased mortality was observed among subjects with clinically confirmed infection with NB-PC versus PB-PC. Our findings affirm the need for faster identification of anaerobic bacteremia to facilitate prompt initiation of effective therapy. Until this need is met, antimicrobial stewardship intervention may consider broadening anaerobic coverage in patients with NB-PC results, especially if the source is due to an unknown or pelvic infection.

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