Interpretation of Positive Blood Cultures When PCR Blood Culture Identification (BCID) Results are "Not Detected"

Nebraska Medicine currently uses a multi-plex PCR-based blood culture identification (BCID) system that is able to identify potential pathogens growing in blood culture. BCID detects over 90% of the most common causative agents in bloodstream infections; however, when microbes not included on the panel are present in a blood culture, it returns a result of "Not Detected." This document aims to provide guidance in these scenarios supported by data collected at Nebraska Medicine from January 2018 to August 2019. A recent update to this test, known as BCID2, expands the number of targets that can be detected from the previous version. It is anticipated that BCID2 will detect most pathogens. This document has been updated to reflect those changes. As more data becomes available with BCID2 implementation this document will be updated.

Table 1: Recommendations for treatment of patients with blood cultures growing organisms not detected on BCID

Gram Stain/Preliminary Culture Result	Likely Organism (% total BCID negative)†	Recommended Treatment
Gram-positive:		
Aerobe (most can also grow in anaerobic bottles)	*Micrococcus* sp. (18.1%) Coagulase-negative *Staphylococcus* (9.3%)*More species detected on BCID2 Diphtheroids (7%)	1 out of 2 blood cultures positive **Do not start antibiotics** 2 out of 2 blood cultures positive **Vancomycin 15 mg/kg q12h**
Anaerobe bottle only	*Peptostreptococcus* sp. (4.4%) *Lactobacillus* sp. (2.6%) *Clostridium* sp. (2.6%)	**None generally recommended** If therapy indicated: Metronidazole 500 mg PO q8h OR Penicillin G 4 million units IV q4h
Gram-negative:		
Aerobe	*Acinetobacter* sp. (1.8%) *Stenotrophomonas maltophilia* (1.6%)*Detected on BCID2 *Pseudomonas fluorescens-putida* group (1%)	**Levofloxacin 750 mg IV/PO q24h**
Anaerobe bottle only	*Bacteroides fragilis* group (9.3%)*Genus detected on BCID2 *Fusobacterium* sp. (4.7%)	**Metronidazole 500 mg IV/PO q8h** or Piperacillin/tazobactam in suspected mixed infection (intra-abdominal, etc.)

Orange text = Cocci, Blue text = Bacilli (rods)

†A full list of isolated organisms can be found below in Table 3

**Indicates new target detected on the BCID2 Panel. For coagulase-negative Staphylococcus, direct species identification for S. epidermidis and S. lugdunensis will be provided along with genus level reporting*

Gram-Positives

When BCID results as "Not Detected" but there is microbial growth, the organism is most frequently gram-positive (71%). Of the gram-positive results, the most common species isolated were *Micrococcus* sp., coagulase-negative *Staphylococcus*, and Diphtheroids (combined 48.5%). These organisms can grow in either aerobic or anaerobic bottles.

They are usually considered contaminants and do not require treatment, but clinical judgment should be used. Instances in which these cultures may warrant treatment are when there are 2 out of 2 blood cultures positive or when the patient has a documented history of infection with the organism. Typically, when multiple cultures are positive with these organisms, the cause is device-related and the primary treatment is removal of the device, when possible.

Anaerobic gram-positive organisms are more rarely isolated, with the most common being *Peptostreptococcus* sp., *Lactobacillus* sp., and *Clostridium* sp. These organisms will grow in an anaerobic bottle only. They are typically considered contaminants and require no treatment, but clinical judgment should be used. If therapy is desired, the recommended antibiotics are metronidazole 500 mg po q8h OR penicillin G 4 million units IV q4h. Either of these options should have activity against common gram-positive anaerobic species.

BCID2: *Enterococcus sp.*

The previous version of BCID included a genus level assay for *Enterococcus*, detecting several different species including *E. faecium* and *E. faecalis*. BCID2 provides updated species level identification for these 2 major *Enterococcus* species associated with bloodstream infection, including the detection of resistance genes (vanA/B), but does not include the genus level assay. This allows rapid identification and tailoring of therapy for the species causing the majority of clinical disease but may result in Not Detected results for less common *Enterococcal* species (*E. avium*, *E. raffinosus*, etc.). In data collected from Nebraska Medicine over 11 months, 14 out of 121 *Enterococcal* bacteremia's (11.5%) were non-*E. faecalis* or *faecium* species. While these Enterococcal species are uncommon when detected in 2 blood cultures, they should be treated. Vancomycin resistance is uncommon and if present generally mediated by non-vanA/B mechanisms. (Rarely isolated from blood, *E. cassiflavus and E. gallinarum/E. flavescens* are intrinsically resistant to vancomycin via VanC, but routinely susceptible to ampicillin)Thus, if Enterococcal bloodstream infection is suspected or detected, vancomycin should be started as per Table 1. Final pathogen identification and susceptibilities are usually available in 24-72 hours and should always be reviewed to determine if therapy adjustments should be made.

Gram-Negatives

When BCID results as "Not Detected" and the gram stain characteristics are negative, the organisms are more commonly anaerobes. Detection of growth in the anaerobic bottle only strongly suggests an anaerobe with *Bacteroides fragilis* group (now detected on BCID2) and *Fusobacterium* sp. the most common. Although these organisms are not commonly seen in the blood, they are typically indicative of an underlying severe infection and are associated with high mortality rates, increasing the importance of appropriate therapy. Metronidazole is the preferred agent for these organisms because of its potent activity and lack of resistance. Penicillins with beta-lactamase inhibitors and carbapenems are also usually active.

Aerobic gram-negative rods that are "Not Detected" are rarer and typically include *Acinetobacter* sp., *Stenotrophomonas maltophilia* (detected on BCID2), and *Pseudomonas fluorescens-putida* group. These organisms are often, but not always, associated with true infection and should generally be treated with an appropriate agent. Levofloxacin has reliable activity against these organisms as well as other aerobic gram-negatives, making it an appropriate empiric choice until identification.

Table 3: Organism Groups Identified by Culture and Not Detected by BCID

Organism Group Stratified by Gram Stain	n	% of Gram Stain	% of Total BCID Negative
Gram Positive	**274**	**100.0%**	**70.8%**
Micrococcus sp.	70	25.5%	18.1%
Coagulase-negative *Staphylococcus*	36	13.1%	9.3%
Diphtheroids	27	9.9%	7.0%
Peptostreptococcus sp.	17	6.2%	4.4%
Bacillus species, not *anthracis*	12	4.4%	3.1%
Rothia sp.	10	3.6%	2.6%
Clostridium sp.	10	3.6%	2.6%
Lactobacillus sp.	10	3.6%	2.6%
Viridans group *Streptococcus*	8	2.9%	2.1%
Corynebacterium striatum group	7	2.6%	1.8%
Abiotrophia/*Granulicatella* sp.	7	2.6%	1.8%
Unable to identify	7	2.6%	1.8%
Gemella sp.	7	2.6%	1.8%
Enterococcus sp.	6	2.2%	1.6%
Actinomyces sp.	5	1.8%	1.3%
Aerococcus sp.	5	1.8%	1.3%
Propionibacterium sp.	5	1.8%	1.3%
Leuconostoc sp.	4	1.5%	1.0%
Peptoniphilus sp.	3	1.1%	0.8%
Parvimonas micra	3	1.1%	0.8%
Eggerthella lenta	3	1.1%	0.8%
Finegoldia magna	3	1.1%	0.8%
Atopobium parvulum	1	0.4%	0.3%
Dermabacter hominis	1	0.4%	0.3%
Staphylococcus aureus	1	0.4%	0.3%
Pediococcus sp.	1	0.4%	0.3%
Blautia producta	1	0.4%	0.3%
Cutibacterium acnes	1	0.4%	0.3%
Group C *Streptococcus*	1	0.4%	0.3%
Eubacterium limosum	1	0.4%	0.3%
Facklamia hominis	1	0.4%	0.3%
Gram Negative	**113**	**100%**	**29.2%**
Bacteroides fragilis group* (detected at species level on BCID2)	36	31.9%	9.3%
Fusobacterium sp.	18	15.9%	4.7%
Acinetobacter sp.	7	6.2%	1.8%
Prevotella sp.	6	5.3%	1.6%
*Stenotrophomonas maltophilia** (detected at species level on BCID2)	6	5.3%	1.6%
Unable to identify	5	4.4%	1.3%
Pseudomonas fluorescens-putida group	4	3.5%	1.0%
Pasteurella multocida	4	3.5%	1.0%
Sphingomonas paucimobilis	3	2.7%	0.8%
*Morganella morganii** (detected at genus level on BCID2)	3	2.7%	0.8%
Veillonella sp.	2	1.8%	0.5%
Moraxella sp.	2	1.8%	0.5%

Roseomonas sp.	2	1.8%	0.5%
Capnocytophaga sputigena	2	1.8%	0.5%
Leptotrichia sp.	2	1.8%	0.5%
Achromobacter xylosoxidans	1	0.9%	0.3%
Neisseria sicca group	1	0.9%	0.3%
Anaerobiospirillum succiniciproducens	1	0.9%	0.3%
Cardiobacterium hominis	1	0.9%	0.3%
Alistipes sp.	1	0.9%	0.3%
Chryseobacterium indologenes	1	0.9%	0.3%
Brevundimonas vesicularis	1	0.9%	0.3%
*Proteus vulgaris** (detected at genus level on BCID2)	1	0.9%	0.3%
Wautersiella falseni	1	0.9%	0.3%
Eikenella corrodens	1	0.9%	0.3%
Flavobacterium odoratum	1	0.9%	0.3%
Grand Total	**387**	**100.0%**	**100.0%**

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