Antimicrobial Stewardship Guidelines

ePlex® Blood Culture Identification (BCID) Guidance Document

This guideline was developed by the Antimicrobial Stewardship Program and Infectious Diseases teams.

This clinical practice guideline includes ***empiric*** treatment recommendations for positive blood cultures based on ePlex® BCID results. The guidance may need to be adapted based on clinical judgement and individual patient situation.

A. ePlex Background

The BJH Microbiology laboratory uses the ePlex® blood culture identification (BCID) rapid diagnostic technology. This platform detects 20 gram-positive targets, 21 gram-negative targets, 10 bacterial resistance genes, and 1 pan-*Candida* target, allowing a move from empiric to targeted antimicrobial treatment for bloodstream infections earlier, which is an important component of antimicrobial stewardship and improving patient outcomes. The empiric treatment recommendations are based on local susceptibility data, where available, and/or expected antimicrobial activity to guide therapy ***until culture and susceptibility testing is finalized*.**

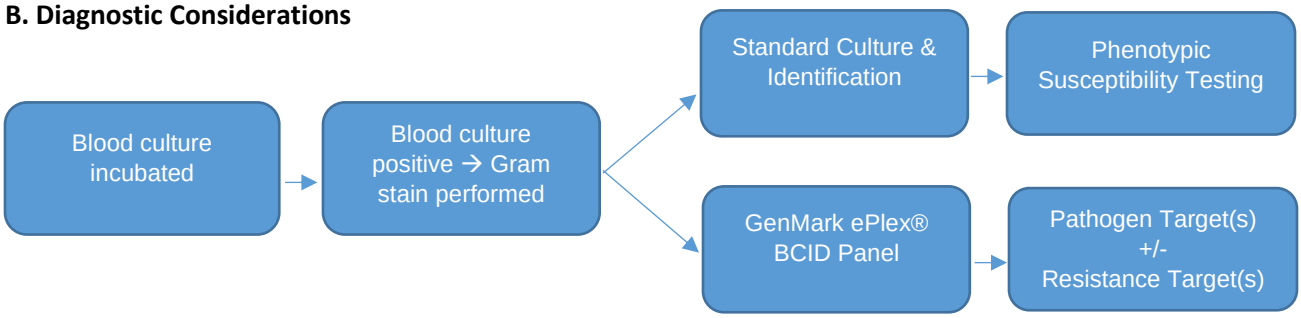
Additional considerations when providing empiric therapy recommendations include: hemodynamic status, immunocompromised status (e.g., febrile neutropenia), presence of central line/hardware, other infectious disease states and microbiological data, and identification of a source of bacteremia. Broader and/or additional antimicrobials may be continued based on such situations.

The following pathogen and resistance genes can be identified on the assay:

Gram Positive Targets	Gram Negative Targets	Fungal Target
• *Bacillus cereus group* • *Bacillus subtilis group* • *Corynebacterium* spp. • *Cutibacterium acnes* • *Enterococcus* spp. • *Enterococcus faecalis* • *Enterococcus faecium* • *Lactobacillus* spp. • *Listeria* spp. • *Listeria monocytogenes* • *Micrococcus* spp. • *Staphylococcus* spp. • *Staphylococcus aureus* • *Staphylococcus epidermidis* • *Staphylococcus lugdunensis* • *Streptococcus spp.* • *Streptococcus agalactiae* (GBS) • *Streptococcus anginosus group* • *Streptococcus pneumoniae* • *Streptococcus pyogenes* (GAS)	• *Acinetobacter baumannii* • *Bacteroides fragilis* • *Citrobacter* spp. • *Cronobacter sakazakii* • *Enterobacter (non-cloacae complex)* • *Enterobacter cloacae complex* • *Escherichia coli* • *Fusobacterium nucleatum* • *Fusobacterium necrophorum* • *Haemophilus influenzae* • *Klebsiella oxytoca* • *Klebsiella pneumoniae* • *Morganella morganii* • *Neisseria meningitidis* • *Proteus* spp. • *Proteus mirabilis* • *Pseudomonas aeruginosa* • *Salmonella* spp. • *Serratia* spp. • *Serratia marcescens* • *Stenotrophomonas maltophilia*	• Pan-Candida target ○ Detects *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis* but not to the species level
Gram Positive Resistance Gene Targets	**Gram Negative Resistance Gene Targets**	
• *mecA or mecC* (methicillin resistance gene) in staphylococci • *vanA* or *vanB* (vancomycin resistance gene) in enterococci	• CTX-M (extended-spectrum B-lactamase gene) • KPC (carbapenemase gene) • IMP (carbapenemase gene) • NDM (carbapenemase gene) • VIM (carbapenemase gene) • OXA (OXA-23 and OXA-48 beta-lactamase genes)	

These recommendations do not establish a standard of care to be followed in every case. Each case is different and the individuals providing health care are expected to use their judgement in determining what is in the best interests of the patient based on the circumstances at the time.
Approved by SLCH PD&T Committee November 2024

B. Diagnostic Considerations



This test does not exclude the possibility of a mixed bacterial infection. Culture and susceptibility data should always be followed-up and reviewed after the initial ePlex® result.

BJH microbiology laboratory testing and reporting

- The ePlex BCID is run after on the *first* blood culture is positive and Gram stain is performed
- Repeated in the following scenarios:
    - New morphology on subsequent Gram stain
    - For each bottle of a set with organisms which could be contaminants
    - After 72 hours
- Results will appear in Epic within hours, displayed within the blood culture result under the Direct Specimen Exam component describing the Molecular Analysis
    - *Note: A result of "No Targets Detected" will **not** be reported. Thus, lack of a Molecular Analysis result several hours after blood culture positivity indicates a positive blood culture with an organism not detectable by BCID. Empiric coverage should be guided by the Gram stain result and clinical scenario.*

Resistance targets

- BCID can detect *mecA* and *mecC* resistance in mixed cultures, but it cannot attribute the resistance to either *S. aureus* or another staphylococcal target (e.g., *S. epidermidis*) if multiple are present
- BCID can detect *vanA* or *vanB* resistance in mixed cultures, but it cannot attribute the resistance to either *E. faecalis* or *E. faecium* if both bacteria are present
- BCID can detect the CTX-M, KPC, IMP, NDM, VIM and OXA for *A. baumannii*, *P. aeruginosa* and Enterobacterales on panel, but it cannot attribute the resistance to a specific pathogen if multiple pathogens are present

Limitations

- Possible cross-reactivity with *E. coli* and *Shigella*: reported as *presumptive E. coli*
- Possible cross-reactivity with *S. pneumoniae* and *S. mitis*: reported as *presumptive S. pneumoniae*
- Potential for lower sensitivity in polymicrobial infections, but improved compared to Verigene

C. Antimicrobial Dosing Resources

The following additional resources are available for dosing considerations:

1. NICU Drug Book
2. Lexi-Comp

D. Antimicrobial Stewardship

The SLCH ASP performs real-time review on all positive BCID results. The review is performed by the ASP pharmacist Monday-Friday during regular business hours and by the first-call infectious diseases physician during off-hours. This review includes ensuring patients are receiving guideline recommended therapy (including agent selection, dose, and duration of therapy) and subsequently contacting the primary service when a therapy modification is recommended.

Gram-Positive Bacterial Targets & Empiric Antimicrobial Recommendations for Pediatric Patients

Pathogen Group	Bacterial Target	Comments	Recommended Therapy	Alternative Therapy
Enterococci				
Enterococcus faecalis[1]	***E. faecalis*** *vanA* or *vanB* not detected		Ampicillin	Vancomycin
	E. faecalis *vanA* or *vanB* detected	Vancomycin-resistant *E. faecalis* (VRE)	Ampicillin	Linezolid or Daptomycin[2]
Enterococcus faecium	***E. faecium*** *vanA* or *vanB* not detected	Vancomycin-susceptible *E. faecium* (VSE)	Vancomycin	Linezolid or Daptomycin[2]
	E. faecium *vanA* or *vanB* detected	Vancomycin-resistant *E. faecium* (VRE)	Linezolid	Daptomycin[2]
Enterococcus spp. [3]	***Enterococcus* spp.** Regardless of *vanA* or *vanB*	Commonly includes: *E. avium, E. durans E. casseliflavus, E. gallinarum, E. raffinosus*	Linezolid	Daptomycin[2]
Staphylococci				
Staphylococcus aureus	***S. aureus*** *mecA or mecC* not detected	Methicillin-susceptible *S. aureus* (MSSA)	Cefazolin[4] Concern for CNS infection: Oxacillin/Nafcillin	
	S. aureus *mecA or mecC* detected	Methicillin-resistant *S. aureus* (MRSA)	Ceftaroline or Daptomycin[2] Concern for CNS infection: Vancomycin	
Staphylococcus lugdunensis	***S. lugdunensis*** *mecA or mecC* not detected	Methicillin-susceptible *S. lugdunensis*	Cefazolin[4] Concern for CNS infection: Oxacillin/Nafcillin	
	S. lugdunensis *mecA or mecC* detected	Methicillin-resistant *S. lugdunensis*	Vancomycin	Daptomycin[2]
Staphylococcus epidermidis	***S, epidermidis*** *mecA or mecC* not detected	Methicillin-susceptible *S. epidermidis* (MSSE)	Consider possibility of contamination if a single positive culture and evaluate clinically if treatment is appropriate: Cefazolin[4] or Oxacillin/Nafcillin	
	S. epidermidis *mecA or mecC* detected	Methicillin-resistant *S. epidermidis* (MRSE)	Consider possibility of contamination if a single positive culture and evaluate clinically if treatment is appropriate: Vancomycin	
Staphylococcus spp.	**Staphylococcus spp.** *mecA or mecC* not detected	Coagulase-negative Staphylococcus species include: *S. haemolyticus, S. hominis, S. capitis, S saprophyticus*	Consider possibility of contamination if a single positive culture and evaluate clinically if treatment is appropriate: Cefazolin[4] or Oxacillin/Nafcillin	
	Staphylococcus spp. *mecA or mecC* detected		Consider possibility of contamination if a single positive culture and evaluate clinically if treatment is appropriate: Vancomycin	

These recommendations do not establish a standard of care to be followed in every case. Each case is different and the individuals providing health care are expected to use their judgement in determining what is in the best interests of the patient based on the circumstances at the time. Approved by SLCH PD&T Committee November 2024

Pathogen Group	Bacterial Target	Comments	Recommended Therapy	Alternative Therapy
Streptococci				
***Streptococcus agalactiae* (GBS)**	***S. agalactiae***	GBS is universally susceptible to beta-lactams and vancomycin	Penicillin G or Ampicillin	Cefazolin[4]
Streptococcus pneumoniae	***S. pneumoniae***		Penicillin G or Ampicillin	Ceftriaxone[5]
			Concern for CNS infection: Ceftriaxone[5] PLUS Vancomycin	
***Streptococcus pyogenes* (GAS)**	***S. pyogenes***	GAS is universally susceptible to beta-lactams and vancomycin	Penicillin G or Ampicillin	Cefazolin[4]
Streptococcus anginosus	***S. anginosus***	Includes: *S. anginosus, S. intermedius, and S. constellatus*	Penicillin G or Ampicillin	Ceftriaxone[5]
			Concern for CNS infection: Ceftriaxone[5] PLUS metronidazole[6]	
***Streptococcus* spp.**	***Streptococcus* spp.**	Includes: *S. dysgalactiae* or viridans group Streptococci (*S. mitis, S. salivarius, S. mutans, S. sanguinis*)	Consider possibility of contamination if a single positive culture and evaluate clinically if treatment is appropriate: Ceftriaxone[5] Hematologic malignancy: Vancomycin	
Other Gram-Positive Targets				
Micrococcus	***Micrococcus***		Consider possibility of contamination if a single positive culture and evaluate clinically if treatment is appropriate: Vancomycin	
Bacillus	***B. cereus* group**	*B. cereus* often resistant to all beta-lactams other than carbapenems		
	***B. subtilis* group**			
Corynebacterium	***Corynebacterium* spp.**	Commonly includes: *C. striatum, C. jeikeium, C. amycolatum*		
Cutibacterium	***Cutibacterium* spp.**	Formerly *Propionibacterium acnes*	Consider possibility of contamination if a single positive culture and evaluate clinically if treatment is appropriate: Penicillin G	
Lactobacillus	***Lactobacillus* spp.**	Commonly includes: *L. rhamnosus, L. casei, L. fermentum* Many species are resistant to vancomycin		
Listeria	***L. monocytogenes***		Ampicillin	Trimethoprim/sulfamethoxazole
	***Listeria* spp.**	Commonly includes: *L. grayi, L. innocua, L. ivanovii, L. seeligeri, L. welshimeri*	Consider possibility of contamination if a single positive culture and evaluate clinically if treatment is appropriate: Ampicillin	

[1]Ampicillin resistance not detected by ePlex; however, antibiogram data demonstrate 100% of isolates are susceptible to ampicillin, regardless of *vanA* or *vanB* detection

[2]Consider daptomycin over linezolid in patients on ECMO; however, daptomycin should NOT be used for treatment of a bacteremia if the source is thought to be respiratory due to inactivation; recent antibiogram data demonstrate lower daptomycin susceptibility rates compared to other agents (e.g., vancomycin or ceftaroline for *S. aureus* and linezolid for *E. faecium*)

[3]Vancomycin resistance can occur via other mechanisms not detected by ePlex (e.g., *vanC*)

[4]Not recommended if concern for CNS infection

[5]Neonates must be ≥7 days of age, corrected GA ≥35 weeks, not receiving calcium-containing solutions or parenteral nutrition, total serum bilirubin <5 mg/dL, **and** albumin within normal limits

[5]Empiric therapy includes the addition of metronidazole if there is concern for sinus disease with intracranial extension due to the polymicrobial nature of such infections

Gram-Negative Bacterial Targets & Empiric Antimicrobial Recommendations for Pediatric Patients

Pathogen Group	Bacterial Target	Comments	Recommended Therapy	Alternative Therapy	
Enterobacterales					
PEK Pathogens Salmonella	***Escherichia coli***		Ceftriaxone Neonate not meeting criteria to receive ceftriaxone[1]: Ceftazidime Hemodynamic instability[2]: Meropenem		****See below if any resistance markers are detected**** (CTX-M, KPC, OXA, VIM, IMP, NDM)
	Klebsiella oxytoca				
	Klebsiella pneumoniae				
	Proteus mirabilis				
	***Salmonella* spp.**	May include: *S. parathyphi, S. typhi, S. choleraesuis, S. typhimurium*			
Low risk for clinically significant inducible AmpC production	***Cronobacter sakazakii***		Ceftriaxone Neonate not meeting criteria to receive ceftriaxone[1]: Ceftazidime Hemodynamic instability[3]: Cefepime		
	Morganella morganii				
	***Proteus* spp.**	May include: P. *penneri, P. vulgaris*			
	Serratia marcescens				
	***Serratia* spp.**	May include*: S. ficaria, S. grimesii, S. odorifera, S. liquefactions*			
Risk for clinically significant inducible AmpC production	***Citrobacter* spp.**	May include: *C. freundii, C. koseri*	Cefepime	Meropenem	
	***Enterobacter cloacae* complex**				
	***Enterobacter* spp.** (non-*cloacae* complex)	May include: *E. aerogenes (Klebsiella aerogenes), E. amnigenus*			
Non-Fermenting GNB					
Acinetobacter	***A. baumannii***		Ampicillin/sulbactam[4,5] Hemodynamic instability: consider extending infusion (over 4h) and/or **addition** of minocycline	Minocycline PLUS cefiderocol	****See below if any resistance markers are detected**** (CTX-M, KPC, OXA, VIM, IMP, NDM)
Pseudomonas	***P. aeruginosa***		Cefepime Hemodynamic instability[6]: consider extending infusion (over 4h) and/or **addition** of tobramycin Risk for MDR *P. aeruginosa*[7]: evaluate prior isolates	Piperacillin/ tazobactam[5]	
Stenotrophomonas	***S. maltophilia***		Trimethoprim/sulfamethoxazole Hemodynamic instability: consider **addition** of cefiderocol, minocycline, or levofloxacin	Cefiderocol Hemodynamic instability: consider **addition** of minocycline or levofloxacin	

Pathogen Group	Bacterial Target	Comments	Recommended Therapy	Alternative Therapy
Gram-Negative Coccobacilli/Diplococci				
Haemophilus	***H. influenzae***		Ceftriaxone Neonate not meeting criteria to receive ceftriaxone[1]: Ceftazidime	Ampicillin/sulbactam[5]
Neisseria	***N. meningitidis***			Meropenem
Anaerobes				
Bacteroides	***B. fragilis***	Clindamycin, cefoxitin, and cefotetan not recommended empirically for *B. fragilis* due to resistance	Metronidazole PLUS ceftriaxone[8]	Piperacillin/tazobactam[5]
Fusobacterium	***F. nucleatum***		Ampicillin-sulbactam[5] Concern for CNS infection: Metronidazole PLUS ceftriaxone	
	F. necrophorum			

Resistance Target	Recommended Therapy
CTX-M extended-spectrum beta-lactamase (ESBL) gene detected	**Enterobacterales:** Meropenem
KPC carbapenemase gene detected	**Enterobacterales:** ceftazidime/avibactam OR meropenem/vaborbactam ***P. aeruginosa*:** ceftazidime/avibactam OR cefiderocol OR imipenem/relebactam[9,10] ***A. baumannii*:** minocycline PLUS either cefiderocol OR sulbactam/durlobactam[9,10]
NDM, VIM, or IMP carbapenemase gene detected	Susceptibility highly variable, limited data; no agents are universally active **Enterobacterales or *P. aeruginosa*:** cefiderocol OR aztreonam PLUS ceftazidime/avibactam ***A. baumannii*:** minocycline PLUS cefiderocol
OXA beta-lactamase gene detected	**Enterobacterales or *P. aeruginosa*:** ceftazidime/avibactam OR cefiderocol ***A. baumannii*:** minocycline PLUS either cefiderocol OR sulbactam/durlobactam[9,10]

[1]Neonates must be ≥7 days of age, corrected GA ≥35 weeks, not receiving calcium-containing solutions or parenteral nutrition, total serum bilirubin <5 mg/dL, **and** albumin within normal limits

[2]Escalation to meropenem may be considered due to the possibility of non-CTX-M extended-spectrum beta-lactamases (e.g., SHV) not detectable by ePlex

[3]Escalation to cefepime may be considered due to the possibility of AmpC production, especially in the setting of infections with high bacterial burden and/or incomplete source control

[4]Sulbactam is active component, while ampicillin does not have activity against *Acinetobacter*; thus, amoxicillin/clavulanic acid cannot be used as alternative therapy. Pediatric-specific antibiogram data is not available for *A. baumannii* given too few isolates, though regional adult antibiogram data demonstrate significantly higher rates of sulbactam vs carbapenem susceptibility; therefore, carbapenems should NOT be considered an empiric escalation of therapy

[5]Not recommended if concern for CNS infection

[6]SLCH and pediatric-specific antibiogram data demonstrate high rates of susceptibility to cefepime and piperacillin/tazobactam, as compared to carbapenems; therefore, carbapenems should NOT be considered an empiric escalation of therapy, unless supported by prior isolates (as described below)

[7]Resistance largely mediated by non-beta-lactamase mechanisms not detectable by ePlex; evaluate prior *P. aeruginosa* isolates within the past 12 months and, if necessary, use previously susceptible beta-lactam agent as empiric therapy (e.g., ceftolozane/tazobactam)

[8]Often represents polymicrobial infection; depending on clinical scenario, possible options, in addition to metronidazole, include ceftriaxone, cefepime, or ciprofloxacin; if a carbapenem or piperacillin/tazobactam is indicated based on other microbiologic data, metronidazole is not necessary

[9]Non-formulary agent; must follow non-formulary ordering process and contact pharmacy for drug procurement

[10]No pediatric dosing, safety, or efficacy data available

Fungal Target & Empiric Antimicrobial Recommendations for Pediatric Patients

Pathogen Group	Fungal Target	Comments	Recommended Therapy	Alternative Therapy
Fungal				
Candida	**Candida spp.**	Detects *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis* but not to the species level	Micafungin Neonate: amphotericin B deoxycholate	Liposomal amphotericin B