Recommendations Regarding Use of Rapid Blood Pathogen Identification Panel Data

Trevor Van Schooneveld MD, Scott Bergman, PharmD, BCPS, Paul Fey, PhD, Mark Rupp, MD

The Clinical Microbiology laboratory at Nebraska Medicine utilizes an FDA approved test called the Blood Pathogen Panel (BPP, performed on the BioFire BCID instrument). This test uses a PCR-based approach to amplify DNA targets directly from positive blood cultures allowing rapid identification of pathogens and earlier transition to most appropriate therapy. This test identifies 21 different Gram-negative, Gram-positive, and yeast pathogens (**Table 1**). It also detects the genes responsible for vancomycin-resistance in Enterococci, methicillin-resistance in Staphylococci, and one of the genes responsible for carbapenem-resistance in the *Enterobacteriaceae*. In addition to multiple species specific assays, the panel also has 4 genus specific assays which allows detection of pathogens for which there are not specific targets (i.e. Citrobacter, Salmonella, etc.). Information regarding which species are detected by these assays is listed in **Table 4**.

Table 1: List of Pathogens and Resistance Genes Detected:

Gram-positive Bacteria	Gram-Negative Bacteria	Yeast	Resistance Gene
Enterococcus genus	*Acinetobacter baumannii*	*Candida albicans*	*mecA* = methicillin (oxacillin) resistance
Listeria monocytogenes	*Enterobacteriaceae* family	*C. glabrata*	*vanA/B* = vancomycin resistance
Staphylococcus genus	*Enterobacter cloacae* complex	*C. krusei*	*kpc* = carbapenem resistance
Staphylococcus aureus	*Escherichia coli*	*C. parapsilosis*	
Streptococcus genus	*Klebsiella oxytoca*	*C. tropicalis*	
Streptococcus agalactiae	*Klebsiella pneumonia*		
Streptococcus pneumoniae	*Proteus* spp		
Streptococcus pyogenes	*Serratia marcescens*		
	Haemophilus influenzae		
	Neisseria meningitidis		
	Pseudomonas aeruginosa		

The microbiology lab notifies clinicians of positive blood culture Gram-stain results immediately after they are performed. They then perform the BPP and results are typically available within One Chart in <2 hours. The rapid reporting of this data allows for early adjustment of antimicrobials to the most appropriate therapy. A list of recommended antibiotic treatment choices are outlined in **Table 2**. The Antimicrobial Stewardship Team based on an analysis of the institutional antibiogram developed these recommendations. Relevant information on susceptibility is provided for gram-negative pathogens where the activity of agents is variable. When blood culture Gram-stain and BPP results are known,

current antimicrobial therapy should be evaluated in light of the clinical picture and adjusted to the most appropriate single agent if possible. In addition, when full susceptibility results become available therapy should be adjusted to the most narrow spectrum appropriate agent.

Implementation of the BPP at NM resulted in earlier implementation of active therapy (6 hours earlier) and more rapid transition to the most narrow spectrum effective therapy (12 hours earlier). Other studies have shown that rapid pathogen identification can result in shorter hospital stays and improved clinical outcomes. The utility and cost-effectiveness of such testing is dependent upon clinicians reacting to the data. The antimicrobial stewardship team currently reviews this data during business hours and contacts the treating team if they feel adjustments in therapy are needed, but it is strongly recommended that this data be utilized in making treatment decisions at the time it is available.

Certain infections are often polymicrobial in nature and the isolation of a single pathogen from the blood culture, while allowing narrowing of therapy, should not result in over-narrowing. An example would be a complicated intra-abdominal infections where anaerobes are frequently present and therapy active against these pathogens should generally be included until definitive cultures of the site of infection have returned.

Final pathogen susceptibilities are usually in 24-72 hours and should always be reviewed to determine if therapy adjustments should be made.

Table 2: Blood Pathogen Panel Results and Recommended Therapy

Use this table to select the most appropriate empiric therapy for treating a blood stream infection (BSI). Patients who responded to a narrow spectrum agent do not need to be escalated, even if this guideline recommends a broader spectrum agent and can usually be safely continued on current therapy. Patients who have not clinically responded to initial therapy (persistent fever, lack of improvement, etc.) should have therapy adjusted to a more active regimen based on the guideline. Allergies, organ dysfunction, and history of antimicrobial resistance should be considered when choosing therapy. Data on susceptibility for various gram-negative pathogens was derived from the 2016 institutional antibiograms including a bloodstream infection specific antibiogram (see **Table 3**).

Pathogen Detected	Preferred Therapy	Comments (susceptibility data from 2016)
***Enterococcus* genus** *van A/B* negative *van A/B* positive = VRE	Vancomycin 15 mg/kg Q12h Linezolid 600mg q12h	Linezolid slightly more active in VRE • Linezolid 89-94% susceptible (89% blood) • Daptomycin 87-90% susceptible (90% blood)
Staphylococcus aureus *mecA* negative = MSSA *mecA* positive = MRSA	Oxacillin 2g q4h Vancomycin 15 mg/kg Q12h	Cefazolin 2g q8h is an alternative Daptomycin is an alternative to vancomycin
***Staphylococcus* genus** with negative *S. aureus* PCR Blood Culture (Bcx) result: 1 of 2 BCX positive 2 of 2 BCX positive *mecA* negative *mecA* positive	Consider withholding or discontinuing therapy as likely contaminant, do not need to routinely draw repeat BCX Oxacillin 2g q4h Vancomycin 15 mg/kg Q12h	In severely ill patients consider starting/continuing therapy until more definitive results return Cefazolin 2g q8h is an alternative
***Streptococcus pyogenes* (Group A Strep) and *Streptococcus agalactiae* (Group B Strep)**	Penicillin 3 million units q4h or Ampicillin 2g IV q4h or Cefazolin 2g IV Q8h	Beta-hemolytic strep are routinely susceptible to penicillin Vancomycin in severe beta-lactam allergy
Streptococcus pneumoniae Source of Infection: Pneumonia CNS Infection	Penicillin 3 million units q4h or Ampicillin 2g IV q4h Ceftriaxone 2g q12h + Vancomycin 15 mg/kg Q12h	Continue vancomycin until susceptibilities return

***Streptococcus* genus** Blood Culture result: 1 of 2 BCX positive 2 of 2 BCX positive	Consider with-holding or discontinuing therapy as likely contaminant Ceftriaxone 2g q24h	In severely ill patients consider starting/continuing therapy until more definitive results return
Listeria monocytogenes	Ampicillin 2g q4h	TMP/SMX in patients with severe beta-lactam allergy
Acinetobacter baumannii	Meropenem 500mg 6h +/- amikacin 15mg/kg daily	**No beta-lactam with >90% activity** • Meropenem 83% susceptible • Cefepime 75% susceptible Consider addition of amikacin in severely ill or non-responding
E. coli	Community-onset (CO): Ceftriaxone 2g q24 **OR** Piperacillin/tazobactam 4.5 g q8h (consider with history of resistance, recurrent UTI, recent FQ exposure, or recent hospital stay) Nosocomial-onset (NO): Piperacillin/tazobactam 4.5 g q8h **OR** Ertapenem 1g q24h	Ceftriaxone: 86-96% susceptible • 91-96% CO susceptible (91% blood) • 78-89% NO susceptible (78% blood) Pip/tazo: 94-98% susceptible • 95-98% CO susceptible (97% blood) • 64-95% NO susceptible (94% blood) Cefepime: 78-97% susceptible • 92-97% CO susceptible (92% blood) • 78-92% NO susceptible (78% blood) Levofloxacin: 69-84% susceptible (75% blood) • 80-84% CO susceptible • 69-74% NO susceptible Ertapenem: 100% susceptible
Klebsiella pneumoniae	Community-onset: Ceftriaxone 2g q24h Nosocomial: Piperacillin/tazobactam 4.5 g q8h **OR** Ertapenem 1g q24h	Ceftriaxone: 92-96% susceptible (92-94% blood) • 92-98% CO susceptible • 88-92% NO susceptible Pip/tazo: 92-97% susceptible (92-98% blood) Levofloxacin: 95-100% susceptible (99% blood) Ertapenem: 99-100% susceptible (100% blood)
Klebsiella oxytoca	Community-onset: Cefepime 1g q6h Nosocomial-onset: Ertapenem 1g q24h	Cefepime:85-97% susceptible(94% blood) • 97% CO susceptible • 85% NO susceptible Levofloxacin: 90-100% susceptible (100% blood) Ertapenem: 99-100% susceptible (100% blood) Pip/tazo: 80-90% susceptible (90% blood)

Serratia marcescens	Cefepime 1g q6h	Cefepime: 91-96% susceptible Levofloxacin: 97-100% susceptible Ertapenem: 97-100% susceptible
Enterobacter cloacae	Merepenem 500mg Q6h	Meropenem: 100% susceptible Levofloxacin: 97-99% susceptible Cefepime: 78-87% susceptible (87% blood) Ertapenem: 79-86% susceptible (87% blood) Pip/tazo: 73-85% susceptible (85% blood)
***Proteus* spp**	Ceftriaxone 2g q24h	97-100% susceptible(100% blood)
***Enterobacteriaceae* family only** (See list of potential pathogens in **Table 4**)	Piperacillin/tazobactam, cefepime, or ertapenem	If on combination therapy (FQ or AG) with pip/tazo, cefepime, or carbapenem consider stopping non-beta lactam agent as all have excellent activity
Pseudomonas aeruginosa	Piperacillin/tazobactam 4.5 g q8h infused over 4h +/- tobramycin 7 mg/kg daily	**No beta-lactam with >90% activity** Pip/tazo: 82-89% susceptible (82% blood) Meropenem: 77-86% susceptible(86% blood) Cefepime: 80-83% susceptible(83% blood) Consider tobramycin addition in severely ill or non-responding patients
Neisseria meningitidis	Penicillin 4 million units q4h or Ceftriaxone 2g q12h	
Haemophilus influenzae	Ampicillin/sulbactam 3g q6h or Ceftriaxone 2g q24h or	
Candida albicans	Fluconazole 800mg load, 400mg daily	93% susceptible, 3% susceptible dose-dependent Consider high dose fluconazole (1600mg load, 800mg daily) if previous azole exposure
Candida glabrata	Micafungin 100mg q24h	99% susceptible
Candida krusei	Micafungin 100mg q24h	100% susceptible
Candida parapsiolosis	Fluconazole 800mg load, 400mg daily	91% susceptible, 6% susceptible-dose dependent Consider high dose fluconazole (1600mg load, 800mg daily) if previous azole exposure
Candida tropicalis	Micafungin100mg q24h	100% susceptible
***mecA* gene**	Vancomycin 15 mg/kg Q12h	Marker for methicillin-resistant Staphylococci (i.e. = MRSA)
***van A/B* gene**	Linezolid 600mg q12h	Marker for vancomycin-resistant Enterococcus (i.e.= VRE)

***kpc* gene**	**Consult ID** Ceftazidime/avibactam (non-formulary) + Colistin +/- Tigecycline	Marker for carbapenem resistant *Enterobacteriaceae* (i.e. = CRE)

Table 3: NM Bloodstream Infection Antibiogram 2016

Antibiogram generated using only positive blood cultures.

	***Enterobacter cloacae* (N=60)**	***E. coli* (N=379)**	***Klebsiella oxytoca* (N=31)**	***Klebsiella pneumoniae* (N=136)**	***Proteus mirabilis* (N=31)**	***Serratia marcesces* (N=116)**	***Pseudomonas aeruginosa* (N=72)**
Amp/Sul	26.7%	48.8%	64.5%	80.1%	90.3%	13%	XXX
Pip/tazo	85%	94.5%	90.3%	64.9%	100.00%	74%	81.9%
Cefuroxime	33.3%	82.3%	80.6%	83.8%	96.8%	XXX	XXX
Ceftazidime	57.1%	86.0%	93.5%	93.9%	100.00%	XXX	87.5%
Ceftriaxone	63.3%	85.8%	90.3%	94.1%	100%	63%	XXX
Cefepime	86.7%	88.1%	93.5%	93.4%	100%	92%	83.3%
Aztreonam	80%	86%	87.1%	94.1%	90.3%	66%	70.8%
Ertapenem	86.7%	99.2%	100%	99.3%	100.00%	98%	XXX
Meropenem	100%	100%	100%	100%	100%	98%	86.1%
Levofloxacin	98.3%	74.9%	100%	99.3%	71%	98%	72.2%
TMP/SMX	90.0%%	66.8%	96.8%	86%	64.5%	96%	XXX
Gentamicin	95%	84.4%	96.8%	96.3%	80.6%	97%	84.7%
Tobramycin	98.3%	84.4%	96.8%	93.4%	80.6%	93%	97.2%
Amikacin	100%	99.5%	100%	100%	100%	99%	95.8%

	***Streptococcus pneumoniae* (N=53)**	***Streptococcus. viridans* group (N=78-98)**	***Enterococcus faecalis* (N=107)**	***Enterococcus faecium* (N=78)**
PCN Non-meningitis	100%	67.3%	100%	XXX
PCN Meningitis	73.2%	XXX	XXX	XXX
Ampicillin	100%	67.3%	100%	12.8%
Ceftriaxone Non-meningitis	100%	94.8%	XXX	XXX
Ceftriaxone Meningitis	94.6%	XXX	XXX	XXX
Meropenem	89.3%	100%	XXX	XXX
Vancomycin	100%	100%	100%	23.1%
Azithromycin	62.3%	50%	34.6%	6.4%
Clindamycin	94.2%	91%	XXX	XXX
Levofloxacin	100%	80.6%	81.3%	9%
Daptomycin	XXX	XXX	100%	89.7%
Linezolid	XXX	XXX	91.6%	88.5%

Table 4: Pathogens Detected by BPP

Genus Specific Assay	Pathogens Detected	Pathogens Not Detected
Enterococcus genus	*E. faecium* *E. faecalis* *E. avium* *E. casseliflavus* *E. durans* *E. gallinarum* *E. hirae* *E. dispar* (reduced sensitivity) *E. saccharolyticus* (reduced sensitivity)	*E. raffinosus*
Staphylococcus genus	*S. aureus* *S. caprae* *S. cohnii* *S. epidermidis* *S. haemolyticus* *S. hominis* *S. lugdunensis* *S. xylosus* *S. capitis* (reduced sensitivity) *S. pasteuri* (reduced sensitivity) *S. saprophyticus* (reduced sensitivity) *S. simulans* (reduced sensitivity) *S. warneri* (reduced sensitivity)	*S. auricularis* *S. carnosus* *S. lentus* *S. pettenkoferi* *S. pseudointermedius* *S. schleiferi* *S. sciuri*
Streptococcus genus Designed to detect multiple Viridans group species and non-Group A/B beta-hemolytic streptococci	*S. anginosus* *S. bovis* *S. constellatus* *S. dysgalactiae* *S. equinus* *S. gallolyticus* *S. gordonii* *S. intermedius* *S. mitis* *S. mutans* *S. oralis* *S. parasanguinis* *S. pseudopneumoniae* *S. salivarius* *S. sanguinis*	

Enterobacteriaceae Designed to detect less common *Enterobacteriaceae*	*Cedeceae* spp. *Citrobacter* spp. *Cronobacter* spp. *Enterobacter* spp. *Escherichia* spp. *Klebsiella* spp. *Kluyvera* spp. *Leclercia adecarboxylata* *Proteus* spp. *Raoultella* spp. *Salmonella* spp. *Shigella* spp. *Serratia marcescens* *Serratia ficaria* *Serratia entomophila* *Yokenella regensbergei* *Edwardsiella* spp. (reduced sensitivity) *Enterobacter gergoviae* (reduced sensitivity) *Hafnia alvei* (reduced sensitivity) *Pantoea* spp. (reduced sensitivity) *Salmonella bongori* (reduced sensitivity) *Serratia fonticola* (reduced sensitivity) *Serratia odorifera* (reduced sensitivity) Serratia rubidaeae (reduced sensitivity)	*Morganella morganii* *Providencia* spp. *Rahnella* spp *Serratia liquefaciens* *Serratia plymuthica* *Tatumella ptyseos* *Yersinia enterocolitica*

Table 5: FDA data

The following table outlines the cumulative data from the BioFire BCID FDA trial comparing BCID results to standard culture that was utilized for approval. A number of studies have been published regarding the sensitivity and specificity of the BPP suggesting the test is highly accurate. One area the BPP may suffer from decreased accuracy is in patients with polymicrobial BSI. Whenever multiple pathogens are noted on the gram stain or detected by the BPP results should be interpreted with caution as they can be both falsely positive and/or negative.

Analyte	Prospective Blood Cultures	
	Sensitivity	Specificity
Antimicrobial Resistance Genes		
mecA (reported with *Staphylococcus*)	98.4%	98.3%
vanA/B (reported with *Enterococcus*)	100%	100%
KPC (reported with *Enterobacteriaceae*, *A. baumannii*, and *P. aeruginosa*)	100%	100%
Gram-Positive		
Enterococcus	97.7%	99.8%
Listeria monocytogenes	100%	100%
Staphylococcus a	96.5%	99.1%
Staphylococcus aureus	98.40%	99.80%
Streptococcus [a]	97.50%	99.80%
Streptococcus agalactiae (Group B)	100%	100%
Streptococcus pneumoniae	97.30%	99.9%
Streptococcus pyogenes (Group A)	100%	99.9%
Gram-Negative		
Acinetobacter baumannii	100%	99.8%
*Enterobacteriaceae*a	98.4%	99.8%
Enterobacter cloacae complex	97.4%	99.9%
Escherichia coli	98.0%	99.8%
Klebsiella oxytoca	92.2%	99.9%
Klebsiella pneumoniae	97.1%	99.6%
Proteus	100%	100%
Serratia marcescens	98.7%	99.9%
Haemophilus influenzae	100%	100%
Neisseria meningitidis	100%	100%
Pseudomonas aeruginosa	98.1%	99.9%
Yeast		
Candida albicans	100%	99.8%
Candida glabrata	100%	99.9%
Candida krusei	100%	100%
Candida parapsilosis	96.7%	99.9%
Candida tropicalis	100%	100%

Updated: June 2017