Clinical Guidance on the Use of Joint Infection Panel

In 2022, the Clinical Microbiology Laboratory at Nebraska Medicine began utilizing an FDA approved test called the BioFire® Joint Infection Panel. This test uses a PCR-based approach to amplify DNA targets directly from synovial fluid cultures allowing rapid identification of pathogens and earlier transition to most appropriate therapy. This test identifies 29 different gram-positive, gram-negative, and yeast pathogens (**Table 1**). It also detects 8 genes associated with antimicrobial resistance, including those responsible for methicillin resistance in staphylococci, vancomycin resistance in enterococci, carbapenem resistance in gram-negative bacteria, and the most common gene encoding an extended-spectrum β-lactamase. Additionally, the Joint Infection Panel detects some pathogens as a complex (*E. cloacae* complex), group (*K. Pneumoniae* group), or genus (*Proteus* spp, *Salmonella* spp).

Table 1: List of Pathogens and Resistance Genes Detected

Gram-Positive Bacteria	Gram-Negative Bacteria	Yeast	Resistance Genes
Anaerococcus prevotti/vaginalis *Clostridium perfringens* *Cutibacterium avidum/granulosum* *Enterococcus faecalis* *Enterococcus faecium* *Finegoldia magna* *Parvimonas micra* *Peptoniphilus* *Peptostreptococcus anaerobius* *Staphylococcus aureus* *Staphylococcus lugdunesis* *Streptococcus* genus *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*	*Bacteroides fragilis* *Citrobacter* *Enterobacter cloacae* complex *Escherichia coli* *Haemophilus influenzae* *Kingella kingae* *Klebsiella aerogenes* *Klebsiella pneumoniae* group *Morganella morganii* *Neisseria gonorrhoeae* *Proteus* genus *Pseudomonas aeruginosa* *Salmonella* genus *Serratia marcescens*	*Candida* genus *Candida albicans*	Carbapenemases • *IMP* • *KPC* • *NDM* • *Oxa-48-like* • *VIM* ESBL • *CTX-M* Methicillin Resistance • *mecA/C* and *MREJ* Vancomycin Resistance • *vanA/B*

Criteria for Joint Infection Panel Use

The BioFire Joint Infection Panel should be considered as part of synovial fluid testing in patients with suspected native joint septic arthritis or prosthetic joint infection. Patients who either have evidence of native joint septic arthritis on synovial fluid analysis or who have clinically suspected prosthetic joint infection should receive Orthopedic and Infectious Disease consultations.

Diagnosis: Septic arthritis of a native joint can lead to rapid joint destruction and loss of function. Prompt diagnosis and treatment are essential to reducing these long-term sequelae. Patients with native joint septic arthritis typically present with pain limiting weightbearing and/or range of motion, accompanied by local inflammation (e.g. swelling, erythema, warmth) of the infected joint. Fever is often absent. Septic arthritis cannot be readily distinguished from other inflammatory arthropathies (e.g. gout) by history and examination alone, and infection and exacerbation of other inflammatory arthropathies can occur together.

Testing: When septic arthritis is suspected the following blood tests are indicated: CBC with differential, ESR, CRP, procalcitonin, and blood cultures. Blood cultures should be obtained before antibiotics are started as they are

frequently positive. Plain radiographs of the joint can also be obtained if the presence of a foreign body is suspected or there is a concern for fracture.

Synovial Fluid Testing and Interpretation: While suggestive, blood tests are usually inadequate to rule in or rule out infection in a patient with acute monoarthritis. Therefore, when septic arthritis is suspected, arthrocentesis of the potentially infected joint should be performed to establish the diagnosis. Obtain cell count and differential, Gram stain plus bacterial culture, and crystal identification along with BioFire Joint Infection Panel.

Fungal and mycobacterial cultures may be indicated if the patient has a major immunocompromising condition (e.g. hematologic malignancy or organ transplantation), if the time course of infection was unusually indolent (e.g. symptoms arising over weeks to months), or if the patient has a known history of systemic AFB or fungal infection.

For native joint septic arthritis, synovial WBCs are usually >25,000 cells/µL and have an elevated neutrophil percentage; the synovial WBC count is more specific for infection at higher levels. Synovial fluid culture will yield a result 80% to 90% of the time if there has been no pre-treatment with antibiotics.

Biofire Joint Infection Panel: The BioFire Joint Infection panel is a rapid, PCR based molecular test to diagnose the causative agent of septic arthritis. This has been found to have an overall sensitivity of 91.7% and a specificity of 99.8% compared with standard cultures. It requires 0.2 mL of synovial fluid to run, takes about 2 hours, and should be included in tests ordered on synovial fluid aspirate of suspected native joint septic arthritis. For patients with suspected infection of a prosthetic joint, the Joint Infection Panel should be ordered in consultation with the Orthopedic surgery and Infectious Diseases team as it does not include several important pathogens causing these infections and a negative result should be interpreted in the context of operative cultures.

Orthopedic surgery and Infectious Diseases consults are recommended to guide interpretation of the Biofire Joint Panel results and management decisions when native joint septic arthritis or prosthetic joint infection is suspected.

Empiric Treatment: Patients presenting with evidence of sepsis or clinical instability from an infected joint should begin therapy with vancomycin and ceftriaxone. Patients without signs of clinical instability should have antibiotic therapy withheld until joint analysis data (cell count, gram stain, joint panel, etc.) returns. Therapy should be tailored to Gram stain and panel results as below.

Table 2: Joint Infection Panel Results and Recommended Therapy

Use this table to assist with selecting the most appropriate empiric therapy for treating a joint infection. Results from this PCR test should be utilized with respect to the patient's clinical syndrome. Cultures should be monitored for pathogens which may not be detected by the panel and therapy adjusted if needed. Patients with joint infections benefit from Infectious Diseases consultation as prolonged courses of antibiotics are typically required. Pathogens detected by the panel many not be found in subsequent culture and in these cases ID consultation can assist in determining if continued treatment is appropriate. Patients who have responded clinically to a narrow spectrum agent do not need to be escalated and should continue their current therapy, even if this guideline recommends a broader spectrum agent. Patients who have not clinically responded to initial therapy (persistent fever, lack of improvement, etc.) may have their therapy adjusted to a more active regimen based on the guideline. Allergies, organ dysfunction, and risk factors for or personal history of antimicrobial resistance should be considered when choosing therapy. Data on susceptibility for pathogens was derived from the 2021 institutional antibiograms where available.

Joint Panel Result	Preferred Therapy	Comments
Gram Positive Pathogens		
Anaerococcus prevotti/vaginalis	Penicillin 3 million units IV q4h OR Ampicillin 2 g IV q4h	PCN highly active Alternatives: Ceftriaxone, metronidazole, or vancomycin
Clostridium perfringens	Penicillin 3 million units IV q4h OR Ampicillin 2 g IV q4h	PCN highly active Alternatives: Ceftriaxone, metronidazole, or vancomycin
Cutibacterium avidum/granulosum	Penicillin 3 million units IV q4h OR Ceftriaxone 2 g IV q24h	PCN highly active, **can be resistant to metronidazole** Alternatives: Vancomycin
Enterococcus faecalis *Van A/B* negative *Van A/B* positive = VRE (uncommon in this species)	 Ampicillin 2 g IV q4h Ampicillin 2 g IV q4h	Ampicillin 100% susceptible at NM in this species, even when VRE PCN allergy: Vancomycin; linezolid or daptomycin if VRE
Enterococcus faecium *Van A/B* negative *Van A/B* positive = VRE (common)	 Vancomycin Linezolid 600 mg q12h	 Vancomycin 100% susceptible in *Van A/B* negative isolates Linezolid 100% susceptible at NM Daptomycin is an alternative but confirmatory testing may be needed
Finegoldia magna	Penicillin 3 million units IV q4h OR Ampicillin 2 g IV q4h	PCN highly active Alternatives: Metronidazole, ceftriaxone, or vancomycin
Parvimonas micra	Penicillin 3 million units IV q4h OR Ampicillin 2 g IV q4h	PCN highly active Alternative: Metronidazole (some resistance exists), or ertapenem
Peptoniphilus	Penicillin 3 million units IV q4h OR Ampicillin 2 g IV q4h	PCN highly active Alternatives: Ceftriaxone, metronidazole, or vancomycin
Peptostreptococcus anaerobius	Penicillin 3 million units IV q4h OR Ampicillin 2 g IV q4h	PCN highly active Alternatives: Ceftriaxone, metronidazole, or vancomycin

Staphylococcus aureus *mecA* and MREJ negative = MSSA *mecA* and MREJ positive = MRSA	Cefazolin 2 g IV q8h Vancomycin	Oxacillin 2 g q4h is an alternative Alternative: Daptomycin, linezolid, ceftaroline[NF] **Recommend ID consult**
Staphylococcus lugdunensis *mecA* negative = oxacillin susceptible *mecA* positive = oxacillin resistant	Cefazolin 2 g IV q8h Vancomycin	Oxacillin 2 g q24h is an alternative Alternative: Daptomycin, linezolid, ceftaroline[NF] **Recommend ID consult**
***Streptococcus genus,* <u>alone</u> without any other Strep species detected** (non-*S. agalactiae, S. pyogenes* or *S. pneumoniae)*	Ceftriaxone 2 g IV q24h	Severe beta-lactam allergy: vancomycin or levofloxacin
Streptococcus pyogenes (Group A Strep) **or *Streptococcus agalactiae*** (Group B Strep)	Penicillin 3 million units IV q4h OR Ampicillin 2 g IV q4h OR Cefazolin 2 g IV q8h	These beta-hemolytic Strep are routinely susceptible to penicillins and cephalosporins Alternatives: Ceftriaxone or levofloxacin
Streptococcus pneumoniae	Penicillin 3 million units IV q4h OR Ampicillin 2 g IV q4h	PCN highly active against pneumococcus locally Alternatives: Ceftriaxone or levofloxacin
Gram Negative Pathogens		
Bacteroides fragilis	Metronidazole 500 mg q8h	Alternatives: Ampicillin/sulbactam, piperacillin/tazobactam
Citrobacter *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	<u>CTX-M Negative</u>: Cefepime 1 g IV q6h <u>CTX-M Positive or Nosocomial-onset:</u> Ertapenem 1 g IV q24h OR Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	*C. freundii* is more common overall and can produce ampC beta-lactamase, conferring ceftriaxone resistance, while *C.koseri* does not *C. freundii* – cefepime (94%), levofloxacin (90%) *C. koseri* – ceftriaxone (100%), amoxicillin/clavulanate (100%)
***Enterobacter cloacae* complex** *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	<u>CTX-M Negative</u>: Cefepime 1 g IV q6h <u>CTX-M Positive or Nosocomial-onset:</u> Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	Alternative/oral step-down: Levofloxacin (98%)
Escherichia coli *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	<u>CTX-M Negative</u>: Ceftriaxone 2 g IV q24h <u>CTX-M Positive or Nosocomial-onset:</u> Ertapenem 1 g IV q24h OR Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	Alternative/oral step-down: No oral therapy is reliably active in our area. Use susceptibility data to determine oral therapy.

Haemophilus influenzae	Ampicillin/sulbactam 3 g IV q6h OR Ceftriaxone 2 g IV q24h	Alternative: Levofloxacin Oral step-down: Amoxicillin-clavulanate
Kingella kingae	Ampicillin/sulbactam 3 g IV q6h OR Ceftriaxone 2 g IV q24h	Alternative: Levofloxacin Oral step-down: Amoxicillin-clavulanate
Klebsiella aerogenes *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	CTX-M Negative: Cefepime 1 g IV q6h CTX-M Positive: Ertapenem 1 g IV q24h OR Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	Alternative/oral step-down: Levofloxacin
***Klebsiella pneumoniae* group** *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	CTX-M Negative: Ceftriaxone 2 g IV q24h CTX-M Positive or Nosocomial-onset: Ertapenem 1 g IV q24h OR Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	Alternative: Levofloxacin (92%)
Morganella morganii *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	CTX-M Negative: Cefepime 1 g IV q6h CTX-M Positive or Nosocomial-onset: Ertapenem 1 g IV q24h OR Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	Alternative/oral step-down: Levofloxacin, ceftriaxone
Neisseria gonorrhoeae	Ceftriaxone 1-2 g IV q24h	If chlamydial infection not excluded, add doxycycline 100 mg PO BID x 7 days
***Proteus* spp.** *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	CTX-M Negative: Ceftriaxone 2 g IV q24h CTX-M Positive: Ertapenem 1 g IV q24h OR Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	Oral step-down: Amoxicillin/clavulanate (for CTX-M negative)
***Salmonella* spp.** *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	CTX-M Negative: Ceftriaxone 2 g IV q24h CTX-M Positive: Ertapenem 1 g IV q24h OR Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	Alternative: Levofloxacin (often preferred if susceptible; consider ID consult)
Serratia marcescens *CTX-M* + = Possible Extended-Spectrum Beta-Lactamase (ESBL) present *KPC, IMP, VIM, NDM, OXA-48-like* + = Carbapenemase detected	CTX-M Negative: Cefepime 1 g IV q6h CTX-M Positive: Ertapenem 1 g IV q24h OR Meropenem 500 mg IV q6h **Carbapenemase Positive: Consult ID**	Alternative/oral Step-down: Levofloxacin (96%)

Yeast Pathogens		
***Candida genus,* alone without a species detected** (i.e. non-*C. albicans)*	Micafungin 100 mg q24h Consult ID	Alternatives: Fluconazole[+] [+]*C. glabrata*: 91% susceptible dose-dependent (12mg/kg/day) [+]*C. parapsilosis*: 93% susceptible [+]*C. tropicalis*: 96% susceptible
Candida albicans	Fluconazole 12 mg/kg load, 6 mg/kg q24h OR Micafungin 100 mg q24h	97% susceptible to fluconazole Consider micafungin if previous azole exposure
Gram Negative Resistance Genes		
IMP, KPC, OXA-48-like, NDM, VIM	Consult ID	Markers for carbapenem-resistance in gram negative pathogens (i.e., CRE)
CTX-M	Ertapenem 1 g q24h OR Meropenem 500 mg q6h	Marker for most common Extended-Spectrum Beta-Lactamase (ESBL) found in gram-negative pathogens (esp. *E. coli* and *Klebsiella* spp.) ESBLs hydrolyze expanded spectrum cephalosporins (ceftriaxone, cefepime) and piperacillin/tazobactam A negative result does not exclude the presence of other ESBL enzymes or other beta-lactamases
Gram Positive Resistance Genes		
mecA/C	Vancomycin	*mecA/C* is a marker for methicillin/oxacillin-resistance in *Staphylococci*. Reported by itself in non-*S. aureus,* (i.e., MRSE) *S. epidermidis* and *S. lugdunensis.*
***mecA/C* and MREJ**	Vancomycin	MREJ is only evaluated in *S. aureus* and when present with *mecA/C* is specific for MRSA
Van A/B	Linezolid 600 mg q12h Consult ID	Marker for vancomycin-resistant *Enterococcus* (i.e., VRE)

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