Guideline/Protocol Title:	Guideline for Antibiotic Management Based on Rapid Diagnostic Blood Culture Results in Adult and Pediatric Patients
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P&T Approval Date:	11/4/20
Last revision Date:	

PURPOSE/SCOPE:	To provide standardized guidelines for frontline clinicians to interpret and respond to preliminary microbiology results based on Gram stain, Verigene Gram-positive rapid diagnostic test results, and disk diffusion (Kirby-Bauer). These guidelines apply to pediatric and adult patients at UCSF Health with microbiology results reported from the UCSF Clinical Microbiology Laboratory.

EXECUTIVE SUMMARY

The Verigene Gram-positive panel for bloodstream isolates allows for rapid detection of Gram-positive organisms and some associated resistance genes, permitting earlier targeted antibiotic therapy and identification of blood culture contaminants compared to traditional microbiology methods. Clinical algorithms for interpretation of these results were developed based on manufacturer-provided information, published performance standards, local susceptibility data, and other published literature.

This guideline also provides interpretation and therapeutic recommendations for disk diffusion (Kirby-Bauer) susceptibility testing of Gram-negative organisms. Disk diffusion results are available within 12-24 hours and are highly concordant with traditional susceptibility testing methods, potentially accelerating the time to appropriate Gram-negative therapy.

Additional information contained in this guideline include an overview of organism identification processes in the UCSF Clinical Microbiology Laboratory and decision-support for identification and management of possible blood culture contaminants.

BACKGROUND / INTRODUCTION

Rapid molecular tests can identify and detect antibiotic resistance markers in pathogenic bacteria before conventional methods. Prior studies indicate that rapid molecular tests are associated with earlier optimization of therapy and, in some cases, improved clinical outcomes. Rapid identification and

susceptibility testing can also facilitate de-escalation of antibiotics, reducing potential adverse effects including emergence of resistance. For patients with infections due to staphylococci, rapid molecular testing improves therapy by promoting earlier optimization of therapy for MSSA bacteremia and possibly early discontinuation of unnecessary antibiotics for false-positive coagulase-negative staphylococci cultures, as well as possibly improved clinical outcomes. For infections caused by vancomycin-resistant enterococci and *Enterococcus faecium*, rapid identification decreases time to effective therapy, and may decrease costs and mortality.

SUPPORTING EVIDENCE

Sources considered in development of the guidelines include references below and bloodstream infection antibiogram data for adult and pediatric inpatients from 2015-2020. The decision to incorporate rapid diagnostics for blood culture results was approved by the UCSF Infectious Diseases Management Program. This guideline has been reviewed by all key collaborators and their additional recommendations incorporated.

APPENDIX

Appendix 1. Interpreting and Optimizing Antibiotic Therapy Based on Initial Blood Culture Results (Clinician-Facing Guideline)

Appendix 2. Additional Verigene Panel Interpretations: Antimicrobial Stewardship Program and Infectious Diseases (Adult/Pediatric) Consult Resource

Reference #	Citation
1	Wojewoda CM, Sercia L, Navas M, et al. Evaluation of the Verigene Gram-positive blood culture nucleic acid test for rapid detection of bacteria and resistance determinants. J Clin Microbiol. 2013;51(7):2072-6.
2	Alby K, Daniels LM, Weber DJ, Miller MB. Development of a treatment algorithm for streptococci and enterococci from positive blood cultures identified with the Verigene Gram-positive blood culture assay. J Clin Microbiol. 2013;51(11):3869-71.
3	Rödel J, Karrasch M, Edel B, et al. Antibiotic treatment algorithm development based on a microarray nucleic acid assay for rapid bacterial identification and resistance determination from positive blood cultures. Diagn Microbiol Infect Dis. 2016;84(3):252-7.
4	Verigene Gram-Positive Blood Culture Nucleic Acid Test (BC-GP) [package insert]. Northbrook, IL: Nanosphere, Inc; revised March 2016. Available at https://www.e-labeling.eu/NAN098

Revision History

Revision Date	Update(s)

APPENDIX I: Interpreting and Optimizing Antibiotic Therapy Based on Initial Blood Culture Results

Clinician-Facing Guideline

These guidelines inform selection and modification of antibiotic therapy based on preliminary blood culture results. They are not intended to replace clinical judgement. Modification of therapy may be indicated based on patient comorbidities, previous antibiotic therapy, or infection history. These guidelines apply to patients at UCSF Medical Center and UCSF Benioff Children's Hospital San Francisco who have positive blood culture results from the UCSF Clinical Microbiology Laboratory.

1.1 Infectious Diseases Consultation for Patients with Positive Blood Culture Results

Infectious Diseases consultation is required for some patients with positive blood culture results and is encouraged for other situations when the clinical team believes that consultation would be helpful.

Location	**Positive blood culture for *Staphylococcus aureus* (including cultures from other facilities outside UCSF)**	**Positive blood culture with another organism or preliminary (includes cultures from other facilities outside UCSF)**
UCSFMC Parnassus, Mount Zion, or Mission Bay Adult Services	Consult to Adult Infectious Diseases service required	Consult at the discretion of primary clinical team. Reasons for consultation may include but are not limited to complicated infection, delayed clearance of cultures, antimicrobial allergies, or the presence of multidrug resistant organisms.
UCSF BCH San Francisco	Consult to Pediatric Infectious Diseases service required	Consult to Pediatric Infectious Diseases service required

The Antimicrobial Stewardship Team (Adult ASP at Parnassus, Pediatric ASP at Mission Bay) is available during daytime hours on weekdays for focused consultation, interpretation of results, and therapeutic recommendations for patients who are not actively followed by an ID consult team. When either ID consult or ASP is readily available, they should be the primary resource for questions regarding interpretation of preliminary blood culture results.

Exceptions to this general guideline should be considered for:

- Infections that are likely to be polymicrobial (e.g. intra-abdominal source)
- Multiple types of bacteria reported on Gram stain or culture (e.g. Gram-negative rods and Gram-positive cocci)
- Patients with febrile neutropenia, though de-escalation is encouraged if deemed clinically appropriate per UCSF Guidelines for Inpatient Management of Febrile Neutropenia in Adults and UCSF Management of Fever in Pediatric Oncology and BMT Patients

- Patients receiving antimicrobial therapy for another concurrent microbiologically or clinically documented infection
- Decompensating patients who are undergoing further microbiologic evaluation with additional cultures collected

1.2 Reporting Timeline for Species Identification and Susceptibilities:

Time from Positive Blood Culture	Result Available to Clinical Team	Additional Explanation
1-2 hours	Gram stain	See Section 1.3
2-8 hours	Gram-positive organism identification and resistance mechanism, inpatient only	Verigene results of Gram-positive organisms only; see Section 1.4
12- 15 hours	Gram-negative preliminary susceptibilities reported	Disk diffusion results for Gram-negative organisms; see Section 1.6
24-48 hours	Definitive organism identification	MALDI-TOF results confirming Verigene results for Gram-positive organisms or new identification for Gram-negative organisms
48-72 hours	Definitive susceptibility results	Traditional susceptibility testing to confirm Verigene resistance mechanisms for Gram-positive organisms and disk diffusion results for Gram-negative organisms; see Section 1.7

1.3 Gram Stain Results:

Gram stain results are available upon notification of positive blood culture. In general, antibiotic therapy directed against Gram-negative organisms should be discontinued if the blood culture shows a Gram-positive, non-contaminant pathogen (and vice versa); exceptions to changing therapy should be considered for certain infection-specific and patient-specific characteristics listed in Section 1.1.

1.4 Verigene Gram-Positive Panel Result Interpretation and Treatment Recommendations:

Below are general recommendations based on our hospital-specific antibiogram, medication formulary, and Verigene performance characteristics. These recommendations are not intended to replace clinical judgement.

<u>Verigene Gram-Positive Blood Culture Panel (BC-GP) Performance Characteristics</u>

The Verigene assay is an FDA-approved nucleic acid test that identifies twelve Gram-positive organisms and two antibiotic resistance markers (mecA = methicillin resistance; vanA/vanB = vancomycin resistance) directly from blood samples. This assay demonstrates excellent concordance with traditional susceptibility methods.

Resistance Marker	Organism	**Sensitivity:** Verigene BC-GP concordance with conventional methods for the detection of resistance markers % ($n_{Verigene}$ / $n_{conventional}$)	**Specificity:** Verigene BC-GP concordance with conventional methods for the absence of resistance markers % ($n_{Verigene}$ / $n_{conventional}$)
MecA	*Staphylococcus aureus* (n=335)*	97.5% (157/161)	98.8% (172/174)
	Staphylococcus epidermidis (n=330)+	92.0% (219/238)	81.5% (75/92)
VanA	*Enterococcus faecalis* (n=109)^	85.7% (12/14)	100% (95/95)
	Enterococcus faecium (n=114)#	97.2% (69/71)	93.0% (40/43)
VanB	*Enterococcus faecalis* (n=109)^	100% (7/7)	100% (102/102)
	Enterococcus faecium (n=114)#	97.0% (32/33)	100% (81/81)

*For *Staphylococcus aureus* isolates, Verigene BC-GP correctly identified the presence of the mecA gene in 97.5% of isolates that were later identified as methicillin-resistant using conventional biochemical methods (culture and cefoxitin disk diffusion). Verigene BC-GP did not identify mecA in 98.8% of *Staphylococcus aureus* isolates that were later identified as methicillin-susceptible by conventional methods.

+For *Staphylococcus epidermidis* isolates, Verigene BC-GP correctly identified the presence of the mecA gene in 92% of isolates that were later identified as methicillin-resistant using conventional biochemical methods (culture and cefoxitin disk diffusion). Verigene BC-GP did not identify mecA in 81.5% of *Staphylococcus epidermidis* isolates that were later identified as methicillin-susceptible by conventional methods.

^For *Enterococcus faecalis* isolates, Verigene BC-GP correctly identified the presence of the vanA or vanB genes in 85.7% and 100% of isolates, respectively, that were later identified as vancomycin-resistant using conventional biochemical methods (culture and bidirectional sequencing). Verigene BC-GP did not identify vanA or vanB in 100% and 100% of isolates, respectively, that were later identified as vancomycin-susceptible by conventional methods.

#For *Enterococcus faecium* isolates, Verigene BC-GP correctly identified the presence of the vanA or vanB genes in 97.2% and 97% of isolates, respectively, that were later identified as vancomycin-resistant using conventional biochemical methods (culture and bidirectional sequencing). Verigene BC-GP did not identify vanA or vanB in 93% and 100% of isolates, respectively, that were later identified as vancomycin-susceptible by conventional methods.

Limitation of the Verigene Gram-Positive Panel (BC-GP):

- In mixed cultures containing Gram-positive bacteria and other organisms, BC-GP may not identify all the detectable organisms in the specimen. For these reasons, Verigene results should always be confirmed with final organism identification and susceptibilities.
- Verigene only identifies vancomycin resistance mediated by vanA/vanB. While these are the most common causes of vancomycin resistance amongst enterococci, vancomycin resistance can be caused by genes other than vanA and vanB.
- There is a risk of false positive results due to cross-contamination by target bacteria and their nucleic acids.
- The assay detects the presence of resistance genes (e.g. mecA and vanA/vanB), but does not determine which organisms produced the gene.

For more information on the Verigene Assay Test Characteristics, please consult the package insert: http://www.nanosphere.us/sites/default/files/support-docs/027-00030-01_g_bc-gp_ivd_package_insert.pdf

Verigene results are available **within 2-8 hours** of the first positive blood culture. These results will only be reported for inpatients or ED patients if the initial Gram stain shows a Gram-positive organism. While the recommendations below address the most common results, additional Gram-positive organisms may be identified. The ASP teams may be contacted with questions regarding result interpretation and therapy selection. Exceptions to changing therapy based on Verigene results should be considered for certain infection-specific and patient-specific characteristics listed in Section 1.1.

Verigene Gram-Positive Panel Result	**Interpretation**	**Treatment Recommendation***	**Comments**
Staphylococcus aureus mecA detected	**Methicillin-resistant** *Staphylococcus aureus* (MRSA)	Vancomycin If allergy/intolerance to vancomycin: consult ID	We recommend ID consult for all patients with *S. aureus* bacteremia.
Staphylococcus aureus mecA not detected	Methicillin-susceptible *Staphylococcus aureus* (MSSA)	STOP vancomycin and START cefazolin (preferred) OR nafcillin Use nafcillin if meningitis suspected or in preterm neonate If beta-lactam allergy: refer to UCSF Beta-Lactam Allergy Guideline	We recommend ID consult for all patients with *S. aureus* bacteremia. Vancomycin is inferior to cefazolin/nafcillin for MSSA treatment
Staphylococcus epidermidis mecA detected	**Methicillin-resistant** *Staphylococcus epidermidis*	If treatment indicated: vancomycin If allergy/intolerance to vancomycin: consult ASP or ID	Frequent contaminant; see section 1.5 [online: link to section] below titled “Assessing for Blood Culture Contamination”
Staphylococcus epidermidis mecA not detected	Methicillin-susceptible *Staphylococcus epidermidis*	If treatment indicated: STOP vancomycin and START cefazolin (preferred) OR nafcillin Use nafcillin if meningitis suspected or in preterm neonate	Frequent contaminant; see section 1.5 [online: link to section] below titled “ Assessing for Blood Culture Contamination”

		If beta-lactam allergy: refer to UCSF Beta-Lactam Allergy Guideline	
Staphylococcus lugdunensis Note that the presence of mecA will NOT be detected for this species	*Staphylococcus lugdunensis*	If treatment indicated: vancomycin If allergy/intolerance to vancomycin: consult ID	Although *S. lugdunensis* is a type of coagulase-negative *Staphylococcus*, it tends to be more pathogenic. Consult ID if further assessment is desired. If methicillin susceptibility is confirmed by conventional testing, STOP vancomycin and START cefazolin (preferred) OR nafcillin. Use nafcillin if meningitis suspected or in preterm neonate
Enterococcus faecalis vanA OR vanB detected OR vanA AND vanB not detected	**Vancomycin-resistant** *Enterococcus faecalis* *OR* Vancomycin-susceptible *Enterococcus faecalis*	Ampicillin Ampicillin If beta-lactam allergy: refer to UCSF Beta-Lactam Allergy Guideline	At UCSF, all *E. faecalis* bloodstream isolates in recent years have been ampicillin-susceptible, including the low number of vancomycin-resistant isolates ID consult recommended for all VRE bloodstream infections in adult patients, especially if suspected/confirmed endocarditis.
Enterococcus faecium vanA detected OR vanB detected	**Vancomycin-resistant** *Enterococcus faecium*	1st line: Linezolid ● Preferred, unless high-risk drug interactions with serotonergic meds	ID consult recommended for all VRE bloodstream infections in adult patients, especially if suspected/confirmed endocarditis.

		2nd line: Daptomycin^ ● Consider for patients with high-risk serotonergic drug interactions ● Do not use daptomycin if concerned for pulmonary infection	Consult clinical pharmacist regarding drug interaction assessment
Enterococcus faecium vanA not detected AND vanB not detected	Vancomycin-susceptible *Enterococcus faecium*	Vancomycin If allergy/Intolerance to vancomycin: consult ASP or ID	If ampicillin susceptibility is confirmed by conventional testing, STOP vancomycin and START ampicillin. If suspected/confirmed endocarditis, ID consult recommended
Other result	Mixed culture (containing >1 organism) Panel also detects *Streptococcus agalactiae* (GBS), *Streptococcus anginosus* group, *Streptococcus pneumoniae, Streptococcus pyogenes* (GAS), *Listeria* species, and may result with *Staphylococcus* or *Streptococcus* genus without species detected	Contact ID or ASP for guidance or modify therapy according to detected organism and anticipated susceptibility	

*Refer to Antimicrobial Dosing Guidelines

^These antibiotics are restricted and require prior authorization from the ASP or ID team:

- During daytime hours:
  - For adult patients: Antimicrobial Stewardship Pharmacist Pager or Antimicrobial Stewardship Pharmacist on Voalte
  - For BCHSF/pediatric patients: Pediatric ID/ASP Pharmacist or Pediatric ID/ASP Provider on Voalte, or page Pediatric ID Consult team.
- After hours: Verifying pharmacist will approve a one-time dose overnight; page appropriate ASP/ID point-of-contact listed above the next day for continued approval.

1.5 Assessing for Blood Culture Contamination

Roughly 50% of blood cultures may grow organisms not truly representing bacteremia, referred to as contaminants. Coagulase-negative staphylococci (e.g. *Staphylococcus epidermidis* group) are the most common blood culture contaminants. If the patient is clinically stable with low pretest probability for bloodstream infection (e.g. lack of central venous catheter or endovascular prosthetic material), antibiotics may not be indicated for all blood cultures growing coagulase-negative staphylococci.

The following practices may minimize contamination, or maximize the ability to recognize contamination:

- Draw at least 2 blood cultures at the same time (3 cultures are recommended for suspected sepsis).
- Draw each set of cultures from multiple venipuncture sites.
- Avoid drawing cultures from a peripheral venous or arterial catheter as these are associated with higher rates of contamination.
- Use time to positivity to assess likelihood of true vs. false positive. For example, a culture is more likely to represent a true pathogen if it is reported positive in <24 hours versus 3 days.

A provider may opt to conservatively treat a possible blood culture contaminant with antibiotics in certain situations based on lack of diagnostic certainty and/or relative patient risk for complications. If patient-specific evaluation is desired, then ID consultation should be requested.

The following algorithm provides guidance for interpreting a possibly contaminated blood culture:

<table>
<tr><th>Organism Identification (by Verigene or MALDI-TOF)</th><th>Recommended Action(s)</th><th>Recommended Action Following Repeat Cultures (if applicable)</th></tr>
<tr><td rowspan="2">1 out of 2 blood cultures
or
1 out of 1 blood cultures with coagulase-negative staphylococcus</td><td>If patient is hemodynamically <u>UNSTABLE</u> OR has implanted prosthetic material:
Start or continue an antimicrobial with activity against coagulase-negative staphylococci based on mecA status, as defined in Section 1.4 above [online: link to section].
Repeat two sets of blood cultures (before new antimicrobial is added, if not started initially)</td><td>If patient has implanted prosthetic material:
Consider ID consult
If repeat cultures are positive for the same species of coagulase-negative staphylococcus:
Continue directed therapy against coagulase-negative staphylococcus
If repeat cultures are positive for a different species of coagulase-negative staphylococcus:
Discontinue therapy, as this likely represents contamination
If repeat cultures are negative and the patient is hemodynamically <u>UNSTABLE</u>:
Continue current antimicrobial and consider ID consult</td></tr>
<tr><td>If patient is hemodynamically</td><td>If repeat blood cultures are positive for the</td></tr>
</table>

	<u>STABLE</u> and does <u>NOT</u> have implanted prosthetic material: ● Discontinue or do not start Gram-positive antimicrobial ● Consider repeating two sets of blood cultures if still concerned for a bloodstream infection	**same** species of coagulase-negative staphylococcus: ● In some cases, this is more consistent with a true bloodstream infection. Re-start Gram-positive antimicrobial or consult ID/ASP if additional guidance is desired. If repeat cultures are **positive** for a **different** species of coagulase-negative staphylococcus: ● Discontinue therapy, as this likely represents contamination If repeat blood cultures are **negative**: ● Discontinue Gram-positive antibiotic (if not already)
2 out of 2 blood cultures with the same coagulase-negative staphylococcus	In some cases, this is more consistent with a true bloodstream infection. However, this scenario could still represent contamination. Use clinical judgement to determine the need for antimicrobial therapy pending definitive biochemical identification or contact ASP/ID for additional guidance.	

1.6 Preliminary/Direct Susceptibility by Disk Diffusion (Kirby-Bauer) Susceptibility on Gram Negative Organisms:

For Gram-negative organisms, preliminary susceptibility results from disk diffusion will appear in the chart **~**12-24 hours from positive blood culture. Based on available literature, disk diffusion results have >95% concordance with final susceptibilities attained via broth microdilution applying standard breakpoints. The likelihood of falsely concluding susceptibility to an antibiotic based on these results is <1.5% across multiple studies. Disk diffusion results will not show a numerical minimum inhibitory concentration, but will report a sensitive or resistant interpretation. The UCSF Clinical Microbiology Laboratory will <u>not</u> report preliminary results that are in the intermediate range. We recommend that clinicians use these preliminary susceptibility results to modify antibiotic selection (see table below). Exceptions to changing therapy based on disk diffusion results should be considered for certain infection-specific and patient-specific characteristics listed in Section 1.1.

Interpretation and Treatment Recommendations for Gram-Negative Preliminary Susceptibilities

Preliminary Susceptibility Result	Interpretation	Treatment Recommendation	Comments
Ertapenem-sensitive, without other preliminary susceptibilities reported	Possible ESBL-producing Gram-negative organism	Start or continue a carbapenem antibiotic	If beta-lactam allergy: refer to UCSF Beta-Lactam Allergy Guideline
Other antibiotic susceptibility results reported	Gram-negative organism is susceptible to the reported antibiotics	In most situations, it is appropriate to de-escalate antibiotics based on the preliminary susceptibility results In certain clinical situations listed in Section 1.1., it is reasonable to continue broader antibiotics while obtaining additional data	If beta-lactam allergy: refer to UCSF Beta-Lactam Allergy Guideline

1.7 Final Susceptibilities:

Final susceptibilities for both Gram-positive and Gram-negative organisms are typically available ~48-72 hours from positive blood culture. These results should always be reviewed. In most cases, the narrowest, most effective antibiotic should be selected to complete the course of therapy. There may be opportunities to refine antimicrobial treatment based on the final susceptibility results.