

Blood Culture Guidance in Non-Severely Immunocompromised Adult Inpatients

Background

- Blood cultures (BCx) are the gold standard for diagnosing bloodstream infections (e.g., bacteremia, candidemia), but most BCx are negative (~90%) and 24-40% of positive BCx detect only contaminants.¹
- Low rates of blood culture positivity are primarily due to obtaining BCx in patients with low pre-test probability of bacteremia but may also be due to poor collection techniques (underfilling or overfilling the bottle, single set collection)
- Conditions like septic shock warrant BCx, but others such as isolated fever or leukocytosis without other focal signs/symptoms of infection do not correlate well with presence of bacteremia²
- Judicious BCx use is important due to the unintended consequences of contaminated BCx:^{1,3-5}
 - Unnecessary antibiotic use (e.g., primarily vancomycin with associated acute kidney injury and drug allergy): 0.8 day longer duration of antibiotics at our institution⁶
 - Further unneeded testing (more BCx, echocardiography, therapeutic drug monitoring, further cultures or susceptibility testing) with associated costs
 - Unwarranted central venous catheter removal
 - Cancellation of surgical procedures
 - Unnecessary consultations (e.g., infectious diseases)
 - Increased hospital length of stay: 0.8 day longer length of hospitalization at our institution⁶
 - Iatrogenic anemia and increased need for blood products
 - Diagnostic delays due to anchoring bias on blood culture contaminants as cause of symptoms
 - National Healthcare Safety Network-defined central line associated bloodstream infection (CLABSI), despite not being a true bloodstream infection
- The current Clinical Laboratory Standards Institute benchmark for BCx contamination rates is 1%⁷
 - The 2022 NM BCx contamination rate was 2.4% which means ~45 contaminated BCx per month and >500 per year resulting in at least 400 unnecessary days of antibiotics and over 400 additional days hospitalized

- In order to optimize our yield of BCx and minimize false positive contaminants, we provide guidance in this document on appropriate BCx practices. This document and associated algorithms are not a substitute for clinical judgment or hospital policy.

Best Practices in Blood Culture Obtainment

- If BCx deemed necessary, always obtain prior to initiation or escalation of antimicrobials
 - Antimicrobials decrease absolute BCx yield 12% within 2 hours and >20% in 4 hours.⁸
- Always obtain two sets of BCx from two separate peripheral venipuncture sites (each set consists of 1 aerobic and 1 anaerobic bottles).
 - Single set BCx should NEVER be obtained (especially a single set from a central line), as this increases likelihood of contamination, makes interpretation of BCx results challenging, and decreases the likelihood of detecting bacteremia¹
- Each BCx bottle should contain 8-10ml of blood volume, meaning at least 32-40ml is collected per two sets of BCx on each patient⁹
- BCx bottle tops should be cleaned with a 70% alcohol wipe for 5 seconds and allowed to dry prior to inoculation.
- If indicated (see “When to Obtain Blood Cultures from Central Lines” below), one BCx set can be obtained from a central line coupled with one BCx set from peripheral venipuncture.⁹ For details on obtaining central line blood cultures, see nursing policy VAD-4.
 - BCx from a central line should ALWAYS be paired with a peripheral BCx with each BCx clearly labeled by source
 - After removing the catheter connector, the central line hub should be scrubbed with 70% alcohol for 15 seconds prior to obtaining blood for culture.
 - Infusions via the central line should be stopped (if possible) prior to drawing BCx. Avoid lumens locked with an antimicrobial or where antibiotics are currently running, if possible.
 - Blood cultures should NOT be obtained from new or existing peripheral intravenous catheters (PIV), arterial lines, or midline catheters

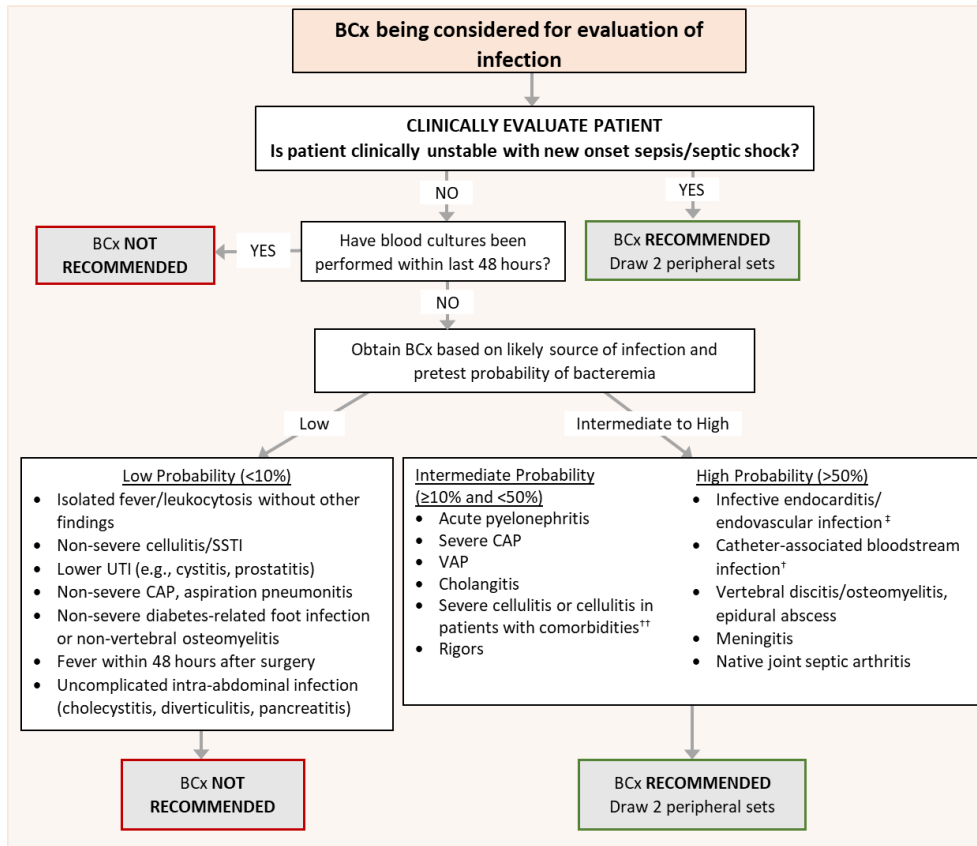
When Should BCx be Obtained as Part of Initial Infection Investigation

- The decision to obtain BCx should be based on the pre-test probability of detection of bacteremia and likelihood it will impact subsequent clinical decision making.
 - Clinicians should avoid reflexively ordering BCx in response to isolated fever or lab values (e.g., leukocytosis) unless there is significant concern for sepsis or septic shock
 - Patients with new onset signs/symptoms concerning for infection should be clinically evaluated and the most-likely source of infection determined
 - After clinical evaluation BCx utilization should be based on the presumed source of infection and pre-test probability of bacteremia.
 - In conditions with low pre-test probability, BCx should be avoided for the reasons noted above.

- Table 1 and Figure 1 below defines conditions where BCx are indicated or not recommended.

Table 1: Indications for INITIAL Blood Cultures (BCx) in Adult Patients*	
Step 1: Evaluate patient clinically, assess hemodynamic stability, and identify possible sources of infection	
Step 2: If unstable (sepsis/septic shock), obtain BCx and strongly consider empiric antibiotics.	
Step 3: If stable, evaluate for potential source of infection and determine if BCx and/or empiric antibiotics are indicated	
BCx <u>NOT</u> Indicated	BCx Indicated
<ul style="list-style-type: none"> ● Syndromes with low risk of bacteremia (<10%): <ul style="list-style-type: none"> ○ Non-severe cellulitis/skin and soft tissue infection (SSTI) ○ Lower urinary tract infection (e.g., cystitis, prostatitis) ○ Non-severe community-acquired pneumonia (CAP) ○ Non-severe diabetes-related foot infection ○ Colitis (including <i>C. difficile</i>) ○ Aspiration pneumonitis ○ Uncomplicated cholecystitis, diverticulitis, or pancreatitis ● Fever or leukocytosis explained by a non-infectious cause (e.g., drug withdrawal, trauma, pulmonary embolism, etc.) ● Isolated fever and/or leukocytosis without other findings ● Post-operative fever within 48 hours ● Persistent fever or leukocytosis in patient with negative BCx in past 48-72 hours without new localizing signs of infection <ul style="list-style-type: none"> ○ Other cultures or imaging more appropriate than blood cultures ○ Consider expert consultation ● All forms of surveillance blood cultures in patients without suspicion of bacteremia (e.g., from central line prior to TPN initiation, prior to central line placement) 	<ul style="list-style-type: none"> ● Sepsis/septic shock ● Systemic signs of infection AND asplenia ● Syndromes with high risk of bacteremia (≥50%): <ul style="list-style-type: none"> ○ Infective endocarditis/endovascular infection (septic thrombophlebitis, infected cardiac/vascular devices) ○ Catheter-related bloodstream infection ○ Vertebral discitis/osteomyelitis ○ Epidural abscess ○ Native joint septic arthritis ○ Meningitis ● Syndromes with intermediate risk of bacteremia (>10% - <50%) <ul style="list-style-type: none"> ○ Cholangitis ○ Pyelonephritis ○ Severe pneumonia (<u>CAP and VAP</u>) ○ Severe cellulitis/SSTI or with severe comorbidities (necrotizing soft tissue infection, severe immunocompromise, end-stage renal or liver disease)
<u>Peripheral BCx are preferred over central lines blood cultures due to improved specificity.</u>	
Always draw 2 peripheral sets (i.e., 4 bottles with 8-10cc/bottle).	
*Excludes severely immunosuppressed patients (neutropenia, hematopoietic stem cell or solid organ transplant)	

Figure 1: Indications for Initial Blood Cultures in Adult Patients*



*Excludes severely immunosuppressed patients (neutropenia, hematopoietic stem cell transplant, solid organ transplant)

High pre-test probability of bacteremia (≥50% positivity)⁵: BCx recommended

- Sepsis/Septic shock
- Endovascular infections (e.g., infective endocarditis, septic thrombophlebitis, vascular graft infection)
- Catheter-related bloodstream infections
- Meningitis
- Native vertebral discitis/osteomyelitis or epidural abscess
- Non-traumatic native septic joints
- Ventriculoatrial shunt infections

Moderate pre-test probability of bacteremia (20-50% positivity)⁵: BCx recommended, although other sources have higher yield for pathogen detection and BCx may not change management even if positive⁵

- Pyelonephritis – Obtain urine culture as higher yield (>95% yield)
- Severe community-acquired pneumonia – Obtain sputum culture as higher yield (>65% yield)
- Ventilator-associated pneumonia – Obtain sputum culture as higher yield
- Severe skin and soft tissue infection (SSTI) or SSTI with severe comorbidities – Obtain abscess culture if purulent cellulitis (30-70% yield). Obtain BCX if following criteria met:

- Severe disease: ICU level of care (sepsis/septic shock), necrotizing soft tissue infections
- Co-morbidities: end-stage renal or liver disease, solid organ transplant, hematopoietic stem cell transplant, immunosuppressive medications
- Cholangitis – Biliary cultures higher yield and preferred (>90% yield)
- Pyogenic liver abscess – Abscess culture higher yield and preferred (>80% yield)
- Nonvascular shunt (e.g., ventriculoperitoneal shunt) – Patients with concern for shunt infection should have a tap performed and cultures sent
- Shaking chills (i.e., rigors)²
 - Typical chills are not predictive of bacteremia, only true shaking chills
- Signs of infection in asplenia

Low pre-test probability of bacteremia (<10%)⁵: DO NOT OBTAIN BCx. These conditions are very unlikely to be associated with bacteremia and the number of contaminated BCx detected outnumbers the yield of true positive BCx.

- Isolated fever (<5%)
- Isolated tachycardia
- Isolated leukocytosis
- Fever or leukocytosis within 48 hours of surgery (<5%)
- Non-infectious or viral etiology of fever/infection including COVID-19
- Aspiration event, tracheitis
- Non-severe cellulitis, including preseptal cellulitis (<10%)
- Lower urinary tract infection (cystitis, prostatitis) (<10%) – Obtain urine culture
- Non-severe community-acquired pneumonia (<10%) – Sputum cultures also low yield
- Uncomplicated intra-abdominal infection (appendicitis, cholecystitis, diverticulitis, colitis)
- *Clostridioides difficile* colitis
- Diabetes-related foot infection or non-vertebral osteomyelitis
- Surveillance cultures in patients without suspected bacteremia (i.e., prior to initiation of TPN, prior to placing central line)

When Should Follow-up BCx be Obtained to Document Clearance of Bacteremia

- Most patients do not need follow-up BCx, but some do
- Only a few specific pathogens (e.g., *Staph aureus*, *Candida* spp) and certain clinical findings or infectious syndromes should prompt routine use of follow-up BCx
- Otherwise, patients who are clinically improving do not warrant follow-up BCx
- When follow-up BCx are performed, they should be spaced apart at least 48 hours
- Table 2 and Figure 2 define conditions in which follow-up BCx should and should not be obtained

Table 2: Indications for FOLLOW-UP Blood Cultures (BCx) in Adult Patients* with Positive BCx

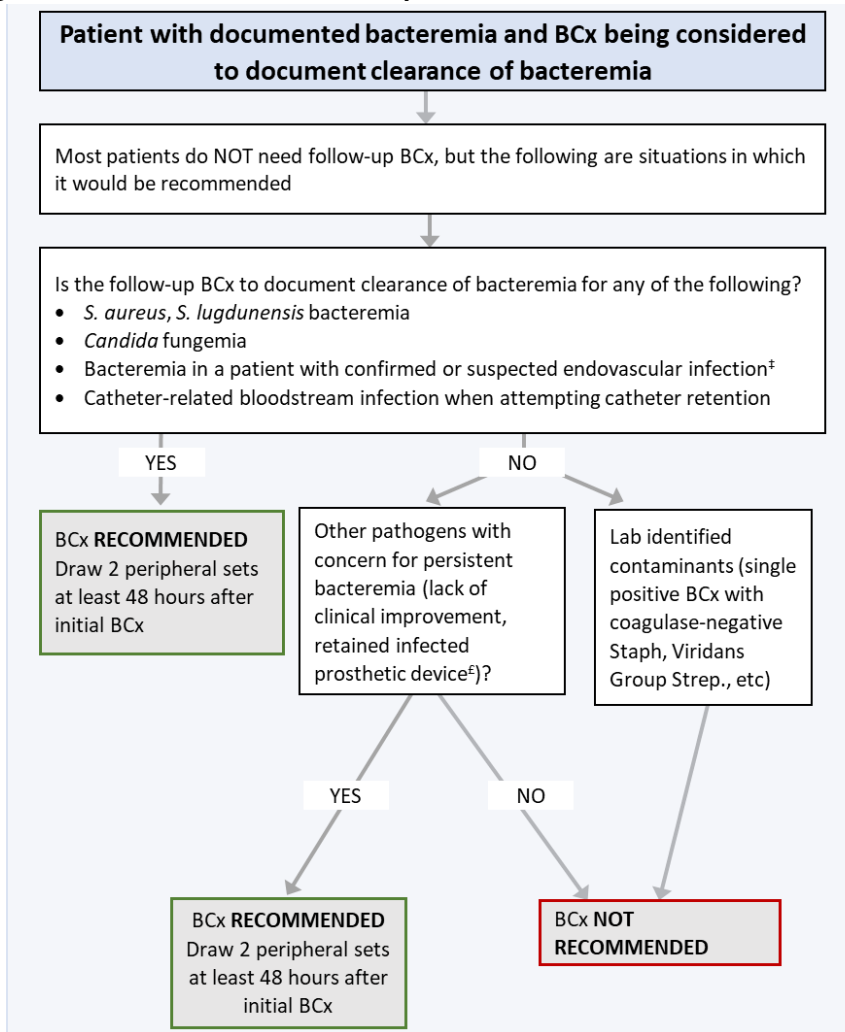
BCx <u>Not</u> Indicated	Follow-Up BCx Indicated
<ul style="list-style-type: none"> • Single positive blood culture with skin flora (i.e., coagulase-negative Staphylococci, <i>Cutibacterium acnes</i>, <i>Micrococcus</i>, viridans group Streptococci, <i>Corynebacterium</i> spp, <i>Aerococcus</i> spp, <i>Bacillus</i> spp) • Examples of syndromes which do not need FU BCx if clinically improving: <ul style="list-style-type: none"> ○ <i>Enterococcus</i> bacteremia from urinary or biliary source ○ <i>S. pneumoniae</i> bacteremia from pulmonary source ○ Gram-negative bacteremia from urinary/abdominal source ○ Cases likely to represent contamination (e.g., single BCx with coagulase-negative staphylococci) • Note: <u>Strep other than</u> <i>S. pneumoniae</i> or beta-hemolytic streptococci (i.e., <i>S. pyogenes</i>) are potential infective endocarditis pathogens. Assess patient risk factors for endovascular infection and clinical presentation to determine significance of <i>Streptococci</i> in blood and need for repeat BCx (see below). 	<ul style="list-style-type: none"> • All bacteremia/fungemia cases due to: <ul style="list-style-type: none"> ○ <i>S. aureus</i> ○ <i>S. lugdunensis</i> ○ <i>Candida</i> spp. • All cases with suspected endovascular infection <ul style="list-style-type: none"> ○ Infective endocarditis ○ Septic thrombophlebitis ○ Implantable cardioverter defibrillator (ICD)/pacemaker lead infections ○ LVAD line infections ○ Vascular graft infections • Select cases in patients at risk of endovascular infection, particularly with gram positive bacteremia <ul style="list-style-type: none"> ○ ICD/pacemaker ○ Vascular graft ○ Prosthetic valves ○ History of infective endocarditis ○ Valvulopathy in heart transplant recipient • Infected prosthetic device that is retained (catheter or other prosthetic) • Concern for persistent bacteremia due to lack of clinical improvement after 48 hours of effective therapy <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p><u>Draw 2 peripheral sets at least 48 hours after initial BCx.</u></p> <p>Single sets are not adequate to detect bacteremia.</p> </div>

Peripheral BCx are preferred over central lines blood cultures due to lower false positive results.

Always draw 2 peripheral sets (i.e., 4 bottles with 8-10cc/bottle).

***Excludes severely immunosuppressed patients (neutropenia, hematopoietic stem cell or solid organ transplant)**

Figure 2: Indications for Follow up Blood Cultures in Adult Patients with Positive BCX*



*Excludes severely immunosuppressed patients (neutropenia, hematopoietic stem cell transplant, solid organ transplant)

Indications for Obtaining Follow Up Blood Cultures: obtain follow-up BCx

- Pathogen-based reasons
 - *Staphylococcus aureus* or *S. lugdenensis* bacteremia^{5,10}
 - *Candida* spp fungemia¹¹
- Syndromic-based reasons
 - Suspected endovascular source^{10,12}
 - Infective endocarditis
 - Septic thrombophlebitis
 - Implantable cardioverter defibrillator (ICD)/pacemaker lead infections
 - LVAD line infections
 - Vascular graft infections
 - Suspicion for persistent bacteremia due to lack of clinical improvement after 48 hours of effective therapy
 - Catheter-related bacteremia when attempting catheter retention or other retained infected prosthetic device

- For all cases of *S. aureus* and *Candida* bloodstream infections, catheters should be removed. Catheter retention is not recommended.

Conditions in which Follow-up Blood Cultures May Be Considered: consider follow-up BCx based on clinical scenario

- Pathogen-based reasons:
 - *Enterococcus faecalis* with 2+ positive BCx bottles
 - Streptococcal species other than *S. pneumoniae* or beta-hemolytic streptococci (i.e., *S. pyogenes*): potential infective endocarditis pathogens. Assess patient risk factors for endovascular infection, clinical presentation, and specific species to determine significance of *Streptococci* in blood and need for repeat cultures
 - Risk of endocarditis based on Streptococcal species (prevalence)^{13,14}

Low IE Risk (<3%)	Moderate IE risk (3-10%)	High IE risk (10-30%)	Very high IE risk (>30%)
<i>S. pneumoniae</i> <i>S. pyogenes</i> <i>S. intermedius</i>	<i>S. agalactiae</i> <i>S. anginosus</i> <i>S. constellatus</i> <i>S. dysgalactiae</i> <i>S. salivarius</i> <i>S. thermophilus</i>	<i>S. mitis/orals</i> <i>S. parasanguinis</i> Nutritionally variant Strep species (<i>Granulicatella adiacens</i> , <i>Abiotrphia spp.</i> , <i>Gemella spp.</i>)	<i>S. gallolyticus</i> (previously <i>S. bovis</i>) <i>S. gordonii</i> <i>S. mutans</i> <i>S. sanguinis</i>

- Note: ≥3/4 positive BCx bottles increases risk of endocarditis as do risk factors for endovascular infection
- HACEK Organisms: *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*
- In patients with risk factors for endovascular infection, consider repeat BCx, especially for gram-positive bacteremias
 - Presence of ICD/pacemaker
 - Vascular graft
 - Prosthetic heart valve or prosthetic material for cardiac valve repair
 - History of infective endocarditis
 - Heart transplant-associated valvulopathy
 - Endovascular thrombi
- Syndrome-based reasons:
 - Suspected epidural abscess or vertebral discitis/osteomyelitis^{10,12}: associated with increased risk of persistent bacteremia
 - Bacteremia of unclear source

Low Yield Conditions for Repeating Blood Cultures: do NOT obtain follow-up BCx

- Single positive blood culture with skin flora
 - Coagulase-negative Staphylococci, *Cutibacterium acnes*, *Micrococcus*, viridans group Streptococci, *Corynebacterium spp.*, *Aerococcus spp.*, *Bacillus spp.*
- Clinically stable patients with persistent fever or leukocytosis with two sets of negative BCx within last 72 hours (excludes *S. aureus* or *Candida* bloodstream infections)

- Uncomplicated gram-negative bacteremia^{5,10}
 - Non-endovascular source, clinically improving at 72 hours, source controlled
- Uncomplicated streptococcal bacteremia (especially *Streptococcus pneumoniae*, Viridans Group Streptococci, Beta-Hemolytic Streptococci) bacteremia^{5,10,12}
 - Uncomplicated: clinical improvement without concerns for uncontrolled source, endocarditis, or endovascular infection
 - See above regarding risk of endocarditis with specific Streptococcal species

When to Obtain Blood Cultures from Central Venous Catheters (CVCs)

Obtaining blood cultures from CVCs should generally be avoided but may be considered in the following situations:

- Evidence of local infection at the CVC insertion site: erythema, induration, purulence, drainage
- Fever/rigors and signs of sepsis (tachycardia, hypotension) developing shortly after infusion through CVC or while on hemodialysis
- Fever/rigors and signs of sepsis (tachycardia, hypotension) in a patient with a CVC without other identified site of infection based on history or physical exam.
 - If another site of infection is identified (e.g., patient has cough and dyspnea with concerns for pneumonia), avoid drawing blood cultures from CVC and proceed with further workup of suspected source
- Note: all patients with *S. aureus* and *Candida* spp bloodstream infections should have catheters removed, so BCx do not need to be obtained from a line if these infections have already been identified, rather these catheters should just be removed
- Note: in hemodynamically unstable patients with concern for a central line-related bloodstream infection, the central line should be promptly removed to achieve source control
- Do NOT obtain blood cultures from central lines in place for <48 hours as it is unlikely that the infection is related to the catheter.
- When obtaining central line cultures, a peripheral culture should ALWAYS be obtained concurrently.
- If a patient has multiple central venous catheters, recommend obtaining one peripheral culture and one from the central line that is suspected to be infected. If there is no other identified source of infection based on history or physical exam, it is reasonable to obtain one peripheral culture along with one BCx from each line.
- Do NOT routinely culture multiple lumens of a CVC

How to Interpret Positive Blood Culture Results

- When a BCx flags as “positive” from the BCx incubator, a gram stain is performed and the results of the gram stain are immediately communicated to the clinician via phone.
- Within 2 hours of the gram stain, a BCx rapid identification (BCID) molecular panel will be performed and reported to the EMR.⁹ See BCID Guidance document for further information on interpretation and treatment guidance (<https://www.unmc.edu/intmed/documents/id/asp/news/bcid2-final-8-11-21.pdf>).

- The decision to start antibiotics should be based upon the clinical stability of the patient and the likelihood that the organism detected represents a true bacteremia
 - In clinically stable patients where the suspicion for true bacteremia is low, antibiotics should be withheld until the organism is identified
- Organisms considered likely to be contaminants where antibiotics should be withheld unless found in multiple BCx sets:⁴ coagulase-negative *Staphylococcus* (exception: *S. lugdenensis*), *Corynebacterium* (exception: *C. diphtheriae*), *Bacillus* species (exception: *B. anthracis*), *Micrococcus*, and *Cutibacterium*
- Organisms with variable significance when found in a single BCx bottle where antibiotics may be considered (requires clinical interpretation):⁴ *Enterococcus* spp., *Clostridium* spp.
 - Viridans group Streptococci: frequent contaminant when only found in one BCx set, particularly in non-severely immunocompromised patients. Even when found in the bloodstream and clinical scenario is consistent with this pathogen, management strategy likely does not change (i.e. patient with intra-abdominal infection and Viridans group Streptococci in BCx)
- Organisms considered to nearly always be pathogenic where starting antibiotics is recommended:⁴ *Staphylococcus aureus*, *Streptococcus pneumoniae*, beta-hemolytic Streptococci, *Listeria monocytogenes*, Gram negative organisms (*Enterobacteriales*, *Pseudomonas* spp., *Neisseria meningitidis*, *Haemophilus influenzae*), gram-negative anaerobes (*Bacteroides*, *Fusobacterium*), and *Candida* spp.

Fungal Blood Cultures¹⁵

- The utility of fungal BCx is very limited and should be reserved for select patients as directed by infectious diseases
- Routine blood cultures are equivalent to fungal blood cultures for detecting common yeasts, such as *Candida* spp and *Cryptococcus* spp
- Several fungal pathogens, such as *Histoplasma*, *Coccidioides*, *Blastomyces*, and *Cryptococcus*, are detected by fungal blood cultures; however, yield is much lower and time to detection is much slower compared to non-culture based methodologies (e.g., urine/serum *Histoplasma* antigens, *Coccidioides* antibodies, *Blastomyces* urine antigen, and *Cryptococcus* serum/CSF lateral flow assay for antigen)¹⁵
- Pathogens such as *Aspergillus* spp and *Mucorales* spp are very rarely found on fungal blood cultures and are better detected using biopsy with tissue culture or serologic studies (*Aspergillus* galactomannan)
- If clinical concern for a disseminated fungal infection is high, infectious diseases consultation is recommended to optimize antifungal diagnostics and need for empiric/targeted treatment
- Similar to routine blood cultures, fungal blood cultures are prone to contamination, especially when the overall yield is low¹⁶

Indications for Fungal Blood Cultures¹⁵

- Concern for *Fusarium* spp or other filamentous fungal infection: severely immunocompromised patients with concern for fungal pathology (e.g., skin lesions)

- Concern for *Malassezia* spp: patient with fevers, negative routine blood cultures, and receiving TPN

Recommended Alternatives to Fungal Blood Cultures¹⁵

- Fungal BCx should be avoided in most patients with concern for fungal infection. Utility of fungal BCx varies depending on the specific fungal pathogen
- If concern for the following fungal infections, consider the following tests:
 - Candidemia: Obtain 2 sets of routine blood cultures, consider use of beta-D-glucan (Fungitell) although only moderate sensitivity and specificity.
 - Cryptococcal infection: Obtain Cryptococcus antigen from serum and/or cerebrospinal fluid, PCR from meningitis/encephalitis panel is highly specific but lacks sensitivity compared to antigen; routine BCx and CSF cultures can detect
 - Dimorphic fungal infections
 - Histoplasmosis: recommend serum/urine Histoplasma antigens
 - Coccidioides: recommend Coccidioides antibody
 - Blastomycosis: recommend urine Blastomyces antigen
 - Aspergillus: obtain Aspergillus galactomannan and tissue biopsy for histopathology and fungal culture, can consider beta-D-glucan but non-specific
 - Mucorales: obtain tissue biopsy for histopathology and fungal culture

When to Obtain AFB Blood Cultures¹⁷

- The utility of AFB BCx is very limited and should be reserved for select patients as directed by infectious diseases
- Clinical concern for disseminated Mycobacterial infection in the following settings:
 - Advanced HIV (CD4<50): *Mycobacterium avium* complex, others
 - Culture-negative prosthetic valve endocarditis or LVAD infections: especially *M. chimaera* infection post-cardiac surgery
 - Disseminated *Mycobacterium bovis* Bacillus Calmette-Guerin (BCG): history of bladder cancer treated with BCG presenting with fever of unknown etiology
 - Disseminated/miliary tuberculosis: other modalities such as biopsy with AFB smear/culture, sputum AFB smear/culture, and MTB PCR have higher yield
 - Primary immunodeficiencies

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