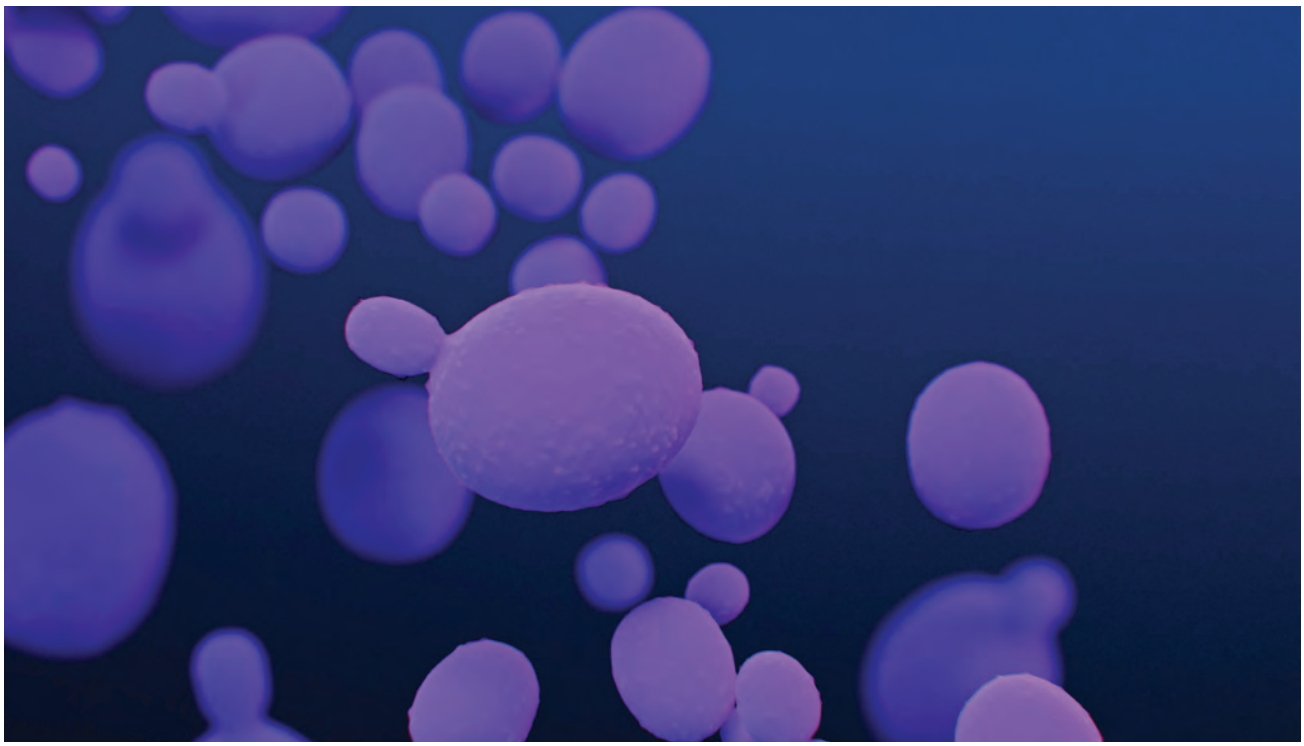

CDC/ Antibiotic Resistance Coordination and Strategy Unit

# For bloodstream infection testing, don't forget the fungal pathogens

By Chris Gardner

The testing landscape for bloodstream infections has shifted significantly over the years, particularly as certain types of bacteria have become more or less prevalent. In recent decades, however, fungal pathogens have emerged as another important cause of bloodstream infections that must be factored into standard clinical laboratory testing algorithms for optimal patient care.

Both bacterial bloodstream infections (bacteremia) and fungal bloodstream infections (typically candidemia, named for the *Candida* genus of yeasts that represents the lion's share of fungal bloodstream infections) can cause aggravated inflammatory responses and lead to the dangerous and potentially deadly condition of sepsis. In both cases, it is essential to identify the causal pathogen and, where applicable, any markers of antimicrobial resistance in order to adjust treatment plans.

When patients can be given appropriate, early treatment after the onset of sepsis, their odds of survival are highest. Unfortunately, too many patients must wait days before this diagnostic information is available, and during that time they may be prescribed medications that are not appropriately targeted for their infection. Patients' odds of survival drop substantially the longer they go without getting an effective treatment, and the risk of triggering antimicrobial resistance increases when these therapies are deployed unnecessarily.

Bloodstream infections and sepsis take a heavy toll in hospitals. Worldwide, experts estimate that some 30 million people are diagnosed with bloodstream infections annually and that 6 million of those patients die from their infections or subsequent complications from sepsis.[1,2] Most cases of bacteremia are caused by *Enterococcus* species, *Staphylococcus aureus*, and coagulase-negative staphylococci.[1,3,4] Approximately one-third of bloodstream infections acquired within a hospital are attributed to gram-negative bacteria; these cases have higher mortality than gram-positive bacteria and are often associated with antibiotic resistance.[5-12] Fungal pathogens are less common, but over the years they have been gaining prevalence. Fungal infections leading to sepsis are the cause of 10 to 15 percent of healthcare-associated infections, and *Candida* species may be responsible for 70 percent or more of those cases.[13]

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### LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. List the different types of bloodstream infections currently infecting patients.
2. Discuss healthcare statistics among bloodstream infections.
3. Identify fungal blood stream infections and discuss the need to rapidly identify them.
4. Discuss the importance of adding fungal pathogen ID panels to molecular testing platforms.

For the best possible patient outcomes, clinical laboratories must test suspected cases of bloodstream infection for fungal as well as bacterial pathogens — and identify the species or strain responsible. Just as physicians need to know the causal bacterial strain to select the best treatment, they also need to know the specific type of fungal pathogen for the most accurate prognosis and therapeutic choice. Ideally, a bloodstream infection panel test would cover the likely bacterial or fungal culprits (as distinguished by Gram stain) simultaneously to generate results in a clinically relevant time frame.

## Traditional testing

When a hospitalized patient is suspected of having a bloodstream infection, standard protocols are followed. Based on a rapid assessment of relevant factors — the patient's immune status, travel history, prior use of antibiotics, and local outbreak data — the clinical care team will likely start the patient on a combination of broad-spectrum antibiotics.[14]

Before treatment is underway, however, blood samples will be collected and sent to the laboratory for analysis. Culture-based testing has long been the gold standard for identifying a pathogen and any useful antimicrobial resistance information. But for bloodstream infections, and their inherent risk of triggering sepsis, waiting several days or even longer for culture results is too great a delay to get patients on appropriate therapy.

A basic Gram stain can generate information quickly, differentiating between gram-positive and gram-negative bacteria. The same process can even reveal the presence of a fungal pathogen, as these organisms have a distinctive morphology. However, this high-level identification lacks the detail needed to provide clear treatment guidance.

If the identity of the causal pathogen is unknown, the patient will likely continue to receive treatment that may not be effective. Should the patient become septic, each passing hour without appropriate treatment can increase the risk of mortality. Even without the dangers of sepsis, keeping a patient on broad-spectrum antibiotics for an extended period increases the chances of selecting for resistance in the bacterial species exposed to the antibiotic, and disrupting the patient's microbiome.[15]

## Molecular testing

While culture-based testing remains the most familiar approach for revealing the pathogens responsible for infections, molecular tests are now widely used to generate reliable results more quickly. For some clinical situations, such as respiratory testing, guidelines now recommend the use of molecular assays instead of culture tests because they allow for a much faster selection of appropriate treatments.[16] Molecular tests are bolstered by an extensive history, well-documented validation, and a series of economic and clinical utility studies available to help users select the most appropriate test for their patients' needs.[17]

For bloodstream infections, molecular tests exist to complement the culture workflow, allowing lab staff to continue the use of culture-based testing while adding the advantages of rapid and accurate molecular results. Once the culture bottle comes up positive and Gram staining is performed, a sample from that same bottle can be run in an assay designed to look for gram-negative or gram-positive bacteria. This type of approach complements the standard culture workflow.

While molecular tests do not have the century-long track record of culture testing, they offer a broad range of benefits. In the context of bloodstream infections and sepsis, their most noteworthy advantage is speed. Using the positive culture bottles, molecular tests can pinpoint the causal pathogen and report key genetic factors associated with antibiotic resistance in just a couple of hours. This slashes 24 to 48 hours from the standard culture turnaround time and allows clinical teams to get the patient on appropriate treatment much faster. Molecular tests are also highly accurate, ensuring that those rapid results can be trusted.

## Targeting fungal pathogens

As fungal pathogen threats increase, having molecular tests limited to bacterial pathogens for bloodstream infections is insufficient. Ideally, clinical labs should have access to rapid molecular panel tests that could be used for gram-positive or gram-negative bacteria as well as the most common fungal culprits. After all, fungal pathogens such as *C. auris* and *C. tropicalis* share many similar morphological traits, but they have different clinical profiles and recommended treatments.

While fungal invaders are not a new concern in the realm of bloodstream infections, they are becoming more common — and more dangerous. A landmark epidemiological study of sepsis in the United States published in 2003 found that, in the period from 1979 to 2000, "the rate of sepsis due to fungal organisms increased by 207 percent."[18] That represents a change from approximately 5,200 cases of fungus-associated sepsis in 1979 to more than 16,000 cases in 2000. Now, the Centers for Disease Control and Prevention (CDC) estimates that some 25,000 cases of invasive candidemia occur in the United States annually.[19]

There are many reasons for changes in pathogen prevalence, but scientists are increasingly pointing to climate change as one of the biggest drivers of the rising threat from fungi. The International Society of Dermatology (ISD) Climate Change Committee, for instance, recently reviewed the available literature to present the epidemiological landscape of fungal pathogens and how that has evolved due to climate change.[20]

While fungi's ability to infect mammals has been limited due to their past sensitivity to higher temperatures, mounting evidence and scientific consensus now support the idea that fungi can develop heat tolerance.[21,22] As fungi are exposed to higher temperatures in the wild, those that were once unable to survive in the temperature of the human body are now growing acclimated to withstand such a temperature, thus creating new potential pathogens in our population. This new tolerance also allows fungi to expand into new geographic territories, putting more people at risk if these organisms become pathogenic. It also poses a new challenge to clinicians in those areas, and to those who treat patients who have traveled from areas where those infections are more common. As the ISD committee notes, "Physicians who completed their training or practice in regions where certain climate-sensitive fungal diseases were historically rare or absent may find it difficult to recognize, diagnose, and treat them."

As more fungal threats arise, it is becoming clear that they have the potential to wreak havoc in their hosts — in some cases, they appear to be more dangerous than known bacterial or viral pathogens. For example, researchers in China analyzed data from more than 18,000 sepsis cases and found that 18.8 percent of those cases had positive yeast cultures.[23] "Patients with positive yeast cultures had higher in-hospital all-cause mortality, 60-day all-cause mortality, and longer lengths of ICU stay and hospital stay than those with negative yeast cultures," they reported. Similar results have come from several other studies around the world.[13,24,25]

These dangers worsen from the rise of highly resistant fungi such as *Candida auris*. First identified in a patient about 15 years ago, *C. auris* has now been found across Asia, Europe,

the Middle East, Africa, and the Americas.[26] In a 2023 study from the CDC, 20 percent of reported *C. auris* cases in the United States between 2017 and 2022 were bloodstream infections.[27] The pathogen was particularly deadly in these cases: "Estimated crude mortality rates were 47% for bloodstream *C. auris* versus 31% for non-bloodstream," the scientists noted.

Knowing that a fungal pathogen is the cause of a patient's infection is not enough; the treatment plan for a likely drug-resistant *C. auris* infection is quite different from what would be needed for, say, a likely susceptible *C. albicans* infection. With the rising threat of fungal pathogens for bloodstream infections and sepsis, rapid molecular testing should be performed to detect the most common fungal infection causes when a fungal source is suspected. Similar to the gram-positive and gram-negative bacteria panel tests, if this data can be generated within a few hours, there is hope for tailoring therapy appropriately to give each patient the best possible chance of recovery.

## Looking ahead

Historically, looking solely for bacterial pathogens in bloodstream infection testing may have been enough for some patient populations — but unfortunately, that is no longer the case. Whenever possible, clinical laboratories should seek out rapid molecular testing options that also allow for the detection of these increasingly common, and highly dangerous, fungal pathogens. Identifying the cause of such an infection in just a few hours should help to ensure that treatment selection can be adjusted quickly to the most appropriate therapy, de-escalating from broad-spectrum antibiotics when advisable and shifting to antifungals when needed. Getting patients on the right treatment faster is associated with better health outcomes, lower costs, and shorter hospital stays.

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