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Practice Forum

# Rapid diagnostics for bloodstream infections: A primer for infection preventionists

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Accurate and rapid antimicrobial susceptibility testing with pathogen identification in bloodstream infections is critical to life results for early sepsis intervention. Advancements in rapid diagnostics have shortened the time to results from days to hours and have had positive effects on clinical outcomes and on efforts to combat antimicrobial resistance when paired with robust antimicrobial stewardship programs. This article provides infection preventionists with a working knowledge of available rapid diagnostics for bloodstream infections.



The accurate and rapid determination of the identity and antimicrobial susceptibility of pathogens plays a critical role in the management of bloodstream infections (BSIs).[1-3] While organism identification (ID) is important and can provide direction in antimicrobial choice for some bacteria, antimicrobial susceptibility testing (AST) is required for effective management of BSIs caused by common pathogens, such as *Staphylococcus aureus*, *Enterobacteriaceae, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Antimicrobial resistance rates of these organisms represent a major public health concern. For example, 65% of Acinetobacter pneumonia infections in the United States and Europe are caused by carbapenem-resistant species; the rate of carbapenem-resistant enterobacteriaceae has risen 5-fold in community hospitals in the southeastern United States; and the latest methicillin-resistant *S. aureus* (MRSA) prevalence rates in the United States are reported to be as high as 66.4 per 1000 inpatients.[4-6] The prevalence of antibiotic-resistant organisms varies between communities, but collectively they are responsible for over 2 million infections and 23,000 deaths each year in the United States alone.[7] Antibiotic-resistant organisms have been implicated in a significant proportion of hospital-acquired BSIs, particularly among patients in intensive care units, where as many as half of isolates have been identified as multidrug resistant.[8-10]

The emergence of multidrug-resistant organisms (MDROs) has led to use of broad-spectrum, empiric antimicrobial therapy as the standard of care approach to managing patients with suspected BSIs, pending the ID and AST of the infecting bacteria. Traditionally, such testing typically takes 48-72 hours for the laboratory to perform. Decreasing the time patients are on broad-spectrum therapy through rapid diagnostics that include ID and AST information may have implications not only for ensuring appropriate treatment, whether it involves escalating or de-escalating antimicrobial therapy, but also for reducing *Clostridium difficile* infection (CDI) and reducing antimicrobial resistance incidence by mitigating the selective pressure placed on microorganisms.[11,12]

The pace at which new rapid diagnostic technologies, heralded as “game changers” by some in the infectious disease community,[13] are evolving presents a challenge to infection preventionists (IPs), whose role and responsibilities have already undergone a dramatic expansion.[14] Maintaining a working knowledge of the basic principles of the different rapid methods and the information they provide; determining which technology best meets the needs and goals of their antimicrobial stewardship program (ASP) and infection prevention programs; and learning how they can advocate for the technology in their institution often requires time and resources that IPs no longer have. This is substantiated by surveys of

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IPs reporting a lack of understanding of certain technologies and a desire for more education on laboratory diagnostics.[15,16] Furthermore, it has repeatedly been shown that rapid diagnostics rarely have an effect on antimicrobial use or patient outcomes unless they are paired with a robust ASP intervention; thus, it is imperative that IPs have a working knowledge of the available technologies.[3,17-21] The aim of this article is to provide a basic framework of available BSI rapid diagnostics for IPs.

## BSIS: THE SEPSIS BURDEN

Sepsis presents the most substantial diagnostic and therapeutic challenge of all BSIs, although the term BSI can also refer to various grades of bacteremia. Bacteremia is defined as the presence of bacteria in the bloodstream and can be diagnosed as transient, intermittent, or continuous.[11] When these circulating bacteria and their toxins elicit a dysregulated host response, resulting in significant organ dysfunction, circulatory collapse, and metabolic deterioration, sepsis, a true medical crisis, occurs.[22] Understanding the burden placed on the healthcare system by sepsis is key to appreciating the need for rapid diagnosis of the causative organism(s) and their antimicrobial susceptibility. The most recent report on sepsis by the Agency for Healthcare Research and Quality revealed that sepsis-related hospital stays increased by 153% between 1993 and 2009, with an average annual increase of 6%.[23] Sepsis is also the single-most expensive reason for hospitalization, with an annual cost estimated in excess of $20 billion.[23,24] In-hospital mortality rates from sepsis are a staggering 16%, over 8 times higher than other diagnoses,[12] with as many as 600 deaths occurring per day in the United States alone.[25]

The critical value of rapid ID and AST in sepsis is perhaps best demonstrated by the work of Kumar et al., who documented a 7.6% drop in survival of patients with severe sepsis and septic shock for every hour of delay prior to administration of effective antimicrobial therapy.[26] Furthermore, studies have shown that as many as 20%-30% of septic patients receive inadequate empiric antimicrobial therapy, which is strongly associated with increased mortality.[1,27,28]

The use of broad-spectrum, empiric therapy in treating BSIs, including sepsis, has repeatedly been implicated as a contributor to antimicrobial resistance.[18,19,25,29-31] Despite this, empiric therapy remains a mainstay of BSI—and particularly sepsis—treatment for several valid reasons. In fact, the international Surviving Sepsis Campaign Guidelines recommend "empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)."[32]

This practice is based on the fact that, in many cases of primary BSIs, the clinical picture belies a specific microbiologic diagnosis, leading healthcare providers to initiate therapy that covers a broad range of potential pathogens.[1] Additionally, the acuity of BSIs and the knowledge that mortality directly correlates with time to effective therapy precludes waiting for ID and AST results.[1,18,19,26,31] Thus, the longer the turnaround time (TAT) for those results, the longer it takes to de-escalate therapy and the more likely the empiric therapy is to contribute to downstream resistance. A vicious cycle ensues in which suspicion of resistant organisms as causative pathogens in BSI leads to the use of increasingly broad-spectrum antibiotics.

### *Traditional approach to microbiology testing of patients with suspected bacteremia or sepsis*

Standard of care for suspected bacteremia and sepsis has long included collection of blood cultures and concomitant administration of empiric antimicrobial therapy, along with other sepsis bundle interventions outlined by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine's collaborative Surviving Sepsis Campaign.[33] When the blood culture bottle turns positive, a cascade of additional diagnostic testing begins, including the Gram stain, the results of which are phoned to the team caring for the patient, and subculturing of the blood to solid media so that the organism can be grown in pure culture, as shown in Figure 1. The following day, bacterial colonies are identified and AST is performed, using a suspension of the organism. AST is performed by exposing the bacteria to a panel of antibiotics and observing if growth is inhibited—a process performed in most North American laboratories using automated instrumentation. Additional manual techniques, such as gradient strips or disk diffusion, may be required to confirm results or to test antibiotics not available on the assay panels provided for these automated systems.[34] Although advancements in culture media and monitoring systems have improved the sensitivity and TAT of blood cultures over the past several decades,[24,35] they are inherently hampered by several limitations: 12 hours to 5 days before detection of bacteria, issues arise with contamination of skin flora, and limited efficacy is seen in the case of prior antibiotic exposure and/or infections caused by fastidious organisms.[11,12] This is compounded by the time required to subculture the bacteria from positive blood cultures, obtain a pure culture, and test on automated ASTs.

## RAPID DIAGNOSTICS FOR BSI FROM POSITIVE BLOOD CULTURES: CURRENT TECHNOLOGIES AND THEIR DIAGNOSTIC CAPABILITIES

Rapid diagnostics represent a significant advance from traditional culture methods on the continuum of BSI diagnostic capabilities. Blood culture and traditional AST methods are still the core laboratory practice; however, they are increasingly being supplemented with novel diagnostics that yield information hours to days faster than the traditional techniques. Most of these rapid diagnostics dramatically improved the time-to-result associated with ID of the most common bacteria and yeast that cause BSIs. Significantly, until early 2017, advances in time-to-result in new AST methods have generally lagged behind those for ID and resistance marker testing.

One means of distinguishing among the commercially available fast diagnostic technologies is to categorize them by technology type and their diagnostic capabilities (e.g., ID and/or genotypic/phenotypic AST), as demonstrated in Table 1. Accurate bacterial ID, beginning with a Gram stain, is clearly the first step toward achieving appropriate antimicrobial therapy and is a critical step in providing initial information on targeting therapy (either through escalation or de-escalation) and potential contaminants. For example, identification of *Streptococcus pneumoniae* or Group A or B Streptococcus can facilitate antimicrobial de-escalation based on the high susceptibility profile of these organisms to penicillins.[36-38] Community, facility, unit, or specimen type (e.g., blood, sputum, or wound) antibiograms may then facilitate a more effective antibiotic selection. Unfortunately, even antibiograms updated annually, grouped by unit or specimen type, still represent a "best guess" for the susceptibility profile of organisms. It is not uncommon to find specific drug/bug combinations where 20%-30% of isolates are resistant to a common therapy choice (e.g., in 1 large, urban academic medical center's intensive care unit, 26% of *Klebsiella pneumoniae* isolates were resistant to cefazolin, which is an antimicrobial frequently used for *K. pneuominae* infections).[39] As such, in many cases, targeted therapy cannot be implemented until AST is performed. AST, in its current forms, still lags behind ID in TAT but is important in progressing from a "more effective" antimicrobial selection, in which the chosen antibiotic is generally known to cover the