Early Identification and Treatment of Pathogens in Sepsis

Molecular Diagnostics and Antibiotic Choice

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KEYWORDS

• Sepsis • Bacteremia • Nucleic acid amplification • Microarrays • Antimicrobial stewardship • Patient outcomes • Resistance markers

KEY POINTS

- Sepsis and septic shock are significant medical problems, with high mortality rates and are the 10th leading cause of death in the United States.
- Although blood cultures are considered the gold standard, emerging molecular diagnostic methods are providing rapid identification for key organisms and antimicrobial resistance markers from positive blood cultures.
- Assays that provide detection and identification of bacteria directly from whole-blood are in development, and are not yet able to replace existing culture amplification-dependent methods.
- Rapid diagnostic methods can significantly reduce the time to identification of organisms and resistance genes and have the greatest impact on improving time to optimal therapy and patient outcomes when coupled with an antimicrobial stewardship program.

INTRODUCTION

Sepsis, severe sepsis, and septic shock are stages of increasing severity of the systemic host response to bloodstream infections.[1,2] Since the 1980s, the epidemiologic burden of sepsis in the United States and other developed countries has steadily increased. Despite significant improvements in medical care and the development of newer and more broad-spectrum antibiotics for treatment, sepsis still accounts for significant morbidity and mortality in the United States, and is considered among the top 10 leading causes of death.[3] In 2013, the Agency for Healthcare Research and Quality published data from the Healthcare Cost and Utilization Project, indicating that sepsis was among the top 4 conditions associated with the highest cost to hospitals in the United States.[4,5] Aside from the high mortality rate and economic burden during the acute phase of the illness, sepsis and severe sepsis have

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associated indirect costs, such as health care expenditures after hospital discharge and nontrivial productivity loss among sepsis survivors (eg, work absenteeism, early retirement, and overall increased morbidity and mortality).[6] In addition, several other studies described an increased risk of death lasting up to 5 years after survival of 1 episode of sepsis, although many of the mechanisms of the increased morbidity and mortality years after surviving sepsis remain unclear to date. All stages of sepsis combined pose a significant financial and humanistic burden, not only to the individual patients but also to society as a whole.

Despite the technical improvements of continuous monitoring blood culture systems, the value of blood cultures for confirming the clinical suspicion of sepsis has been shown to be suboptimal. The diagnostic limitations and uncertainties of blood cultures related to a low sensitivity (ie, positivity rate), prolonged time to pathogen detection and turn-around-times (TAT) of results, and frequent contamination of blood cultures by patients' skin microbiota during blood culture procurement, are often compensated by the liberal use of broad-spectrum antimicrobial therapy.[2] However, considering rising antimicrobial resistance rates and the emergence of novel antimicrobial resistance types (eg, carbapenem-resistant *Enterobacteriaceae*), it is important to exercise a judicial approach to the use of broad-spectrum antimicrobial therapy. The major role of antimicrobial stewardship programs (ASPs) is to optimize the overall utilization, selection, and dosing of antimicrobial agents to minimize adverse events and prevent the emergence of antimicrobial resistance in the health care setting. During the past decade, development of rapid, often molecular, detection methods for both pathogens and antimicrobial resistance markers has seen a significant upsurge. The implementation of such rapid diagnostic technologies in the clinical microbiology laboratory is critical not only for the confirmatory diagnosis of sepsis, but also for support of ASPs. This article provides an update and assessment of recent improvements in pathogen and antimicrobial resistance detection in sepsis, focusing primarily on diagnostic molecular technologies.

MOLECULAR METHODS FOR DETECTION OF BACTEREMIA

Tremendous progress has been made over the last 2 decades in the development of diagnostic assays to speed up the detection of bacteria and yeast in blood. The initial wave of these assays involved testing positive blood culture bottles at the time of positivity with molecular methods that determine both the identity of a pathogen or pathogens and associated resistance markers. The second wave, direct from whole blood testing, has been ushered in by the T2 Biosystems *Candida* assay (described in more detail elsewhere in this article), the first such assay to obtain US Food and Drug Administration (FDA) approval; **Table 1** summarizes the assays discussed in this review. Several other assays are in development or have progressed to the clinical trial stage. This section of the review discusses the existing molecular platforms and their performance characteristics. The next section discusses the impact of these methods on antimicrobial stewardship activities and patient outcomes where available.

NONAMPLIFIED, GROWTH-DEPENDENT METHODS

Rapid pathogen detection is of pivotal importance for the diagnosis of sepsis, and a variety of molecular techniques have been developed over time for the detection of specific pathogens. However, many of these technologies still require an initial growth of the pathogen(s) in blood culture bottles. Fluorescence in situ hybridization (FISH) technologies were among the earliest developed and most studied techniques for the detection of pathogens from positive blood cultures.[2,7] These technologies are typically pathogen specific, and allow for the detection of only a small number (1–3) of organisms per test. Broad-based methods on the other hand detect various pathogens from positive blood culture bottles without nucleic acid amplification; these multiplex, automated methods allow for the identification of genus, species, and specific resistance determinants for the most common organisms implicated in bloodstream infections.

Pathogen-Specific Methods

Peptide nucleic acid PNA-(FISH) technology (AdvanDx, Woburn, MA) is probably the most studied commercially available technology suitable for the detection of pathogens from positive blood cultures.[7,8] The first technology to be commercially available for rapid organism detection, it is now, becoming rapidly surpassed by other molecular detection methods. PNA FISH technology uses fluorescein-labeled probes that target pathogen-specific 16S rRNA of bacteria or 26S rRNA of yeast. FDA-approved PNA FISH probes are available for the following common pathogens implicated in BSIs: *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS); *Enterococcus faecalis* and other *Enterococcus* spp.; *Escherichia*