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Commentary

Advancing Sepsis Care: The Promise and Challenges of Emerging AST Technologies

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DESCRIPTION

Sepsis is a life-threatening condition caused by the invasion and proliferation of pathogens in the bloodstream, accompanied by an excessive inflammatory response and organ dysfunction. Globally, sepsis affects around 40 million people each year, with mortality rates rapidly increasing over time after onset and ultimately reaching 20%-50%. To improve the prognosis of sepsis patients, timely administration of appropriate therapy is essential. However, Antimicrobial Susceptibility Testing (AST) performed in current hospitals to determine the optimal treatment often takes 2 to 3 days, or even longer depending on the invading species and patient condition. This delay has compelled clinicians to prescribe broad-spectrum antibiotics before drug susceptibility profiles are confirmed. Yet, studies have revealed that 18% to 78% of these first-line, empirical treatments are rather ineffective, leading to reduced treatment efficacy and accelerating the development of antimicrobial resistance.

The traditional process of selecting patient-specific optimal antibiotics, AST, involves four key steps: Blood culture to expand the number of pathogens and confirm the presence of infection; pure culture (or subculture) to separate and purify pathogens from blood components; pathogen identification to determine the species responsible for the infection; drug susceptibility testing to analyze the response over various types and concentrations of antimicrobial agents. In order to expedite and streamline this lengthy process, 'Rapid AST (RAST)' technologies have evolved over the past years, incorporating additional sample processing steps through various engineering approaches to eliminate the need for pure culture, which typically takes around one day. This has resulted in a time reduction of 30-40 hours compared to traditional AST methods, significantly minimizing the time required for AST. Clinical studies have demonstrated that RAST technologies can reduce patient mortality rates by more than half in specific subgroups, particularly among patients infected with resistant pathogens, underscoring their significant potential to improve patient outcomes. As a result of these advancements, numerous startups have also emerged since the mid-2010s, with several now making their entry into the market with the hope of saving patient lives.

Continuing this trajectory of innovation, an ultra-Rapid AST (uRAST) method was recently published in Nature in 1st July, marking a significant advancement in which all necessary tests for optimal antibiotic prescription can now be completed within a single day. What makes uRAST particularly unique is its ability to perform both pathogen identification and AST directly from whole blood, entirely bypassing conventional culture procedures. This method utilizes magnetic nanoparticles coated with synthetic peptides to capture a broad spectrum of pathogens directly from whole blood. The species of the enriched pathogens are then identified through a quick-mapping assay employing multiple silica-coated microdiscs with distinct hole patterns, where complementary bug-specific DNA probes hybridize. Drug susceptibility is tested simultaneously by briefly expanding the isolated pathogen, mixing the bacteria with liquid agarose, and loading them onto a 96-well microfluidic chip containing various types and concentrations of antibiotics. By monitoring bacterial growth in the wells over time through algorithms, the pathogen's susceptibility to each antibiotic condition can be assessed. The report also details a clinical trial involving 190 suspected sepsis patients, where uRAST demonstrated its effectiveness by completing all required tests 60 hours faster than conventional AST methods. Considering the strong correlation between reduced testing time and improved mortality rates, the potential life-saving impact of these advancements becomes increasingly evident.

However, despite ongoing advancements in the technical field, these new AST methods have yet to achieve widespread adoption in hospitals. One of the major obstacles is the strict yet somewhat outdated regulatory standards, with criteria based on traditional AST methods that continue to be applied to emerging technologies, often overlooking urgent needs and

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potential patient benefits. Additionally, these new technologies must undergo extensive clinical evaluations to be approved and covered by insurance, a highly conservative and demanding process that the developing company must navigate on its own. Furthermore, since the AST process involves multiple stages and requires the expertise of various medical specialists, implementing these changes in hospitals, such as training staff, reconfiguring roles, and altering workflows, poses significant barriers, particularly in light of the hesitancy to adopt new technologies. The associated financial considerations must also be addressed as part of the overall overhaul. Nevertheless, with flexible regulatory adaptations, proactive efforts, coordinated understanding across multiple institutions, and strategic investment, committing to the integration of these innovative AST methods into clinical practice, though challenging, will be essential for improving patient outcomes, particularly for those facing life-threatening conditions such as sepsis.

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