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Mini Review* | *Open Access

Fast Track Diagnostic Requisite for Sepsis and its Antimicrobial Resistance in Low Resource Settings: A Step Towards Antimicrobial Stewardship

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1. Abstract

Sepsis due to multidrug resistant bacteria (MDR) is a growing challenge. WHO developed the global action plan on antimicrobial resistance and adopted a resolution for improving the prevention, diagnosis and clinical management of the sepsis. At an early stage, sepsis frequently remains under-diagnosed when it is potentially reversible. Laboratories in low resource settings often face the issue of poor infrastructure, irregular supply of reagents, maintenance and new investment costs. Currently, molecular diagnostics have met the criteria of rapidity, ease of use, cost, automation and can be used for point-of-care (POC) testing. However, there scarcity of POC diagnostics in the resource limited settings. The present review describes real time polymerase-based tests and commercially available systems for their capability for bacterial and resistance profile detection. We highlight the need for innovative, small and cost-effective POC devices for clinical utility. It will help to plan more effective antibiotic treatments and quality of health care services in developing countries.

2. Introduction

Since the discovery of the wonder drug "Penicillin" in 1928, there has been tremendous increase in the development and production of many other antibiotics. Annually about 100,000 tons of antibiotics are being manufactured worldwide to treat infections. Yet, their persistent use, self-medication, inappropriate prescriptions and exposure to infections in hospitals have triggered the emergence of multidrug-resistant (MDR) bacteria. Further, there is an increased risk of mortality in patients exhibiting MDR bacterial infections compared to those without MDR infections [1-3]. The prevalence of MDR is predicted to increase to 10 million deaths per year by 2050 if no action is taken. World Health Organization (WHO) published the list of pathogens in February 2017 and recognized sepsis as a major public health problem for which new antimicrobial development is urgently needed [4].

3. Prevalence

Sepsis due to multidrug resistant (MDR) bacteria is a major public health problem particularly in the low- and middle-income countries. It is an often a fatal condition that arises when the immune response to an infection causes widespread systemic organ injury [5]. WHO data shows that approximately 20% of all-cause global deaths are due to sepsis in 2020. It has shown to affect 49 million people and cause 11 million deaths globally every year [6].

Delay in antimicrobial administration results has been shown to be associated with a fivefold reduction of survival in patients with septic shock in high income countries [7]. Although the literature suggests that sepsis is predominantly a healthcare issue in resource-rich countries, the global burden of acute infections is highest in resource-limited areas. The rates of resistant bacteria are reported to be as high as 50% in low and middle- income countries [8-10]. Although sepsis is treatable, patients infected with sepsis or septic shock, and exhibiting MDR bacteria have a higher risk of mortality, in spite of early antibiotic therapy [11].

4. Pathogenesis

Sepsis has heterogeneous causes and the bacterial pathogens implicated in sepsis include species of *Enterobacter, S. aureus, Klebsiella, Acinetobacter, and Pseudomonas and E. coli*. It affects the individuals of all ages including neonates, pregnant women, elderly, people living in low-resource settings and patients with comorbidities. Sepsis diagnosis and management in the children is of particular importance as there is highest burden of infection-related deaths in resource-limited areas in the age group <5 year.

5. Methods for Pathogen Detection

When an individual is suspected with sepsis, then question arises whether an infection is present. If it exists, can broad-spectrum antibiotics be used for its treatment. The basic detection tests involve culture and staining by visual detection and further antibiotic susceptibility testing (AST) which typically take 1–5 days. Culture-based methods are hindered in their practicality as they usually require pure cultures and are labor-intensive leading to compromised clinical outcomes. In quantitative antimicrobial AST, it is not always possible to obtain a significant correlation between susceptibility phenotype and resistance markers [12]. Further, there are chances of obtaining false-positive or negative results with culture contamination. As the time required for bacterial identification is more, the patient has to be given empirical therapy, often with broad-spectrum antibiotics which may further contribute to antimicrobial resistance (AMR). It is suggested that detection of resistant bacteria can be facilitated with rapid identification and molecular-based techniques to identify MDR organisms such as methicillin-resistant *Staphylococcus areus* (MRSA), vancomycin-resistant enterococcus (VRE), or carbapenem-resistant Enterobacteriaceae (CREs) as early as 2 hr after sample collection [13]. It is predicted that the market will experience a shift towards point-of-care (POC) devices for sepsis detection in the coming years [14].

Over the last few years, advancements in the accelerated phenotypic techniques, mass spectroscopy and molecular techniques has changed detection approaches. Currently, molecular diagnostics, such as nucleic acid amplification technique enables the use of non- purified samples and provide real time monitoring. Real time polymerase reaction (RT-PCR) based tests or devices are fulfilling the requirement of rapidity, ease of use, cost, automation and can be used for POC testing. Publications also support the use of PCR based tests for the detection of viral and bacterial infections in intensive care units, near-patient testing as well as outpatient clinics. Few RT-PCR tests are approved by CE-IVD and are commercially available for the identification of sepsis-relevant microorganisms.

6. Molecular Platforms in Market

The LightCycler® SeptiFast (Roche Diagnostics, Penzberg, Germany) simultaneously analyses about 20 sepsis causing pathogens using multiplex RT-PCR within 6 hrs including extraction, detection and analysis with the blood volumes as low as 100 µL. The test is reported to provide higher sensitivity (90.5%) but have lower specificity (80.0%) [15]. SepsiTest™-UMD system developed by Molzym (Molzym GmbH & Co. KG), targets 16S and 18S rRNA genes of bacteria and fungi from various sample types (whole blood, CSF, BAL, synovial aspirates, ascites fluid, peritoneal aspirates, pus, blood culture and ultrasonic fluids) within 7 hr using RT-PCR. The specificity of the test ranges from 70%-94.4% with a sensitivity from 66.7-100% for whole blood sample (https://www.molzym.com/images/products/Flyer_App_Notes/AN_SepsiTest-UMD_2_17.pdf). The VYOO® (SIRS-Lab GmbH, Jena, Germany), a multiplex PCR system can detect 34 bacterial and 6 fungal test within 8 hr. However, it is reported to be associated with a significant number of false positive results. The concordance in bacterial identification between microbiology and the VYOO® test is reported to be 46.2% [16]. Further, the Magicplex™ Sepsis test (Seegene, Seoul, South Korea) is also based on RT-PCR and detects 73 Gram-positive, 12 Gram-

negative bacteria and 6 fungi, as well as 3 drug- resistant genes (*mecA, vanA*, and *vanB*) with turnaround time of 6 hr [17]. It is observed that the analytical performance of these tests varies according to the type of sample, study population, extraction process, algorithm used for analysis and comparative methods. Some of these systems require different kits for nucleic acid extraction and PCR, need technical experts for execution and are also expensive for routine use.

Some molecular diagnostics have also been commercialized that identify the presence of genes or mutations responsible for the drug resistance. RT-PCR assays, such as BD GeneOhm MRSA assay (BD GeneOhm™, San Diego, CA, USA), Xpert MRSA assay panels (Cepheid, Sunnyvale, CA, USA), GeneXpert MRSA/SA ETA (RMRSA/SA-ETA-10, Cepheid, USA) are currently available for detection of *Staphylococcus aureus.* The Xpert MRSA assay (Cepheid, Sunnyvale, CA, USA) developed by Oh et al is a RT-PCR based assay developed for the detection of MRSA-specific DNA sequence within the staphylococcal cassette chromosome in 2 hours. This assay performed better than a single-locus real-time PCR assay but showed fewer false-positive results [18]. It is observed that most of these assays target Methicillin- resistant *Staphylococcus aureus* (MRSA) and not other bacteria involved in the sepsis.

Labs in low resource settings often face the issue of availability of materials due to the high cost. According to a WHO report (2016), only 15 of the 48 high TB-burden countries have used the Xpert tests for all suspected TB cases (WHO, 2017b) and same could happen in case of sepsis. In India, only two diagnostic platforms are under development stage (TRL4) for Sepsis (bacteraemia) and neonatal sepsis detection and no diagnostic has yet been released for clinical utility [19] indicating a need for indigenously developed rapid POC diagnostics for AMR containment in India.

7. Conclusion

In order to bridge these challenges and to improve AMR testing in low- and middle-income countries, development of sample-to-result portable system that eliminates the huge infrastructure and capital cost of the molecular lab is urgently needed. Integration of automated sample preparation and assay setup for both, the sepsis and AMR detection, would help to maximize the efficiency. Further, automated system with a auto-feed protocol, barcode reading, self sanitization, and LIMS (Laboratory Information Management Systems) connectivity would be a boon for ICU patients. Mylab Discovery Solutions has consistently provided innovative and high-quality diagnostics with economical perspective and contributed significantly to a healthcare system. Considering AMR as a global health threat, we are committed to address this issue with an aim to provide actionable answers.

8. Conflicts of Interest

None.

9. References

1. Vardakas KZ, Rafailidis PI, Konstantelias AA, Falagas ME. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: the study, the patient, the bug or the drug? J Infect. 2013;66(5):401–414.
2. Cornaglia G, Giamarellou H, Rossolini GM. Metallo-beta-lactamases: a last frontier for beta-lactams? Lancet Infect Dis. 2011;11(5):381–393.
3. Zavascki AP, Barth AL, Gonçalves ALS, Moro ALD, Fernandes JF, Martins AF, et al. The influence of metallo-beta-lactamase production on mortality in nosocomial Pseudomonas aeruginosa infections. *J Antimicrob Chemother*. 2006;58(2):387–392.
4. World Health Organization (2018). Sepsis. World Health Organization. Available online at: http://www.who.int/sepsis/en/ (Accessed Oct 15, 2018)
5. Min J, Nothing M, Coble B, Zheng H, Park J, Im H, et al. Integrated Biosensor for Rapid and Point-of-Care Sepsis Diagnosis. ACS Nano. 2018 Apr 24;12(4):3378-3384.
6. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al.. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. (2020) 395:200–11.
7. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009 Nov;136(5):1237- 1248.
8. Bataar O, Khuderchuluun C, Lundeg G, Chimeddorj S, Brunauer A, Gradwohl-Matis I, et al. Rate and pattern of antibiotic resistance and microbiological cultures of sepsis patients in a low-middle-income country's ICU. Middle East J Anaesthesiol. 2013;22:293–300.
9. Jacob ST, Moore CC, Banura P, Pinkerton R, Meya D, et al. (2009) Severe Sepsis in Two Ugandan Hospitals: a Prospective Observational Study of Management and Outcomes in a Predominantly HIV-1 Infected Population. PLoS ONE 4(11): e7782. doi:10.1371/journal.pone.0007782.
10. The 10 leading causes of death by country income group. WHO factsheets. 2012. http://www.who.int/mediacentre/factsheets/fs310/en/index1.html.
11. Busani S, Serafini G, Mantovani E, Venturelli C, Giannella M, Viale P, et al. Mortality in Patients With Septic Shock by Multidrug Resistant Bacteria: Risk Factors and Impact of Sepsis Treatments. J Intensive Care Med. 2019 Jan;34(1):48-54.

12. Maurer FP, Christner M, Hentschke M, Rohde H. Advances in rapid identification and susceptibility testing of bacteria in the clinical microbiology laboratory: implications for patient care and antimicrobial stewardship programs. *Infect Dis Rep*. 2017;**9**(1):6839.

13. Ho VP, Kaafarani H, Rattan R, Namias N, Evans H, Zakrison TL. Sepsis 2019: What Surgeons Need to Know. Surg Infect (Larchmt). 2020 Apr;21(3):195-204. doi: 10.1089/sur.2019.126.

14. Oeschger T, McCloskey D, Kopparthy V, Singh A, Erickson D. Point of care technologies for sepsis diagnosis and treatment. Lab Chip. 2019 Feb 26;19(5):728-737.

15. Straub J, Paula H, Mayr M, Kasper D, Assadian O, Berger A, et al. Diagnostic accuracy of the ROCHE Septifast PCR system for the rapid detection of blood pathogens in neonatal sepsis-A prospective clinical trial. PLoS One. 2017 Nov 8;12(11):e0187688.

16. Fitting C, Parlato M, Adib-Conquy M, Memain N, Philippart F, Misset B, et al. (2012) DNAemia Detection by Multiplex PCR and Biomarkers for Infection in Systemic Inflammatory Response Syndrome Patients. PLoS ONE 7(6): e38916.

17. Zboromyrska Y, Cillóniz C, Cobos-Trigueros N, Almela M, Hurtado JC, Vergara A, et al. Evaluation of the Magicplex™ Sepsis Real-Time Test for the Rapid Diagnosis of Bloodstream Infections in Adults. Front Cell Infect Microbiol. 2019 Mar 12;9:56.

18. Oh AC, Lee JK, Lee HN, Hong YJ, Chang YH, Hong SI, et al. Clinical utility of the Xpert MRSA assay for early detection of methicillin-resistant Staphylococcus aureus. Mol Med Rep. 2013;7(1):11-5.

19. Sharma M, Gangakhedkar RR,Bhattacharya S, Walia K. Understanding complexities in the uptake of indigenously developed rapid point-of-care diagnostics for containment of antimicrobial resistance in India. BMJ Global Health 2021;6:e006628.