Nepalese Medical Journal, (2019) Vol. 2, 177 - 180

Review Article

Rapid Diagnosis of Blood Stream Infections in ICU: Recent Advances

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ABSTRACT

Blood stream infections and sepsis are major causes of hospitalization in most intensive care units around the globe, especially in developing countries like Nepal. Although the sepsis guidelines emphasize the role of early institution of appropriate antibiotics, it is practically challenging due to delayed turnover time of currently available diagnostic tests. Modifications in traditional blood culture methods, use of molecular techniques and availability of biomarkers have raised hope in rapid detection of blood stream infections.

Keywords: Bacteremia; Infections; Nucleic acid testing; Sepsis

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Submitted: 21st April 2019
Accepted: 15th May 2019
Published: 20th June 2019

Source of Support: None
Conflict of Interest: None

Citation: Pangeni RP. Rapid diagnosis of blood stream infections in ICU: recent advances. Nep Med J 2019;2(1):177-80. DOI 10.3126/nmj.v2i1.23980

INTRODUCTION

Although less than one-tenth of hospital beds are occupied by critically ill patients in an intensive care unit (ICU), it accounts for more than a quarter of hospital acquired infections which carries a significant burden to both patients and the hospital in terms of hospital stay, morbidity, mortality and expense.[1] The ICU mortality rate of infected patients is 25%, two times more than non-infected patients in an international study.[2] The surviving sepsis guidelines in 2018 reinforce the usage of antimicrobials as early as possible, preferably within an hour, to reduce the mortality related to sepsis.[3,4] Unfortunately, the current culture-based diagnostic strategies often take 2 to 3 days to provide a result, most of them either negative or inconclusive due to contaminants.[5] This holds true more so in countries like Nepal where patients often have already received concurrent antibiotics by the time they are seen by a physician, hence the treatment remains mostly empiric.[6] In addition, the frequent isolation of multi-drug resistant pathogens hinders the initiation of appropriate selection of effective empiric antibiotic therapy. This emphasizes the role of rapid microbiological diagnosis of infection in an ICU and this review tries to focus on some of the rapid diagnostic tools currently available.

CATHETER RELATED BLOOD STREAM INFECTIONS

Intravenous catheters are frequently inserted in critically ill patients for hemodynamic monitoring and for administration of fluid, blood, medicines and nutritional solutions. Unfortunately, they remain a potential source for bacteremia and septicemia in ICU. Catheter-related bloodstream infection (CR-BSI) is defined as the presence of bacteremia originating from an intravenous catheter. CR-BSI is one of the most frequent, lethal and costly complication of central venous catherization.[7] The diagnosis is established when the organism isolated from blood is causally linked with the catheter inserted, which may be performed with or without catheter removal.[8] In a patient with signs and symptoms suggestive of systemic infection, CR-BSI is suspected when one or more blood cultures obtained from a peripheral vein are

positive and there is no apparent source for the bloodstream infection except the catheter. However, fever and chills that are often associated with CR-BSI are non-specific and local catheter site inflammation can occur without blood stream infection, hence has poor correlation with sensitivity of 3% or less. This highlights the importance of microbiological evidence to suggest catheter as the source of infection. The rapid techniques to diagnose CR-BSI without removal of catheters are convenient and potentially avoid unnecessary removals restricting the vascular access. They include:

a. **Non-paired cultures:** Catheter drawn quantitative blood culture showing bacterial load >100CFU/ml has a sensitivity of 81-86% and specificity of 85-96 percent. However, it cannot differentiate between CR-BSI and high grade bacteremia.[9]

b. **Paired cultures:** Paired positive blood cultures from the central catheter and simultaneously drawn peripheral blood sample is usually accepted as a proof of CR-BSI if the ratio of the colony counts (differential colony count) is more than 5:1 with a sensitivity and specificity above 90 percent.[10] However, it is labor intensive and costly.

c. **Differential time to positivity:** This is conducted using continuous automated culture monitoring system and requires inoculating the same amount of blood in each culture bottle. Differential time to positivity is considered significant when the culture drawn from the central catheter becomes positive more than 2 hours earlier than the simultaneously drawn blood culture drawn from a peripheral vein. This has a sensitivity of around 90% and specificity of around 80% and can rapidly detect CR-BSIs.[10] The interpretation might be difficult in patients receiving antibiotics through the catheter.

SEPSIS IN ICU AND LIMITATIONS OF BLOOD CULTURES

The need for rapid detection of infection in critically ill patients cannot be overemphasized. Each hour delay in detection of sepsis and antibiotic use results in nearly 8% drop in survival.[11] On the other hand, inappropriate antibiotic use results in three to five fold increased risk of multi-drug resistance and mortality.[12,13] The diagnosis of blood stream infection or sepsis in ICU is a major challenge and blood cultures still remain the gold standard. However, cultures require incubation times of up to 96 hours and can only detect viable microorganisms and have low sensitivity for slow growing, intra-cellular, fastidious organisms and in patients pre-treated with antimicrobials. Conventional recommendations for blood culture requisitions suggest at least 20 to 30 ml volume of blood per set of 2 to 3 culture-bottle sets including those for anaerobes, which is not practically feasible in our setting.[14] Despite improvement in technology that improve culture detection time such as the use of liquid media, adsorbing agents against growth inhibitors/metabolic products/remnant antibiotics, automated instruments for continuous growth monitoring and co-application of other techniques for species identification, the time to positivity still remains more than 15 hours.[15] The positivity rate of blood cultures has been quoted as 30-40% in western studies whereas the rate drops down to 10-25% in Indian scenario.[15-18] This further emphasizes the role of rapid and more sensitive diagnostic tests for the detection of these micro-organisms.

MOLECULAR TESTING FOR SEPSIS IN ICU: WHERE ARE WE NOW?

To overcome the limitations of blood cultures as cited above, researchers have been developing and improvising on various culture-independent technologies for the identification of the infections in ICU. One of the major advances made during the last few years is the molecular identification methodology which is capable of identifying pathogens directly from the sample or by co-application with other culture based techniques. These techniques are evolving and are likely to impact clinical decision making regarding selection of antibiotics. Among a variety of molecular methods such as nucleic acid testing, (NAT) and serology, NAT by quantitative real time polymerase chain reaction (PCR) is by far the most universal methodology used for pathogen detection. Currently available commercial diagnostic tests that use this technology are all based on a similar procedure: pathogen lysis, nucleic acid extraction and purification, amplification of nucleic acids by PCR, and identification by various methods, such as ELISA-based hybridization, fluorescence based real-time detection, liquid or solid phase microarray detection, sequencing and database recognition.[10]

A wide range of culture based NATs are currently available and are US-FDA approved that are also capable of detecting genes encoding resistance to antimicrobials such as as mecA in staphylococci or van genes in enterococci, allowing a faster phenotypic detection of resistance bugs namely methicillin resistant staphylococci (MRSA) or vancomycin resistant enterococci (VRE) and are capable of identifying organisms within 5 hours. Several micro-array based broad range multiplex assays such as Prove-it Sepsis (Mobidiag, Helsinki, Finland) and BlackLight (BlackBio, Madrid, Spain) are also in use that can identify various gram positive and negative bacteria by covering three regions of the 16S ribosomal gene and more than 400 fungal and yeast sequences based on the 18SrRNA with a turn-around time of 4 hours.They cover around 90% of all sepsis-causing pathogens, including fungi with sensitivity and specificity of over 95%, but is a labour- and expertise-demanding approach and needs positive culture for identification.[19,20] Hence the limitations are similar to those of culture based techniques.

During the past 20 years, several PCR assays capable of direct detection of pathogens from the blood, body fluids or biopsy specimens without the need of positive blood cultures have also been introduced. These are either 'pathogen or genus specific', 'broad range' that utilize sequential multiple steps or 'multiplex' assays that target several DNAs simultaneously and can detect most of the clinically important pathogens including bacteria, virus and fungi within a turnaround time of less than 6 hours.[15] The latter 'multiplex assay based on real time PCR and microarrays' currently seems to be the most promising technology. Polymerase chain reaction/electrospray ionization–mass spectrometry (PCR/ESI-MS), for example, can detect >800 different pathogens — and identify markers associated with methicillin, vancomycin, and carbapenem resistance — in a single assay in about 6 hours. The latest commercially available technology MagicPlex (SeeGene, Korea) utilizes multiplex device with several platforms, including

Magicplex Sepsis, which is able to detect more than 73 Gram-positive and 12 Gram-negative bacteria, 3 drug resistance markers (mecA, vanA and vanB) and 6 fungi, covering over 90% of sepsis-related microorganisms.[21] Current commercially available 'sepsis screening package' in Indian subcontinent utilizes broad based DNA-PCR in blood samples and claims to be able to detect 345 clinically relevant pathogens including wide range of bacteria, viruses and fungi.[22] However, its utility in other body fluids has not been validated.

There are limited large scale studies regarding the clinical utility of these techniques in diagnosis and management of ICU infections. Bacconi et al in 2014 analyzed 5ml each of 331 blood samples from patients with suspected blood stream infection and used this technique (PCR followed by electrospray ionization mass spectrometry-PCR/ESI-MS) and demonstrated 83% sensitivity and 94% specificity as compared to blood cultures.[24] Similarly, Vincent et al in the RADICAL study enrolled 529 critically ill adults admitted in nine European ICUs with suspected or proven severe infections and compared PCR/ESI-MS with standard blood culture.[5] Sixty-three percent had received antibiotics during the current hospitalization but before study enrollment; 75% had received them within 30 days. Culture yielded positive results for 68 of 616 whole-blood specimens (11%), whereas PCR/ESI-MS did so for 228 (37%). For 185 respiratory specimens and 110 specimens from usually sterile sites, culture identified pathogens in 81 (44%) and 53 (48%), respectively, whereas PCR/ESI-MS did so in 117 (63%) and 78 (71%). Culture was positive and PCR/ESI-MS nonconcordant in 13 cases; both were negative in 384. These studies highlight the utility of the molecular technology that is fast and three times more likely than standard culture to identify pathogens causing severe infection, potentially provide early information for guiding antibiotic therapy. The affect of these tests in patient related outcomes is unclear.

These molecular techniques have several limitations. Apart from the issues related to availability, labour intensiveness and cost, there may also be difficulties faced during interpretation of the results. A positive molecular test with a concurrent negative blood culture may either reflect detection of pathogens due to its higher sensitivity, or may represent non-proliferating, dead or degraded pathogens, contamination (such as coagulase negative staphylococci) or carry-over nucleic acids after successful treatment. The carry-over nucleic acids may be detected several weeks after the successful treatment of infection.[15] In our setting, there may be other associated factors that affect sensitivity of these tests such as issues related to preservation and transportation of samples, batch-analysis of the samples for cost reduction and availability of staff during off-hours. These factors nullify the benefits of early identification of potential pathogens causing sepsis in ICU.

ROLE OF BIOMARKERS IN ICU INFECTIONS

An ideal biomarker that can be used in an acute care setting should have a good accuracy, reproducibility and predictive value (diagnostic), able to detect patients at risk of complication (prognostic), useful during follow up of therapy (therapeutic) and be available and acceptable at low cost (accessibility). Serum C - reactive protein (CRP) and procalcitonin levels are two of the several biomarkers which are widely studied and quoted in literatures for these indications. Despite conflicting results, CRP measurements are widely used to initiate or to adjust the duration of antimicrobial therapy in ICU infections.[24,25] The sensitivity of CRP as a diagnostic test for acute infections has been reported from 30-97.2%, and specificity values of 75–100%, PPV values of 31–100% and NPV values of 81–97%, the disparity being mostly due to variable cut-offs that have been used.[26] Its routine use as a biomarker in acute infection has not been recommended.[27] Similarly, several well designed trials and meta-analyses have been published on the role of procalcitonin (PCT) as a marker for initiating, monitoring and de-escalating antibiotics in acutely ill patients, mostly in lower respiratory tract infections. The rapid upregulation and sustainment of PCT levels in the serum during infection makes it an ideal biomarker in an ICU setting. It rises within 2–4 h of infection and peak at 6–8 h, and is known to increase by 1000 fold under inflammatory conditions. As a biomarker of infection, current studies report sensitivity and specificity of 75 to 100% and positive or negative predictive values of 55-100% each, depending upon the cut-off values been used.[26]A review done by Carr et al in 2015 showed that the PCT levels in septic ICU patients were higher (4.5 to 12.0 ng/mL) as compared to 0.24–0.8 μg/L in the respiratory infection/pneumonia patients.[28] A meta-analysis by Simon et al. included studies that evaluated PCT and CRP for the diagnosis of bacterial infections and found PCT to be more sensitive and specific marker than CRP in differentiating infective from non-infective inflammation.[29] Anand et al. recently published a prospective observational single-centre trial that included 208 patients (46 non-infectious SIRS, 90 culture-negative sepsis, and 72 culture-positive sepsis) and found that PCT was significantly elevated in patients with culture-negative and culture-positive groups compared to patients with SIRS only.[30] However, despite its better diagnostic performance as compared to other markers, most of the studies have failed to show change in the patient centered outcomes including mortality and length of ICU stay.[31] Pending large scale studies, routine use of PCT as a diagnostic marker of infection in ICU has not been currently recommended by international guidelines.

Intensive efforts are being made in the search of new diagnostic and prognostic biomarkers, which may be helpful for the management of antibiotic therapy in acute infections. Four of these markers, the soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1), Soluble urokinase-type Plasminogen receptor (suPAR), proadrenomedullin (ProADM), and Presepsin appear promising in recent small scale studies. In view of limited studies on the impact of these new biomarkers on the diagnosis antibiotic management of ICU patients, applicability of these tests in routine clinical practice is unclear and has not been recommended pending larger studies in this field.[27]

CONCLUSIONS

There has been significant progress made recently in the rapid microbiological diagnosis of infections in ICU that include improvisation of previously available culture-based techniques, early microbiological diagnosis using molecular methods and the use of biomarkers. Current approaches in managing ICU infections have focused on reducing the delay in the diagnosis and treatment of many types of infection, such as sepsis, pneumonia, urinary tract infections, skin and soft tissue infections, viral infections or tuberculosis. Molecular methods and biomarkers, though promising, have several limitations and still need further improvisations and made available at low cost especially in resource constraint settings like ours.

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