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Improved Microbial Diagnostics for the Critically Ill Patient with PCR/ESI-MS

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Sepsis is a constant challenge facing those who care for critically ill patients. Sepsis and septic shock contribute substantially to morbidity and mortality in this group, and in 2012 authors of guidelines for appropriate management of these conditions highlighted demand for rapid, reliable microbiological tests (Dellinger et al, 2013). 'In the near future, rapid, non-culture-based diagnostic methods (polymerase chain reaction, mass spectroscopy, microarrays) might be helpful for a quicker identification of pathogens and major antimicrobial resistance determinants.' While speculating that such techniques could be applied to detect fastidious pathogens, and under circumstances where empirical antimicrobials had been given before taking blood cultures, they also cautioned that '... more clinical studies are needed before recommending these non-culture methods as a replacement for standard blood culture methods.'

Clinical studies have been undertaken, supporting the use of molecular-based, non-culture techniques, not only for the rapid detection of microorganisms causing sepsis and septic shock, but also for the rapid detection of bacteria, viruses, fungi and yeasts across the infectious diseases spectrum. This diagnostic step-change could potentially improve patient outcome through better-targeted antimicrobial therapy, thus having the potential to minimise antimicrobial resistance and cost.

IRIDICA, a new platform in the vanguard of this diagnostic revolution relies on the polymerase chain reaction (PCR) coupled to mass spectrometry. Essentially, a broad-spectrum PCR amplifies selected conserved regions of pathogenic nucleic acid; the mass of the amplicons is determined by electrospray ionization mass spectrometry (ESI-MS) allowing to determine their base compositions with a specific database; and a presumptive pathogen's base composition is compared to those stored in a database holding details of over 1,000 species (Ecker, 2014). The turnaround time is typically six to eight hours. The currently commercially available PCR/ESI-MS technology, Abbott's IRIDICA system can detect 780 bacteria 4 antibiotic resistance markers with a single test, 207 molds and yeasts with a single test and 131 viral species in 13 reporting groups with a single test. (Abbott Diagnostics, 2015).

Bacconi et al (2014) reported the analysis of 331 blood samples of patients with suspected sepsis from a single centre with PCR/ESI-MS and compared the molecular results to blood culture. The positivity rate of PCR/ESI-MS (10.6%) was almost double compared to the positivity rate of blood culture (5.4%). The 20 PCR/ESI-MS detections in blood-culture negative samples were repeatedly tested by another operator on another instrument to exclude potential contamination events. In 17 cases the original detection could be confirmed, in 3 cases it was not possible, but in all 3 of these cases the initially detected bacterial load was very low. PCR/ESI-MS was 83% sensitive 94% specific compared to culture. After replicate testing of PCR/ESI-MS samples which initially gave results deviating from culture corroborating the initial findings in most cases, an increased sensitivity of 91% and specificity of 99% was determined (considering the repeated additional detections true positives). The detection of pathogens took 6 to 8 hours from sample to result, a significantly decreased time to result against culture-based methods.

Rising numbers of immunocompromised patients have wrought a concomitant increase in fungal and bacterial lung infections, representing a further diagnostic challenge to clinicians. Again, PCR/ESI-MS has addressed these needs. Shin et al (2013) used PCR/ESI-MS to evaluate a series of 691 bronchoalveolar lavage (BAL) samples that had been cultured and identified by standard procedures, they concluded that it '... provides an advanced tool for rapid and sensitive detection, identification, and determination of the distribution of fungal organisms directly from BAL fluid specimens. Moreover, it detected fungal organisms in specimens in which cultures failed because of bacterial overgrowth.'

Platforms such as PCR/ESI-MS permit detailed exploration of the role of virus infections in diverse pathological processes. For instance, in a study of idiopathic dilated cardiomyopathy (IDCM), Nguyen et al (2013) used PCR/ESI-MS to detect and semi-quantify common cardiotropic viruses in 67 explanted heart samples of 31 IDCM patients. They '... identified single or mixed enterovirus and Parvovirus B19 cardiac infections as potential causes of IDCM.' The system was considered '... to be a valuable tool to rapidly detect and semiquantify common viruses in cardiac tissues and may be of major interest to better understand the role of viruses in unexplained cardiomyopathies.'

Finally, the cost savings made by such diagnostic platforms are significant. Thus, when Perez et al (2013) addressed the challenge of bloodstream infections caused by Gram-negative organisms, they sought to determine the extent to which a combination of mass spectrometry-mediated technology and antibiotic stewardship would improve on conventional laboratory methods. They found that it shortened the time to optimal therapy; decreased time in hospital; and in a 1000-bed quaternary care hospital there were projected annual savings of around \$18 million.

Perhaps the 'near future' alluded to by Dellinger et al (2013) above is here.

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