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Editorial

Direct rapid antimicrobial sensitivity test (dRAST): A distant dream or palpable reality

Bloodstream infections (BSI) globally poses a significant healthcare burden since it could cause organ dysfunction and sepsis, leading to increased mortality, morbidity and prolonged hospital stay, incurring high costs for healthcare systems and to the patient/family.

The emergence and rising rates of antimicrobial-resistant bacteria is a serious cause for concern, which contributes to poor clinical outcomes, and increased mortality due to ineffective antibiotic treatment. In addition, being treated with overly broad-spectrum antibiotics can increase the risk of adverse side effects and further drive development of resistance. Clinical outcomes can be improved by rapid antibiotic susceptibility testing (AST) for positive blood cultures, which will reduce the time required for initiating effective and appropriate antimicrobial therapy.

Recent advances in early identification of pathogens either by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry or by multiplex polymerase chain reaction (PCR) directly from positive blood culture broth along with rapid AST will enable clinical laboratories to provide preliminary identification and AST results to clinicians.

Rapid AST guidelines have been developed in recent years to shorten the diagnosis process, both by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI). Pioneering rapid AST, EUCAST in 2018 published breakpoints for performing the standard disk diffusion test, directly using positive blood culture broth, which could then be incubated and read at 4, 6 and 8 hours or 16–18 hours for the seven most common blood stream pathogens, namely *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Enterococcus faecalis* and *E. faecium*, against seven commonly used antimicrobial agents. EUCAST further improved on this over the years to include more antimicrobial agents and added *Acinetobacter baumanii* to the currently published breakpoints in 2022. CLSI guidelines M100-S31 (2021) vaguely suggested performing a disk diffusion test directly from positive blood culture for seven antimicrobial agents without nominating the organisms. CLSI clarified and confirmed this in M100-S32 (2022) by specifying dRAST only for Enterobacterales and *Pseudomonas aeruginosa*, but results had to be read at 8 - 10 hours of incubation. This guideline remains the same in M100-S33 (2023), with changes of a few zone diameters.

Hence both EUCAST and CLSI agree on performing AST directly from positive blood culture broth, even though the inoculum in the blood culture broth cannot be quantified. This “primary” rapid AST by disk diffusion will take a few more years to be further standardised yet can be used by clinical microbiological laboratories for early and improved management of patients. Although rapid AST could provide early results, it is performed manually. They are also labour-intensive due to the strict timing required for AST interpretations.

Genotypic AST, based on nucleic acid amplification test (NAAT), nucleic acid hybridization or immunodiagnostics, in principle, allow the use of non-purified polymicrobial clinical samples, like the positive blood culture broth used for dRAST. They could deliver extremely rapid AST results within 1-3 hours, by probing for the presence of specific genetic sequences that are known to cause phenotypic

resistance, but this has limited usefulness as there are many more resistance sequences that are yet to be elucidated. Moreover, some resistance mechanisms are beyond the reach of genotypic AST.

On the other hand, rapid phenotypic AST can be performed within a few hours by many automated systems. While some perform end-point analysis, others depend on frequent sampling from culture chambers. Technologies using microbial metabolism, motility or heat production are yet to provide convincing outcomes. Many such systems are still at research and developmental stages.

One well validated system determines growth using both an oxidation-reduction indicator and turbidity growth detection to provide both rapid and accurate susceptibility results. Another promising commercial system uses single cell optical imaging based on time-lapse microscopic imagery of bacterial colony formation in agarose along a linear drug gradient, with early reporting of AST in 4-7 hours, bypassing the lengthy sub-culturing and manual AST procedures used in conventional dRAST methods. These along with rapid identification methods using MALDI-TOF and/or multiplex PCR, will result in early reporting, which in turn will improve clinical outcome of patients.

To reap the benefits of dRAST, to at least use direct AST by conventional culture plates as recommended by CLSI or EUCAST, let alone the automated systems, clinical microbiology laboratories should be operational 24/7/365. In that event, whenever the automated blood culture system flags positive, those blood culture bottles could be retrieved to perform Gram stain and dRAST, either on conventional culture plates, a rapid automated commercial system, or both, along with MALDI-TOF and/or multiplex PCR for identification.

In the current practice of having laboratory operational hours from 8.00 am to 4.00 pm, blood cultures which flag positive after working hours will be attended to only the following day, losing valuable time to initiate and optimize appropriate antimicrobial therapy to influence clinical outcomes of patients. Since any changes to these operational hours will involve many challenges, if not obstacles, including policy changes primarily regarding manpower and finances, a feasible solution would be for an ‘on-call’ staff member to visit the laboratory in the late evening at approximately 9.00 pm and attend to all the positively flagged blood cultures. This will enable the laboratory to obtain preliminary rapid AST results for most positive blood cultures by the following day, using either CLSI or EUCAST guidelines for dRAST. This operational change will not only provide dRAST but will also justify acquiring automated blood culture systems by laboratories and optimise their use, as positive blood cultures lie idle in the automated blood culture system during off-working hours. Similar system change could also be adopted for weekends and public holidays.

Until and unless laboratory policies and practices are changed with commitment, and bold initiatives and actions are instituted, dRAST which is a palpable reality, will elude as a distant dream.

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