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EDITORIAL

Diagnostic Stewardship in LMICs: The Way Forward

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INTRODUCTION

The World Health Organization (WHO) defined "Diagnostic Stewardship" as coordinated guidance and interventions to improve the appropriate use of microbiological diagnostics to guide therapeutic decisions. It should promote appropriate, timely diagnostic testing, including specimen collection and pathogen identification, and accurate, timely reporting of results to guide patient treatment.[1] One of the critical components of this definition is the timeliness of the results to the clinicians. The world is moving very fast, and so is the landscape of diagnostic testing for Infectious Diseases (IDs). We have already gone through a COVID-19 pandemic and are living through another pandemic, i.e., antimicrobial resistance (AMR).

One thing that has been learned through these difficult years is that the time taken for specific aetiological diagnosis is paramount, and so is the time taken for diagnostic testing pertaining to actionable decision-making for the management of patients, such as antimicrobial susceptibility testing (AST). Unfortunately, in low to middle-income countries (LMICs) like India, where the significant burden of IDs lies, the diagnostic testing for both scenarios relies majorly either on insensitive microscopic techniques and slow culture-based testing for etiological diagnosis or AST or serological tests which provide indirect evidence of a particular infectious agent. Even though the COVID-19 pandemic has made sensitive molecular testing techniques popular and cheap for diagnosis in LMICs, they are still utilized sparingly only for selected etiological agents. Lack of a specific diagnosis ultimately leads to continual reliance on empirical antimicrobial treatment and contributes indirectly to the increasing burden of AMR.

THE WAY FORWARD

The answer to the first clinical conundrum lies in using syndromic diagnostic techniques that target multiple pathogens in one go to give a specific diagnosis and lead towards a targeted treatment approach. The molecular syndromic multiplex polymerase chain reaction (PCR) panels have been potentially touted as the 'game changers' in managing IDs in terms of their broad pathogen detection capabilities, ease of use and rapid results. Since 2010, when the first syndromic panel for respiratory pathogen detection was cleared by the United States Food and Drug Administration (USFDA), such diagnostic approach has come a long way to now being expanded to other syndromes, including sepsis, gastrointestinal infections, central nervous system infections, and genital infections. The readers may refer to excellent review articles by Bard et al.,[2] Dumkow et al.,[3] and Lucar et al.,[4] for detailed know-how of the status of these syndromic diagnostic panels.

To deal with the other problem of AMR, the putative solution lies in utilizing diagnostic techniques that can identify causative microorganisms, especially bacterial agents, and give AST results against them early. The identification aspect has been addressed mainly by the

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advent of mass-spectrometry-based (e.g. MALDI-TOF) microbial identification systems, which are now the gold standard of microbial identification. However, we must still traverse significant strides in promptly addressing the real clinical question of 'What is the targeted antimicrobial therapy?'. The AST methods continue to rely on painstakingly slow yet reliable colony isolate-based culture techniques, which usually take 2-3 days to provide some actionable information to the clinicians.

To our good fortune, many researchers have taken up the challenge of reducing this 2 - 3 days for AST results and have developed novel automated systems for determining AST, obviating the need to isolate bacteria on plated media. A comprehensive list of such newer automated AST systems is listed in *Table 1*.

Most of these claim to provide AST results from the positively flagged automated blood culture bottles (+aBCBs) within 2-8 hours in patients with sepsis. Unfortunately, these systems are not validated for AST testing from other clinical samples to enable direct AST determination in different clinical syndromes.

Apart from these newer automated systems, AST testing in cases of culture-positive sepsis can also be expedited using the traditional Kirby-Bauer disk diffusion (KBDD) method by performing it directly from +aBCBs. Various national agencies such as the US-based Clinical and Laboratory Standards Institute (CLSI),5 the European Union-based European Committee on Antimicrobial Susceptibility Testing (EUCAST),6 and France-based Antibiogram Committee

Table 1: Newer commercial systems in the pipeline for enabling rapid antimicrobial susceptibility testing

Name of the System	Manufacturer	Country of Origin	Principle	Current Capabilities		Potential turnaround time	Sample	Current Approval status
				ID	**AST (MIC)**			
Accelerate Pheno™	Accelerate diagnostics	USA	FISH (Identification) Morphokinetic Cellular analysis (AST)	X	X	~ 7 hrs	Isolates, +aBCB	USFDA (Only for ID) CE-IVD
Alfred 60AST™	Alifax	Italy	Light scattering	-	X	~4-6 hrs	Isolates, Urine sample, +aBCB	CE-IVD
VITEK® Reveal™	bioMérieux	France	Colorimetric change in response to emission of volatile organic compounds	-	X (GN Only)	~5.5 hrs	+aBCB (GN only)	CE-IVD
ASTar®	Q-Linea	Sweden	Time-lapse imaging	-	X	~ 6 hrs	+aBCB	CE-IVD
QuickMIC®	Gradientech	Sweden	Microfluidics	-	X (GN only)	~2-4 hrs	aBCB (GN only)	CE-IVD
Phenotech Multistar™	Resistell AG	Switzerland	Cantilever-based nano motion	-	X	~2-4 hrs	+aBCB	CE-IVD
dRAST™ Expert System	Quantamatrix	Korea	Microfluidics, Time-lapse imaging	-	X	~4-6 hrs	+aBCB	CE-IVD
FASTinov™ AST	FASTinov	Portugal	Flow cytometry and single-cell image analysis	-	X	~ 2 hrs	+aBCB	CE-IVD

Abbreviations: ID: Identification, AST: Antimicrobial susceptibility testing, MIC: minimum inhibitory concentration, GN: gram-negatives, hrs: hours, +aBCB: positively flagged automated blood culture bottle, USFDA: United States Food and Drug Administration, CE-IVD: Conformité Européenne for in-vitro diagnostic use

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of the French Society of Microbiology (CAFSM),[7] have established performance criteria for direct disk diffusion from +aBCBs. In 2018, EUCAST published a rapid antimicrobial susceptibility testing (RAST) methodology from positive blood culture bottles, wherein AST results can be interpreted within 4 hours. In its present form, the method is validated for eight major bacterial causes of culture-positive sepsis including *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii* complex, *Staphylococcus aureus, Enterococcus faecalis, E. faecium* and *Streptococcus pneumoniae* with breakpoints validated for reading at 4-, 6-, 8- and 16-20 hours post-procedure. In contrast, the CLSI method for direct AST is validated for Gram-negatives only, including *Enterobacterales*, *P. aeruginosa* and *A. baumannii* complex for reading at 8-10 and 16-18 hours.[8] Such an approach for AST testing for low resource settings, especially in LMICs, ticks all the boxes of the WHO ASSURED criteria for a diagnostic test: affordable, sensitive, specific, user-friendly, rapid, equipment-free, and deliverable.[9]

BARRIERS

There is no doubt that these are future approaches. However, there are considerable challenges in effectively utilizing them in our fight against AMR, especially in LMICs. Firstly, there is poor penetration of microbiology services in our country. Unfortunately, laboratories are neither equipped with specialized equipment nor operated by a specialized workforce beyond the tertiary care settings. Secondly, the newer automated systems for syndromic diagnostic testing and rapid AST panels are associated with considerable costs. Thirdly, given the burden of IDs in LMICs, microbiology services must be more dynamic and robust. Sadly, the microbiology services are still not operational 24/7 and continue to operate partially beyond routine timings of 9 AM to 5 PM. Having the best-automated systems is not the answer to expedite diagnostic testing unless there is marked improvement in the pre-analytical, analytical and post-analytical aspects of microbiological diagnostic testing, which will go a long way in reducing the associated turnaround times. Lastly, these newer diagnostic systems will demand a close association between the clinician and the clinical microbiologist for appropriate interpretation of clinical reports and subsequent practice of antimicrobial stewardship.

To conclude, the upcoming diagnostic pipeline in IDs is both promising and exciting and will be our major arsenal in the continued fight against infectious agents and AMR. These include multiplex PCR panels enabling etiological diagnosis in various clinical syndromes, direct AST determination from positively flagged blood culture bottles using upcoming commercial AST systems, or standardized AST protocols using conventional phenotypic techniques by CLSI, EUCAST or CAFSM. However, employing these techniques without changing our mindset regarding the clinical microbiology laboratory workflow will be futile. Whether we are prepared or equipped enough to use them to facilitate antimicrobial stewardship in the foreseeable future is a difficult question to answer at present.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTION

AG: Conceptualization; Writing the draft; Review and editing

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