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Advances in Diagnostic Testing that Impact Infection Prevention and Antimicrobial Stewardship Programs

Kaede V. Sullivan[1]

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Abstract

Purpose of Review The primary purpose of this review is to provide a summary of new and emerging laboratory technologies and testing platforms that impact infection prevention and antimicrobial stewardship programs. This review also summarizes available data describing the clinical impact of implementing these new technologies.

Recent Findings While there is ample evidence that rapid organism identification technologies for positive blood cultures can ameliorate antimicrobial utilization, an assay that also provides expedited antimicrobial susceptibility testing results is now available and its clinical impact is under investigation. For *C. difficile* infection diagnosis, data related to performance and impact of "ultrasensitive" toxin assays is emerging in the literature although their role in *C. difficile* infection diagnosis remains unclear. For hospital-acquired pneumonia, a variety of rapid, automated, multiplexed, "pneumonia" panels have become commercially available and may impact surveillance definitions for ventilator-associated events. Finally, recent FDA clearance of various biochemical and molecular carbapenemase detection tests will facilitate rapid characterization of carbapenem-resistant organisms.

Summary Innovations in infectious diseases diagnostics have been making swift strides, broadening diagnostic scope; increasing accuracy and sensitivity; and reducing turnaround time. Many of these innovations directly impact infection prevention and antimicrobial stewardship operations. Close collaboration between infection control, antimicrobial stewardship, and the microbiology laboratory is necessary to ensure that new tests improve patient outcomes.

Keywords Infection prevention · Stewardship · Diagnostic test

Introduction

In less than a decade, innovations in infectious diseases diagnostics have led to startlingly swift strides in test attributes long valued by laboratorians and clinicians: broad diagnostic scope, high accuracy and sensitivity, rapid turnaround time, and minimal labor requirements. Disruptive technologies such as mass spectrometry and automated, highly multiplexed, all-in-one molecular platforms have transformed laboratory operations, and in some cases, the quality of clinical services provided to patients. Emergence of these new technologies has also led to deliberations about how to harness them to ensure maximal impact at the patient level. This review summarizes microbiology testing platforms that have recently emerged in the diagnostic testing market and are giving rise to both benefits and challenges for infection prevention and antimicrobial stewardship (AS) programs.

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✉ Kaede V. Sullivan
kaede.ota@tuhs.temple.edu

[1] Department of Pathology and Laboratory Medicine, Temple University Health System, Temple University Hospital, Lewis Katz School of Medicine at Temple University, 3401 N. Broad St., Room A2 F329, Philadelphia, PA 19140, USA

Bloodstream Infections

Rapid Organism Identification in Bloodstream Infections

There are presently a wide range of different assays that generate rapid organism identification (ID) from positive blood

culture bottles. They employ a variety of different technologies including PCR (FilmArray BCID (Salt Lake City, UT); Xpert MRSA/SA BC (Cepheid, Sunnyvale, CA)), microarrays (Verigene BC-GP and Verigene BC-GN, Luminex, Austin, TX), and matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS). Test turnaround time is typically 2 to 2.5 h. In addition, the Accelerate PhenoTest BC assay was FDA-cleared in February 2017. It reports ID within 90 min and a panel of antimicrobial susceptibility testing (AST) results in about 7 h from positive blood cultures. The system uses fluorescence in situ hybridization (FISH) for ID and minimum inhibitory concentrations are determined through morphokinetic cellular analysis, a technology that uses dark-field microscopy of individual, immobilized, growing bacterial cells in the presence of known concentrations of antimicrobial agents. By contrast, other assays provide only limited AST information (ex. presence or absence of *mecA*, *vanA*, *blaKPC*, etc) based on detection of resistance determinants. The Pheno's strength is its ability to link expedited AST results with rapid organism ID in positive blood cultures.

In 2016, as part of a guideline focusing on implementation of AS programs, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology performed a systematic review to examine evidence supporting the use of rapid blood culture testing. Citing data from studies involving FilmArray BCID, MALDI-TOF MS, Xpert MRSA/SA BC, PNA FISH (OpGen, Gaithersburg, MD), and BD GeneOhm StaphSR (BD, Franklin Lakes, NJ; now unavailable), the authors reported reductions in time to initiation of appropriate antibiotics, recurrence of bacteremia, length of stay, mortality, and hospital costs when rapid blood culture testing was implemented and coupled with AS intervention [1]. This resulted in a recommendation supporting the use of rapid blood culture diagnostics to support AS programs and these findings were corroborated by other systematic reviews [2••]. To the author's knowledge, there are no publications demonstrating incremental benefits of expedited AST when coupled with rapid ID in blood stream infections in the current technological era.

Impact of MALDI-TOF MS on CLABSI Reporting

Over the last decade, MALDI-TOF MS has emerged as a faster, more cost-efficient, and more accurate ID method than traditional biochemical methods and its use appears to be increasing. A recent proficiency test survey administered by the College of American Pathologists had 116 of 173 participating laboratories (67%) reporting use of MALDI-TOF MS for bacterial ID [3]. There are two FDA-cleared MALDI-TOF MS systems that are widely in use in the USA: the Bruker Biotyper CA system (Bruker, Billerica, MA), which covers Gram-positive and Gram-negative organisms, anaerobes, and various yeast species; and the VITEK MS (bioMérieux, Durham, NC), which, in addition, recently introduced a database expansion that allows rapid ID of *Nocardia*, *Mycobacteria* species, and a variety of filamentous fungi. The emergence of MALDI-TOF MS has given rise to two challenges for infection prevention in the realm of central line-associated blood stream infections (CLABSI).

The first challenge relates to the vast spectrum of organisms that MALDI-TOF MS can identify. We can now assign a "name" to many bacterial isolates that would have previously been reported as a "diphtheroid" or a member of viridans group streptococci. As an example, *Actinomyces neuii* is a member of the genus *Actinomyces* (which are typically anaerobic, branching Gram-positive rods and are usually considered pathogens). However, *Actinomyces neuii* is a palisading Gram-positive rod that behaves clinically like a diphtheroid [4]. In the USA, National Healthcare Safety Network (NHSN) criteria are used to identify reportable central line-associated blood stream infections (CLABSIs) [5]. The NHSN master organism lists, which differentiate "Common Commensals" from pathogens, are an important tool used by infection prevention teams to correctly apply CLABSI surveillance definitions. These organism lists have been updated to reflect advances in organism ID technology but will need to be reviewed and updated periodically to ensure that organisms added during MALDI-TOF MS database updates are correctly categorized in future versions.

The second challenge relates to the observation that different ID methods perform with different levels of accuracy and precision. According to the NHSN, when a common commensal is recovered from blood cultures, designation of a BSI as a CLABSI requires that the same organism be recovered from two or more blood specimens drawn on separate occasions [5]. This criterion is heavily dependent on the performance of the ID method used and may impact the designation of a BSI as CLABSI. Gomez et al. prospectively identified BSI cases meeting NHSN criteria for CLABSI in which commensal organisms were recovered from successive blood cultures. This team then pursued organism ID using the Bruker CA system and Vitek MS MALDI-TOF MS platforms and a variety of automated biochemical methods including Vitek 2 (bioMérieux), BD Phoenix (BD, Sparks, MD), and MicroScan (Siemens, Princeton, NJ). They reported that more cases met NHSN CLABSI criteria when MALDI-TOF MS instruments were used compared to the biochemical methods and they attributed this finding to MALDI-TOF MS's ability to generate consistently accurate organism IDs [6]. This raises the question of whether

information related to organism ID method should be submitted to NHSN and if CLABSI metrics should be risk-adjusted by testing method.

C. difficile Infections

The optimal testing method for laboratory detection of *Clostridium difficile* in unformed stool specimens remains controversial in both adults and in children. *C. difficile* toxins (toxin A and toxin B) are necessary but not sufficient for *C. difficile* infection but detection has long been a challenge. Cell cytotoxicity neutralization assay (CCNA), which is highly sensitive and specific, is unfortunately slow, labor intensive, and costly. Enzyme immunoassays that detect *C. difficile* toxins are faster and less labor intensive but suffer from poor sensitivity. EIA was eventually supplanted by nucleic acid amplification tests (NAATs), which are highly sensitive and specific but tend to be costly. In an attempt to reduce costs, a two-step algorithm was introduced, in which specimens are initially tested with a combined glutamate dehydrogenase (GDH) and toxin EIA assay followed by testing of discordant samples (i.e., GDH-positive, EIA-negative) with NAAT [7]. The use of *C. difficile* NAAT alone has come under scrutiny. In a 2015 prospective cohort study, Polage et al. reported that symptoms of patients who tested PCR-positive/toxin-positive were similar to those who tested PCR-negative and suggested that use of NAAT alone leads to over-diagnosis and over-treatment of *C. difficile* infection [8]. Others have also pointed out that the genes encoding *C. difficile* toxins (*tcdA* and *tcdB*) are under complex regulatory control and that various environmental factors (e.g., temperature, antibiotic exposure) can impact expression (i.e., detection of *tcdA* and *tcdB* may not necessary correlate with toxin production) [9]. The Polage et al. study gave support to a "reverse" algorithm in which positive NAAT results are followed by a toxin test to adjudicate whether a patient has CDI or is simply colonized with a strain of *C. difficile* harboring a toxin gene [10]. Challengers of this approach raised concerns about using an insensitive test (i.e., EIA) to inform clinical status and cited adverse events [11].

In this unresolved landscape, one possible solution may be the use of an "ultrasensitive" *C. difficile* toxin assay. A number of such assays have been described in the literature although none are available on the market at this time. The Singulex Clarity C. diff toxins A/B assay (Singulex, Alameda, CA) measures toxin A and toxin B in stool on the Singulex Clarity system, a rapid (< 1 h), automated instrument that uses single-molecule counting technology. A paramagnetic microparticle-based immunoassay uses single-photon fluorescence for measurement of toxin A and toxin B using monoclonal antibodies. Digital enzyme-linked immunosorbent assays (Simoa technology) by Quanterix Inc. (Lexington, MA, USA), are based on efficient capture, labeling, and detection of single protein molecules on paramagnetic beads in arrays of femtoliter-sized wells [12]. Pollack et al. used the Simoa assay to compare toxin A and toxin B loads in two patient groups: asymptomatic individuals and patients with diarrhea. They reported that toxin loads were similar between the two groups and concluded that toxin concentrations generated by this ultrasensitive assay may not differentiate patients with CDI from those with asymptomatic carriage. They suggested that accurate diagnosis of CDI may require toxin measurement coupled with immunological biomarkers to understand why some patients with *C. difficile* toxin are symptomatic while others are not [13••]. The limit of detection for both assays has been reported to be approximately 1 picogram of toxin per milliliter of stool, suggesting that they are about 1000-fold more sensitive than commercially available EIAs and about 100-fold more sensitive than CCNA [9, 12, 13••]. NHSN has recognized that *C. difficile* toxin detection method can significantly impact incidence and has included diagnostic testing method in their LabID-CDI risk adjustment formula [14]. If ultrasensitive toxin tests meet FDA standards and are implemented for clinical use, risk adjustment will need to be reconsidered again, taking into account the incremental increase in diagnostic yield.

Respiratory Virus Detection

Prior to the emergence of rapid molecular respiratory viral assays, rapid antigen detection tests, direct fluorescent antibody testing, viral culture, and laboratory-developed molecular tests (LDTs) were used for respiratory virus detection. The poor sensitivity of rapid antigen tests, DFA, and viral culture favored the use of molecular tests. However, while LDTs at the time were often highly sensitive and specific, the technical skill required to implement LDT panels was difficult achieve in many laboratories [15]. Today, these tests have largely given way to rapid, automated respiratory pathogen panel testing, some of which can be performed on-demand. These include FilmArray Respiratory Panel (bioMérieux; 17 viral targets plus *B. pertussis*, *C. pneumoniae*, and *M. pneumoniae*; the RP2 version also includes *B. parapertussis*); GenMark ePlex Respiratory Pathogen Panel (GenMark Dx, Carlsbad, CA; 15 viral targets plus *C. pneumoniae* and *M. pneumoniae*); Simplexa Flu/RSV assays (Focus Diagnostics, Cypress, CA); Verigene RP flex (Luminex; 13 viral targets plus *B. pertussis*, *B. parapertussis/B. bronchiseptica*, and *B. holmesii*); NxTAG Respiratory Pathogen Panel (Luminex; 18 viral targets plus *C. pneumoniae* and *M.* pneumoniae), Aries FluA/B & RSV (Luminex), and various Xpert Flu assays (Cepheid).

The clinical impact of these multiplexed panels remains unclear. In a recent systematic review that included studies that were published up to June 2017, Vos and colleagues identified 15 studies that described the clinical impact of

commercially available rapid molecular assays that detect respiratory viruses. They reported that due to considerable heterogeneity, the results were inconclusive [16••]. In addition, a recent decision (a local coverage determination) for multiplex nucleic acid amplified test for respiratory viral panels by Medicare A/B Contractor (MAC) Palmetto GBA limited reimbursement to panels that detect 3–5 pathogens that are ordered in urgent care, emergency, or inpatient settings. Outside of these settings, respiratory viral panel tests are reimbursed only when ordered by an infectious diseases specialist. More highly multiplexed tests are no longer covered in Palmetto's jurisdiction [17]. The rationale was that there was insufficient clinical evidence to support the use of the highly multiplexed respiratory viral panels. Perhaps in response to this development, the newly FDA-cleared Panther Fusion line (Hologic, Marlborough, MA) of respiratory virus detection tests has offered respiratory virus detection in three, separate, modular tests with fewer targets: Flu A/B/RSV which detects influenza A, influenza B, and RSV; AdV/hMPV/RV which detects adenovirus, human metapneumovirus, and rhinovirus; and Paraflu which detects parainfluenza 1–4. It is clear that there is an urgent need for high quality data demonstrating the clinical benefits of implementing rapid, automated respiratory pathogen panel testing.

Ventilator-Associated Events

Both clinical and surveillance definitions related to ventilator-associated events require evidence of respiratory deterioration, evidence of infection or inflammation, and laboratory evidence of respiratory infection. According to NHSN, assignment of Possible Ventilator-Associated Pneumonia (PVAP) status requires that a case meet one of the three criteria: (1) positive respiratory culture meeting defined quantitative or semi-quantitative thresholds without requirement of purulent respiratory secretions; (2) purulent respiratory secretions PLUS recovery of an organism in culture from sputum, endotracheal aspirate bronchoalveolar lavage, lung tissue, or protected specimen brush in quantities that do not meet criterion (1); or (3) Positive—organism ID from pleural fluid; findings on lung histopathology; *Legionella* test results; test for a respiratory virus [18]. A number of new tests targeted at diagnosis of nosocomial pneumonia may create an impetus to consider how they may impact the application of these definitions.

The Unyvero lower respiratory tract (LRT) application (Curetis USA, San Diego, CA) is a multiplex PCR test that was FDA-cleared in April 2018 for use on endotracheal tube aspirates. It is a qualitative test (i.e., the result is not quantitative, but rather, positive/negative) that detects 19 bacterial species that are responsible for hospital-acquired pneumonia and a variety of antibiotic resistance determinants. The reported limit of detection ranges from 10^4 to 10^6 colony forming units/mL for bacterial species, which is higher than the limit of detection of a standard quantitative respiratory culture (10^3 CFU/mL per isolate). Because a positive result for a resistance marker cannot be linked to a specific bacterial isolate, standard respiratory culture with organism ID and AST is still required to definitively link AST to a specific isolate.

Further, in November 2018, the BioFire FilmArray Pneumonia Plus was FDA-cleared for use on sputum, endotracheal tube aspirates, bronchoalveolar lavage (BAL), and mini-BAL specimens. This is a semi-quantitative assay that detects 15 bacterial species that are responsible for hospital-acquired pneumonia and assigns positive IDs to "bins" of 10^4, 10^5, 10^6, and $> 10^7$ copies per milliliter. This test also detects seven antibiotic resistance determinants but does not link them to a specific isolate. In addition, it detects *C. pneumoniae, M. pneumoniae,* and *Legionella pneumophila,* and eight respiratory viruses in a qualitative fashion. Biofire states in documentation submitted to the FDA that the semi-quantitative results are not equivalent to CFU/mL [19]. At present, there is no published data correlating this assay's semi-quantitative "bins" to bacterial loads generated by standard quantitative respiratory cultures. Like the Unyvero assay, standard respiratory culture with organism ID and antimicrobial susceptibility testing is still required to link AST results with a specific organism. Also, the manufacturers of both assays have stated in documentation submitted to the FDA that detection of bacterial nucleic acid may indicate colonizing or normal respiratory flora that may not be the causative agent of pneumonia [19, 20].

Detection of Carbapenem-Resistant Organisms

Carbapenem-resistant *Enterobacteriaceae* (CRE) is a significant clinical and public health concern in the United States. Carbapenem resistance is frequently mediated by AmpC or ESBL combined with chromosomal porin mutations that prevent accumulation of β-lactam drugs in bacterial cells [21]. However, reports of carbapenemase producing CRE (CP-CRE) that harbor bla_{KPC}, and more recently, bla_{NDM} has increased significantly over time [22]. Typically, bla_{KPC} and bla_{NDM} reside on plasmids, which are mobile genetic elements that can undergo horizonal transfer through conjugation with other bacterial cells. In addition, plasmids harboring carbapenemase determinants often carry additional resistance determinants. Thus, plasmid-mediated, cell-to-cell transmission of multi-drug resistant CP-CRE has been a major contributor to the rapid spread of CP-CRE in the US and throughout the world [21].

To date, the impetus to demonstrate and report carbapenemase production in CRE has been tempered by the

introduction of two β-lactam/β-lactamase inhibitor combination drugs, ceftazidime-avibactam and meropenem-vaborbactam. Both agents have excellent activity against CRE mediated by KPC [23–25]. While KPC has dominated the CP-CRE landscape in the United States to date, the incidence of metallo-β-lactamases has been increasing. As of December 2017, the Centers for Disease Control and Prevention reported 472 cases of CRE that were determined to harbor metallo-β-lactamases bla_{NDM}, bla_{VIM}, or bla_{IMP} (379, 57, and 36 respectively) [22]. Neither avibactam nor vaborbactam inhibit metallo-β-lactamases and as a result, CRE harboring metallo β-lactamases are uniformly resistant to these drugs [23–25]. In circumstances in which metallo-β-lactamases (particularly NDM) are of concern, documenting carbapenemase production and determining the specific type of carbapenemase can be clinically useful.

The Clinical and Laboratory Standards Institute (CLSI), which publishes recommendations pertaining to AST, has endorsed various phenotypic methods of determining carbapenemase production status in CRE. These include the modified Hodge test (which is no longer recommended by CLSI), the Carba NP test, and the modified carbapenem inactivation (mCIM) method [26]. The modified Hodge and mCIM require overnight incubation and are not rapid [27•]. The Carba NP procedure, as published by CLSI, provides a result in approximately 2 h but implementation is hindered by the labor required for reagent preparation and their short shelf life. The Carba NP has been developed into a number of commercially available kits that provide pre-prepared reagents, greatly reducing the labor required for testing. In the United States, the RAPIDEC Carba NP (bioMérieux) received FDA clearance in April 2017 for use on *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates. This assay detects carbapenemase activity in isolates growing in pure culture within 2 h and has a reported sensitivity and specificity of 98% and 99% [27•]. The Cepheid Xpert Carba-R was FDA-cleared in March 2016 and detects bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, and bla_{OXA-48} from pure colonies of *Enterobacteriaceae*, *Acinetobacter baumannii* complex, and *Pseudomonas aeruginosa*. In June of the same year, the assay was FDA-cleared to be performed on rectal and peri-rectal screening swabs. The Xpert system is fully automated, uses real-time PCR technology and generates results in about 2 h. While very sensitive and specific, as with all molecular-based tests, novel carbapenemases with mutant primer and probe sequences may not be detected.

Conclusion

We are currently experiencing a remarkable era in which new technologies and testing platforms are re-defining our previous understanding of infectious diseases and re-calibrating stakeholder expectations related to breadth of pathogen identification, turnaround time, and cost. Expansion of mass spectrometry, automated multiplexed molecular diagnostics technology, and novel AST methods into the microbiology laboratory has compelled us to reexamine surveillance definitions and reflect on ways to harness these technological advances to improve patient outcomes.

Compliance with Ethical Standards

Conflict of Interest Kaede V. Sullivan declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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