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Current strategies for infectious diseases management

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Rapid techniques for therapeutic optimization. Diagnostic stewardship

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ABSTRACT

Rapid microbiologic methods provide clinicians with information regarding the causative organisms of infections and their resistance to antimicrobials to optimize patient outcomes and antimicrobial use. Diagnostic stewardship requires that appropriate tests are requested and information is translated into appropriate management. The implementation of rapid techniques also provides collaborative opportunities between antimicrobial stewardship and diagnostic stewardship programs contributing to limiting the spread of antimicrobial resistance, and decreasing mortality, hospital length of stay, and healthcare costs.

Keywords: rapid microbiologic methods, antimicrobial stewardship, diagnostic stewardship, PRODIM

INTRODUCTION

The critical role of the microbiology laboratory in infectious disease diagnosis in conjunction with recent advances in microbial diagnostics are revolutionizing clinical microbiology and promise to improve patient outcomes and curb the antimicrobial resistance crisis by improving the use of antibiotics. However, rapid diagnostics only improve clinical outcomes if there is a close relationship between the microbiologists and the infectious disease physicians that properly interpret results and apply them to treatment decisions. This approach may also require expanding the hours of laboratory operation and microbiological assessment 24 h a day, 7 days a week, especially in hospitals with a high health care load and with relevant complexity, which will provide, in addition, an enormous value to the health care team and a cost-effective impact on the clinical management of patients [1-3].

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This minireview focuses on currently available rapid diagnostic microbiologic tests that provide opportunities for antimicrobial stewardship programs to improve antimicrobial use and clinical and economic outcomes. The information presented here is a summary of a lecture given at the XI Updating Course of Antimicrobials and Infectious Diseases last February 2022 in Madrid (Spain).

PROGRAMS FOR OPTIMIZING DIAGNOSTIC MICROBIOLOGY (PRODIM)

The goal of the Programs for Optimizing Diagnostic Microbiology (PRODIM), equivalent to diagnostic stewardship, is to optimize the use of diagnostic techniques and algorithms in order to obtain results that have a tangible and cost-effective impact on the clinical management of patients. These programs, as described by Messacar K, *et al.* aim to select the right test for the right patient, generating accurate, clinically relevant results at the right time to optimally influence clinical care and to conserve health care resources [4].

One of the most important aspects in order to provide a high level of diagnostic quality, is the proper selection of all microbiology specimens as well as their collection and transportation to the microbiology laboratory to optimize analysis and interpretation. Since result interpretation in microbiology depends entirely on the quality of the specimen submitted for analysis, and microbiology specimen selection and collection are the responsibility of the medical personnel, not usually the laboratory, those that collect specimens must ensure its good quality and that specimens arrive at the laboratory for analysis as quickly as possible after collection [5]. Proper specimen management is crucial for an accurate laboratory diagnosis and confirmation, and directly impacts patient care and patient outcomes, patient length of stay, hospital infection control, hospital and laboratory costs and laboratory efficiency, and influences therapeutic decisions and antimicrobial stewardship. In this sense, microbiology laboratory

results that are reported should be accurate, significant, and clinically relevant [2,5,6].

All personnel in charge of the selection, collection, transport and storage of patient specimens must consult the microbiology laboratory to ensure that specimens are adequately managed and call the laboratory to clarify and resolve problems. Some of the relevant aspects to take into account when collecting a specimen include avoiding contamination with commensal microbiota from sites such as lower respiratory tract, nasal sinuses, superficial wounds or fistulae, and sending a specimen (tissues, aspirates, fluids) and not a swab, since these hold small volumes of the specimen (0.05 mL) and make it difficult to get bacteria or fungi away from the swab fibers onto media. However, if flocked swabs are used there is a better release of contents and are more effective. Swabs can be used for collecting nasopharyngeal specimens for the diagnosis of viral respiratory infections. All specimens must be labelled accurately and completely so that interpretation of results will be reliable. In addition, the main criteria for the collection of infected material or blood specimens is that they should be collected prior to the administration of antibiotics, since once antibiotics have been started, the microbiota changes, leading to potentially misleading culture results. Regarding the microbiology laboratory, microbiologists must reject specimens of poor quality and give advice that they will not report everything that grows, since this information is unnecessary and could result in inaccurate diagnosis and inappropriate treatment. Moreover, susceptibility testing should be done only on clinically significant isolates, not on all microorganisms recovered in culture [5].

Selecting the right test for the microbiological diagnosis involves the evaluation of test performance, such as sensitivity and specificity, predictive values, testing volumes, diagnostic yield, laboratory feasibility, cost and clinical impact. Nowadays, the use of nucleic acid amplification and detection techniques, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS) and next generation DNA sequencing, has increased the impact of the microbiological diagnosis, but results can be difficult to interpret when conventional culture-based or serological techniques are unable to confirm the presence of infection and it may be necessary to rely on clinical findings. Nevertheless, since standard techniques for identification of microorganisms require at least 48-72 hours for final results, rapid microbiologic tests provide opportunities for antimicrobial stewardship programs to improve antimicrobial use and clinical and economic outcomes [4].

Rapid tests are defined as those providing a same-day turnaround time (TAT). It is important to distinguish the analytic TAT from the actual TAT of a test (the time from when a test is ordered to when the result is translated into a change in patient care). A rapid test with analytic TAT of 2 hours that is batched and performed once daily represents little improvement in TAT over some conventional culture-based methods. Similarly, tests that require an isolated bacterial colony to perform should not be considered really rapid. Thus, the most useful rapid tests are those that can be applied directly to patient samples, however, there is no reason to use a more expensive test with shorter analytic TAT if the actual TAT of the test will not be meaningfully reduced [7]. Once the appropriate test has been selected for implementation, the next step is directing testing toward the right patients. It is important to know that overuse of rapid diagnostic tests can add to health care costs without having a significant impact on patient care, whereas underuse or inappropriate use may lead to suboptimal clinical outcomes. If rapid testing is to provide any benefit, there must be a postanalytic system in place for the results to be translated into action [4,6,7]. The timely communication of test results requires collaboration between the laboratory and antimicrobial stewardship groups, and within this framework, diagnostic stewardship effectively complements antimicrobial stewardship programs in the adequate microbiological diagnosis and selection of antimicrobial treatments with the goal of improving patient management and to decrease unnecessary antimicrobial use [8].

RAPID DIAGNOSTIC MICROBIOLOGICAL TECHNIQUES

Gram-staining. Direct Gram staining of positive blood cultures, respiratory samples, abscesses, urine, and other clinical material, is an inexpensive, simple examination that is used worldwide, including in lower-income countries, that provides immediate information for detecting causative pathogens and may guide the appropriate use of initial antibiotic therapy [9]. In addition to determining Gram reaction and bacterial morphology, Gram stain can assess the suitability for culture of a sputum sample by determining the numbers of squamous epithelial cells and polymorphonuclear leukocytes present in the specimen. The numbers and morphologies of bacteria seen in direct smears of clinical material is very valuable for early clues as to cause of disease, as well as for comparison to the growth resulting after incubation.

Antigen detection assays. Specific microorganism antigens can be rapidly detected from a clinical specimen through immunoassays. At present there is a wide variety of commercialized immunoassays for detecting microbial antigens (bacteria, viruses, parasites, and fungi) and specific antibodies. These assays have been designed in a variety of formats and can be performed as point-of-care tests in as little as 15 to 30 min. Among the most popular formats is the immunochromatographic method (ICT), more commonly referred to as the lateral-flow immunoassay (LFA). These assays are straightforward to perform, are inexpensive, and do not require specialized instrumentation. In addition, multiplexed strip tests are available to detect 3 to 14 pathogens [10]. The most frequently and useful rapid antigen detection assays applied directly from different clinical specimens include the detection of *Legionella pneumophila* serotype 1, and *Streptococcus pneumoniae* from urine, allowing the rapid diagnosis and treatment of pneumonia, the detection of *Cryptococcus neoformans* antigen from cerebrospinal

fluid, the detection of *Streptococcus pyogenes* antigen from pharyngeal swabs and also from wounds, many respiratory viruses from respiratory samples including respiratory syncytial virus, SARS-CoV-2, and influenza virus, fungi like *Aspergillus* spp., *Histoplasma capsulatum* and *Blastomyces dermatitidis* from different clinical samples, enteric pathogens from gastrointestinal specimens such as norovirus, rotavirus, *Helicobacter pylori*, *Closdridioides difficile, Cryptosporidium* spp., *Giardia* spp., among others, and *Plasmodium* spp. from blood [5,10]. These tests are also useful in patients previously treated with antimicrobials and allow rapid diagnosis and implementation of specific treatments, avoiding the use of inadequate antimicrobials. Because immunoassays are simple to perform and give timely results of sufficient sensitivity for routine clinical diagnosis, they will continue to be widely used.

Antibody detection assays. Antibody detection assays are also available for the rapid diagnosis of infectious diseases. These assays are easy to perform and results are available in 5-15 minutes from serum, providing rapid diagnosis and implementation of adequate treatment. Examples of these rapid assays are the highly sensitive rose Bengal test for the diagnosis of brucellosis, the new immunochromatographic strip and dual-point-of-care tests for the detection of both treponemal and nontreponemal antibodies used for the screening and/or diagnosis of syphilis, and the monospot test for the detection of heterophile antibodies in the course of mononucleosis syndrome due to Epstein-Barr virus. Assays for the detection of SARS-CoV-2 antibodies and HIV antibodies are also widely used. The dengue virus can also be tested by using a rapid diagnostic test which detects either IgM and IgG antibodies or IgM antibodies and the NS1 protein. Performance of all these tests is straightforward and does not require technical expertise or special laboratory equipment and must be considered as part of the standard of care [10,11].

Nucleic acid amplification tests and new technologies. Nucleic acid amplification tests are designed for the detection of one or more RNA or DNA sequences specific to a single pathogen and are available for rapid testing as PCR-based techniques and as isothermal nucleic acid amplification techniques (LAMP). They have greater sensitivity than ICT tests but require a higher degree of technicality and training. Since it is of medical interest to simultaneously test the multiple pathogens that may cause signs and symptoms in the patient (bacteremia, pneumonia, gastroenteritis, meningitis), in order to optimize diagnosis, these tests may also adopt a syndromic approach and may include the simultaneous detection of virus, bacteria, fungi, parasites and some resistance genes. With the use of these tests results can be obtained between 20 and 100 min, and allow to implement antimicrobial treatment within a few hours of specimen collection [10].

New technologies provide rapid identification and detection of resistance markers directly from blood (nuclear magnetic resonance testing) or rapid identification and antimicrobial susceptibility from positive blood cultures (peptic nucleic acid fluorescent, morphokinetic fluorescent cellular analysis, nephelometry, syndromic rapid multiplex polymerase chain reaction, microarray-based or nanoparticle probe technology). These diagnostic techniques improve the management of patients with bloodstream infections, particularly those infected with resistant organisms such as extended-spectrum beta-lactamase-producing or carbapenem-resistant Gram-negative bacilli. They are relatively easy to implement and most seem to have a favourable cost-benefit balance. The use of these tests can also reduce unnecessary antimicrobial exposure and increase the appropriateness of empirical antibiotic therapy in bacteremia, pneumonia, central nervous system and gastrointestinal infections [12].

Rapid identification and susceptibility testing from blood cultures. Rapid identification of organisms from blood is a critical component in providing quality healthcare. The combined use of MALDI-TOF from blood-cultures, direct antimicrobial susceptibility testing and real-time antimicrobial stewardship intervention allows early optimisation of antimicrobial therapy and provides significant hospital savings [1,2,13].

The conventional EUCAST (European Committee on Antimicrobial Susceptibility Testing) standardized antimicrobial susceptibility testing method provides results after 16–20 h incubation from colonies grown in culture. However, since rapid antimicrobial susceptibility testing (RAST) is very important, especially in patients with bloodstream infection in which appropriate early therapy improves the clinical outcome, recently, the EUCAST has validated a rapid disc difussion RAST directly from positive blood culture bottles that provides reliable antimicrobial susceptibility testing results for relevant bloodstream infection pathogens after 4-6 h of incubation. The successful introduction of the RAST method in routine microbiology enables rapid evaluation of empirical antibiotic treatment in bloodstream infections [14].

RAPID DETECTION OF RESISTANCE TO ANTIMICROBIALS AND EPIDEMIOLOGICAL SURVEILLANCE OF MULTIDRUG-RESISTANT PATHOGENS

The spread of multidrug-resistant microorganisms has challenged the clinical microbiology laboratory to recognize the presence of responsible resistance mechanisms and develop techniques for their rapid detection. These resistance mechanisms can be detected by conventional antimicrobial susceptibility testing (phenotypic methods) and results will be obtained after 48-72 h after specimen collection, or by genotypic methods in which results can be obtained directly from different clinical specimens or from positive blood culture bottles in few hours. Rapid commercial phenotypic antimicrobial susceptibility tests now are available for laboratory use, and provide results in 5-7 hours directly from positive blood culture bottles. In addition, detection of resistance genes can be rapidly accomplished in cultures

by immunoassays. Nucleic acid amplification testing-based methods can be used to detect resistance genes (methicillin-resistance, vancomycin-resistance, extended-spectrum-beta-lactamases, carbapenemases) directly from clinical specimens. Whole-genome sequencing directly on specimens is being developed for clinical applications [15].

Finally, it is important to highlight that the microbiology laboratory plays a central role in epidemiological surveillance by detecting the multidrug resistant organisms. This laboratory must provide at least an annual cumulative antimicrobial susceptibility report for specific antibiotic-organism combinations, which is critical for the local guidelines for empirical treatment and monitoring over time the local resistance trends. Stratified antibiograms (e.g., by ward or age) can provide significant differences in susceptibility which can help the antimicrobial stewardship team to develop optimized treatment recommendations and guidelines for different wards [7,8].

CONFLICT OF INTEREST

The author declares no conflict of interest

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