Enfermedades Infecciosas y Microbiología Clínica 40 (2021) 1–4

Enfermedades Infecciosas y Microbiología Clínica

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EDITORIAL - SEIMC positioning

Justification for 24/7 clinical microbiology services

Justificación de los servicios de microbiología clínica 24/7

Introduction

In the last decades, microbiology laboratories have undergone unprecedented technological changes which have revolutionized the diagnosis of infectious diseases. The incorporation of nucleic acid amplification and detection techniques, and especially polymerase chain reaction (PCR), matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-ToF-MS) and next generation DNA sequencing, the latter of which is in the consolidation phase and introduced in only some laboratories, has modified the work dynamics of microbiology laboratories, with microbiological diagnoses having a great impact on early, individualized care of patients with severe infection.

The Programs for Optimizing Diagnostic Microbiology (PRODIM), equivalent to diagnostic stewardship, aim 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.[1] Within this framework, the PRODIM effectively complements antimicrobial stewardship programs in the adequate selection of antimicrobial treatments with the goal of improving patient management and controlling antibiotic multiresistance. Thus, last generation technology is available, which is able to accurately, rapidly and effectively diagnose a wide variety of infectious diseases, while also providing valuable information on antibiotic sensitivity/resistance of the causal microorganism, and notably reducing the morbidity and mortality of the patients as well as improving the management of in-hospital patients. The point of care tests (POCTs) have contributed to generate this rapid information, therefore its implementation in the clinical microbiology setting is crucial and it is important to have a 24/7 clinical microbiology lab set up, however, if this is not possible from the logistic and organizational point of view and it is performed out of the clinical microbiology laboratory, always the performance should be supervised and validated by a clinical microbiologist. Several studies have shown that with the increase in the rapid diagnostic techniques available these technological advancements have a greater impact when clinical microbiology services remain at work beyond the usual 7-h workday.[2,3] It is therefore paradoxical that many clinical microbiology laboratories do not provide 24-h service. Below we discuss the need for clinical microbiology services to work 24 h a day, 7 days a week (24/7).

Clinical impact of 24/7 clinical microbiology services

It is clear, and has been described in the literature, that early appropriate antimicrobial treatment reduces the morbidity and mortality of the patients, reduces pharmaceutical and hospital costs, shortens the length of hospital stay while also helping to control the appearance of multiresistant bacteria associated with the massive use of wide-spectrum antibiotics.[4–9] In addition, apart from identifying the causal microorganism of the infection, in many situations we can rapidly determine the presence of certain mechanisms of resistance “directly from the sample” in order to provide better selection of the most adequate antibiotic.[10,11] Rapid identification of the microorganism has a clear impact on the administration of adequate and timely therapy. For example, empiric antimicrobial therapy that does not cover certain pathogens can be modified before performing susceptibility tests, since these pathogens have different profiles of natural sensitivity to antimicrobials which are well-known by any microbiologist familiarized with the principles of interpretation of antibiogram reading. It also allows adapting antimicrobial treatment based on the expected sensitivity of the bacterial species identified and local epidemiological criteria. In addition, rapid identification of an unsuspected pathogen can condition numerous interventions, including the control of infections or potential epidemic outbreaks.

In the last years, great efforts have been made in the diagnosis of sepsis. The incidence of sepsis is increasing, probably in relation to the aging of the population, potentially affected by comorbidities and also due to better recognition of this pathology.[12] Clinical microbiology services are intensely working on improving the diagnostic response in this group of patients in whom it has been widely demonstrated that time is a highly determinant factor of patient outcome. With regard to the diagnosis of bacteraemia, which is equally severe, although the patient does not fulfill the criteria of sepsis, in a recent study of 152 (85%) of 179 episodes of bacteraemia, the empiric antibiotic therapy had already initiated when the positive Gram staining result of the blood cultures was reported to the clinicians.[13] The microscopy results led to a change in antibacterial therapy in only 14 (8%) of the 179 episodes. In contrast, the information of the bacterial species identified by MALDI-ToF MS led to an adjustment in treatment in 36 (20%) of the 179 episodes. An analysis of changes in therapy revealed that therapy improved in

https://doi.org/10.1016/j.eimce.2021.11.007

26 (72%) out of 36 cases. In the same study, it was found that most (70%) of the blood cultures were positive by the automated system outside the usual clinical microbiology service working hours.[13] Another observational study[14] compared the impact of incubation of the blood cultures of patients suspected of severe sepsis or septic shock processed immediately in a 24/7 laboratory with processing in a remote laboratory (incubation initiated 4 h or more after blood collection for blood culture) and found that the time to the reporting of the microbiological results significantly reduced by 8.5 h ($p < 0.001$). The authors concluded, "the results underline the importance of having a microbiology laboratory active 24 h, 7 days a week to provide 24-h processing of blood culture samples of patients with sepsis and septic shock and immediate reporting of the results to the clinicians". In an editorial published by Blondeau and Idelevich[15] it was concluded that continuous health service activity by clinical microbiology services is essential to achieve optimal patient management.

On the other hand, one study demonstrated that inadequate antimicrobial treatment of infections (both community and hospital-acquired) is an important determinant of in-hospital mortality in patients requiring intensive care unit (ICU) admission. These data suggest that clinical efforts aimed at reducing the administration of inadequate antimicrobial treatment could improve the outcomes of critically ill patients. In addition, previous antimicrobial therapy should be recognized as an important risk factor for the administration of inadequate antimicrobial treatment in patients in the ICU with clinical suspicion of infection.[16] All these studies demonstrate the relevance of early microbiological diagnosis for improving the prognosis of patients with infection and the importance of 24/7 clinical microbiology services.

One notable aspect to take into account is the rapid reporting of the microbiological results obtained. It is of little use to speed up the diagnosis if this is then not given timely. In this sense, rapid reporting of the identification of the microorganism and its profile of sensitivity or resistance to the physician in charge of the patient clearly impacts the optimization of the medical therapy to be administered, which, in addition to reducing mortality, can reduce the selection pressure of resistant mutants and their dispersion. The importance of a rapid, fluid transmission, interpretation and application of microbiological results is highlighted in studies describing the greater cost-effectiveness of microbiological tests when reported to specialized medical teams such as those involved in antimicrobial stewardship. In one study, rapid molecular biology techniques combined with antimicrobial stewardship teams showed 80% of cost-effectiveness compared to the same techniques without antimicrobial stewardship, with only 41% of cost-effectiveness.[17] In addition, full integration of the microbiology laboratory's expert systems into the laboratory information system with clinician alerts and advanced clinical decision support tools to optimize the flow of microbiology data and to translate those data into improved patient care will be very important in the future.[18]

Economic impact of 24/7 clinical microbiology services

In addition to the clinical impact, another relevant aspect to take into account is the economic costs of having 24/7 clinical microbiology services which include at least one clinical microbiologist and one laboratory technician. Within a normal salary range the costs of these personnel would be between 320 and 350€/day for a technician and between 500 and 850€/day for a clinical microbiologist on duty. The cost of the rapid test would be added to this cost, but undoubtedly the sum of the two would be less than the cost derived from inadequate patient hospital stay and treatment, without taking into account the impact on morbidity and mortality. It is also important to consider the economic impact of the reduction of hospital stay, when rapid techniques which allow implementation of adequate antimicrobial treatment are used. One example would be the costs of hospitalization in conventional or critical care units in the health care departments of our country. In 2020, these costs in the Basque Health Care Services (Osakidetza) were 986 and 1713 euros/day, respectively, while in the Galician Health Care Services (SERGAS) the cost was 551.17 and 1190.45 euros/day, respectively. This is undoubtedly another factor which highlights the importance of Clinical Microbiology laboratories providing services 24/7.

Implementation of 24/7 clinical microbiology services would consolidate the base for better responding to new needs or infectious emergencies. For many years there have been rapid diagnostic tests for acute viral and seasonal respiratory infections such as influenza type A and B or the respiratory syncytial virus (RSV). Early diagnosis of these infections in less than 2 h allows decision making regarding patient admission and the establishment of isolation measures. This has acquired important relevance with the spread of influenza type A in the last years. The possible appearance of pandemics was a possibility to consider since the emergence of SARS-CoV in 2003, the avian flu (H5N1) in 2003, influenza type A (H1N1) in 2009 and later MERS-CoV in 2013. At present, the COVID-19 pandemic has promoted the establishment of 24/7 health services in many clinical microbiology laboratories in our country. These departments have responded to the enormous logistic and technical challenges of processing thousands of samples daily, combining different local and commercial protocols to resolve provision problems caused by the elevated demand worldwide. The rapid diagnostic techniques of COVID-19 not only allowed the diagnosis of new patients with infection but have also been useful for rapid classification of patients and the establishment of admission and isolation circuits as well as invasive and surgical procedures. This is a clear example of the profitability of having rapid response 24/7. The development of this strategy is an opportunity for consolidating the structure of continuous 24/7 services and rapid response.

Activities that justify 24/7 services

The activities that justify continuous 24/7 services can be divided into three categories:

CATEGORY 1: "Determinant" diagnostic tests that establish a specific diagnosis and decide the criteria of admission or isolation as well as the administration of treatment. The speed at which a result of these tests is available has a direct impact on the prognosis of the patients and/or the epidemiological conditions of the hospital (imply isolation) or the community.

CATEGORY 2: Diagnostic tests or with a high grade of diagnostic orientation which allow rapid implementation of treatment and avoidance of other tests or maneuvers in the patients.

CATEGORY 3: Weekend and holiday activities which avoid the interruption of the most frequent diagnoses.

CATEGORY 1

- Diagnosis of tuberculosis: staining for the detection of mycobacteria in sputum and respiratory samples and confirmation by rapid molecular diagnosis. Determines treatment and need for isolation.
- Diagnosis of meningitis and encephalitis: Gram-staining of cerebrospinal fluid (CSF) in bacterial meningitis, detection of the *Cryptococcus neoformans* antigen, multiplex PCR tests that allow syndromic diagnosis; i.e. multiplex PCR for the detection of pathogens in CSF. Determines treatment and prognosis.

- Diagnosis of pneumonia caused by *Streptococcus pneumoniae*: Gram-staining of sputum and urinary antigen (immunochromatography). Determines treatment.
- Diagnosis of pneumonia in, mainly, immunosuppressed hospitalized patients by multiplex PCR. Determines treatment.
- Diagnosis of pneumonia caused by *Legionella pneumophila*: urinary antigen (immunochromatography). Determines treatment.
- Diagnosis of pneumonia caused by *Pneumocystis jirovecii.* Determines treatment.
- Etiological diagnosis of influenza syndrome: influenza, respiratory sincitial virus (RSV), (mono or multiplex PCR/antigen). Determines criteria of admission, isolation and treatment.
- Diagnosis of SARS-CoV-2: by antigen and PCR, or serology in cases of high clinical suspicion and negative PCR. Determines criteria of admission and isolation.
- Diagnosis of malaria: by smear and thick blood film and/or immunochromatography. Determines treatment and patient management.
- Rapid processing of blood cultures and other microbiological samples and individualized application of rapid diagnostic tests in the first hours of the onset of sepsis.
- Diagnosis of bacteraemia: "Bacteraemia do not only occur in the morning". Monitoring of the positivity of blood cultures: Gram-staining, MALDI-ToF, subcultures, molecular detection or by immunochromatography of methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase (ESBL) and/or carbapenemase-producing Enterobacterales, according to the identification results of MALDI-ToF MS.
- Early detection of ESBL- and/or carbapenemase-producing Enterobacterales, vancomycin-resistant enterococci, or methicillin-resistant *Staphylococcus aureus*, among others. Determines criteria of isolation of patients attended in the emergency department who are then admitted. These are usually patients with risk factors, from long-term care centers or with a history of previous multiresistant bacteria.
- Detection of *Clostridioides difficile* toxin. Determines treatment and the implementation of contact precautions measures to prevent possible transmission.
- Detection of enteropathogens causing acute gastroenteritis by molecular biology tools in some patient populations such as immunocompromised patients.
- Diagnosis of severe infection during pregnancy or immediate puerperium and prevention of neonatal complications.
- Serology of organ and tissue donors. Determines posterior processing for transplantation.
- Serology of human immunodeficiency virus (HIV), hepatitis C (HCV) or hepatitis B (HBsAg) in other vulnerable groups: overall when there is a need for haemodialysis or emergency surgery, imminent childbirth in non-controlled pregnancy, severe opportunistic infections in patients with unknown serology and in the case of accidental needle prick.
- Observation of hyphae in critical patients (mucormycosis, invasive aspergillosis).

CATEGORY 2

- Detection of anti-Epstein Barr virus (EBV) antibodies by rapid assays.
- Detection of anti-*Brucella* antibodies (Rose Bengal).
- Gram-staining of biological fluids, respiratory secretions or exudates/pus.
- Direct antibiogram and interpretation of antibiograms of blood cultures and sterile biological fluids.

CATEGORY 3

- Follow-up of urine cultures.
- Follow-up of respiratory infections.
- Interpretation of antibiograms of relevant isolates.
- Interpretation of sterile fluid cultures (i.e. CSF).
- Interconsultations. Sample collection. Antimicrobial stewardship consultations.

Conclusion

At present the advances in clinical microbiology diagnostic technologies allow results which condition clinical decisions more rapidly and accurately, and in some situations, in real time. The current practice clearly does not fulfill the criteria of urgent diagnoses and does not satisfy the requirements for the management of sepsis and other severe infections. Microbiological assessment 24 h a day, 7 days a week, is essential for diagnosing these infections and is necessary in hospitals, especially in those with a considerable health care load and with relevant complexity. Clinical Microbiology laboratories can benefit from clinical input, mainly from infectious diseases specialists to select cost-effective diagnostic tests which best address patient needs.[19] As recently stated, the clinicians should take advantages of these rapid tests to adequate the personalized antimicrobial treatment.[20] Optimal patient care requires access to adequate laboratory tests, including microbiological tests, which at present have great differences and do not meet criteria of equity which should prevail in the National Health System. It is very important to structure work hours to shorten the time to obtaining reports with accurate results and with evident clinical impact to not only reduce the mortality of patients with severe infections but also at the level of hospital management of admissions and care in the emergency department. Laboratory results must be rapidly with timely transmitted for adequate clinical decision making.

Conflict of interests

The authors declare having no conflict of interests.

Acknowledgments

We thank MSD for collaboration in the organization of the logistics of the virtual PRODIM 3 meeting held November 17, 2020, in which some of the ideas contained in this manuscript were developed. **People participating in the manuscript:** The names are noted first, followed by their institution. Rafael Benito, Hospital Clínico Universitario Lozano Blesa (Zaragoza); Samuel Bernal, Hospital de Valme (Sevilla); Ana Bordes Benítez, Hospital de Gran Canaria Dr. Negrin (Canarias); Jorge Calvo Montes, Hospital Universitario Marques de Valdecilla (Santander); Andrés Canut Blasco, Hospital Universitario Araba (Álava); Laura Cardeñoso Domingo, Hospital de la Princesa (Madrid); Txema Marimón, Hospital Universitario Donostia, (Donostia-San Sebastián); Mateu Espasa Solei, Hospital Parc Taulí (Barcelona); Ignacio Gadea Girones, Fundación Jiménez Díaz (Madrid); Federico García García, Hospital Clínico Universitario San Cecilio, (Granada); José Luis López Hontangas, Complejo Hospitalario La Fe (Valencia); María Dolores López Prieto, Hospital Universitario de Jerez (Cádiz); Rosario Moreno, Hospital General de Castellón (Castellón); José María Navarro Marí, Hospital Universitario Virgen de las Nieves (Granada); Ferran Navarro Risueño, Hospital de la Santa Creu i Sant Pau (Barcelona); Antonio Oliver Palomo, Hospital Son Espases (Palma de Mallorca); Begoña Palop Borràs, Hospital Carlos Haya (Málaga); Álvaro Tomás Pascual Hernández, Hospital Universitario Virgen Macarena (Sevilla); Luisa Pérez del Molino Bernal, Complejo Hospitalario Universitario de

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