Research Article

Insights on antimicrobial stewardship in the microbiology laboratory: a review

Summary

The objective was to describe the latest perspectives and assignments for microbiology laboratories in Antimicrobial Stewardship programs within the multidisciplinary team of care to patients, including schemes to optimize the use of antibiotics based on microbiological laboratory techniques. Methods: it conducted a review of narrative literature papers published in Pubmed database, from May to September 2018. The search terms used were: "Antimicrobial Stewardship AND Clinical Microbiology" being selected 32 references from the 585 documents found. Results: Antimicrobial Stewardship programs have emerged in recent decades in order to optimize antimicrobial therapy. Microbiology laboratories have important duties to perform tests that support the selection and standardization of restricted antimicrobials in clinical protocols for infection by micro-organisms resistant to multiple drugs. Currently available tests are related to the identification, quantification and determination of resistance patterns and antimicrobial susceptibility among them: classical biochemical and microbiological tests; rapid tests for diagnosis addition of serum procalcitonin. So microbiology laboratories should integrate the various inter-committees that promote the safe and rational use of antimicrobials. We conclude that there is a lack of studies that evaluated effectively, both clinical and financial.

Keywords: infection, microbial sensitivity tests, bacterial drug resistance, Cross Infection, optimization

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Introduction

According to the World Health Organization (WHO), infections are responsible for 25% of deaths worldwide. In 1990, it was estimated that 16 million people died from infections. In 2010, the number of deaths dropped to 15 million, with a decline of only 1% per year. And for 2050, the WHO predicts that 13 million deaths will be attributed to these causes, even with a number of measures for prevention and prophylaxis are recommended and implemented for these conditions.[1] The causative organisms of these infections are increasingly developing resistance mechanisms currently available pharmacological treatment, and multidrug resistant organisms are called (MDR). Microbial resistance is the ability of a microorganism to withstand the action of an antimicrobial agent. This resistance is a major threat to global public health, it increases the morbidity and mortality of the population and impose huge costs on all countries.[2] In the United States, infections caused by MDR organisms burden by more than 20 billion dollars a year and generating spending more than $8 million due to additional hospitalizations.[3] In the European Union, it is estimated that about 25,000 people may die annually infections caused by bacteria and the associated costs are estimated at about 1.5 billion euros per year.[4]

In Brazil, according to the Ministry of Health, more than 70% of the bacteria that cause hospital-acquired infections are resistant to at least one of the antimicrobial agents commonly used for the treatment of patients.[5] The development of infection by MDR organisms depends on factors related to both the patient and the pathogen, and exposure to highly invasive procedures and indiscriminate use of antimicrobial.[6] In hospitals, it is estimated that over 50% of antibiotics are used inappropriately.[7] In this perspective, there is the need for effective control over the prescription and use of antimicrobials through the development and adoption of guidelines and treatment protocols. So this is the primary goal of antimicrobial management for programs such as Antimicrobial Stewardship. This program is defined as actions and attitudes for the best selection, dosage and duration of antimicrobial treatment, which results in better clinical results for the treatment or prevention of infection with minimal toxicity for the patient and minimal impact on resistance.[8] Thus, the aim of this study was to describe the latest perspectives and responsibilities of microbiology laboratories in Antimicrobial Stewardship programs within the multidisciplinary team care for patients. In addition to name and describe the objectives of the program for management and optimization of antimicrobial use and the main laboratory techniques that have fundamental significance for microbiological identification, prevention and control of microbial resistance.

Methods

The design of this study was narrative literature review. The bibliographic productions were analyzed, summarized and integrated to meet the most current scientific evidence related to the research objectives. The survey was conducted in pairs between the months from May to September 2018 in the PubMed database. Therefore, the following search terms were used: "Antimicrobial Stewardship AND Microbiology laboratory." And so we selected 22 articles and 10 documents from the 585 references found that met the selection criteria for response to the problem of this research. The selection criteria were the articles of observational research or literature reviews as well as guidelines from public health agencies that had consistent reports of the objectives, powers and techniques for microbiological determination and antimicrobial susceptibility profiles of microbiology laboratories in the program antimicrobial Stewardship. After this, the data from these studies and divided into three sessions and so held a discussion of these results were gathered.

Results

Antimicrobial Stewardship program objectives

In 2015, the World Health Organization released a report to global action plan on programs to optimize the use of antimicrobials. This action plan sets out five strategic objectives: to improve awareness and understanding of antimicrobial resistance; strengthen knowledge through surveillance and research; reduce the incidence of infection; optimize the use of antimicrobials; and develop sustainable investment to the needs of all countries, increasing investment in new drugs, diagnostic techniques, vaccines and other health interventions.[9]

Antimicrobial usage optimization programs started to be built in recent decades in Infection Control Services, as strategies to combat antimicrobial resistance.[9] The four main objectives of the Antimicrobial Stewardship are to improve the results of antimicrobial therapy in patients (increase cure rates of infection and reduce morbidity and mortality); improve patient safety (to minimize unintended consequences of antimicrobial); reduce cases of multidrug-resistant microorganisms and reduce health care costs without affecting the quality of treatment.[10]

The Antimicrobial Stewardship in hospitals has shown a positive effect, with shorter hospital stay, shorter treatment without increased mortality, as well as the reduction in colonization and infection by resistant bacteria.[11] A systematic review and meta-analysis was conducted to assess the effectiveness of surveillance programs for antimicrobial use in hospital environments in the Asia Pacific from January 2005 to March 2016, the authors found that, from 46 studies, there was a reduction the hazard ratio for mortality grouped patients by 1.03 (95% confidence interval [CI] 0.88 to 1.19) to 0.69 (95% CI, 0.56 to 86). The authors concluded that the Antimicrobial Stewardship programs are safe and effective to reduce the consumption of antimicrobials and improve the results of therapy.[12]

In another review with meta-analysis, the authors proposed to elucidate specific actions within the Antimicrobial Stewardship from a careful review of the literature. Therefore, studies that found 145 together impacts empirical therapy from the pre-established guidelines within the program. This empirical therapy includes: the escalation of therapy, the change from intravenous to oral treatment, a therapeutic drug monitoring, the establishment of a list of restricted antimicrobials. Results showed significant benefits to adopting the empirical therapy from the program guidelines and was associated with a reduction in the relative risk for mortality of 35% (relative risk 0.65, 95% CI 0.40-0.80, $p < 0.0001$) and escalation to 56% (0.44, 95% CI 0.30 to 0, 66, p <0 0001).[13] However for the program to achieve its objectives, there is need for it to be effectively implemented and followed by health institutions. Therefore, it is important to integrate different health professionals. Most programs includes an infectious disease physician, supported by clinical pharmacists trained in infection, in collaboration with the microbiologist, with commissions for infection control and quality assurance of hospital services. It is also the contribution of the nursing staff, the administrative staff, experts in information systems and hospital epidemiologists as demonstrated in Figure 1.[14,15]

Optimization of antimicrobial use

In the United States it is estimated that 30-50% of antibiotics are used inappropriately and, each year, approximately two million people are infected with a resistant microorganism.[7] The indiscriminate use of antibiotics has been named as one of the most important factors for the development of microbial resistance. Over the years, new resistance mechanisms are emerging and spreading globally. This undermines the effectiveness of drugs to treat common infections, resulting in higher costs to health and contributing to the deaths of millions of people worldwide every year. Antimicrobial resistance is characterized as a genetic phenomenon related to genes contained in microorganisms encoding different biochemical mechanisms that prevent the action of drugs.[16]

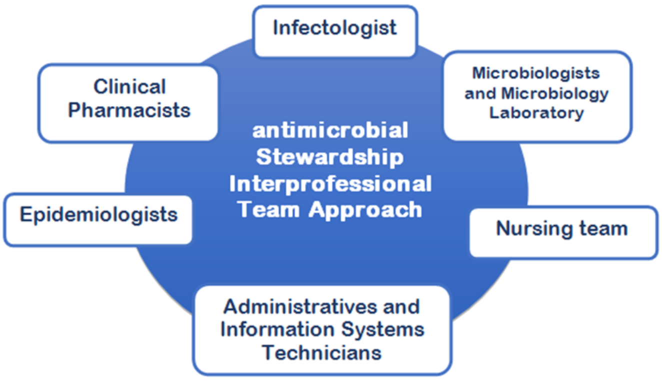

Figure 1 Antimicrobial Stewardship on interprofessional team approach.

Antimicrobial resistance is a natural phenomenon adaptation of bacteria, a result of the ability of the bacterial population to survive a certain environment. In Brazil, according to the National Health Surveillance Agency, the main multiresistant microorganisms that cause healthcare associated infections are Staphylococcus aureus resistant to methicillin (MRSA), enterococci resistant to vancomycin (VRE), producing strains spectrum beta-lactamases extended (ESBL) and gram-negative bacteria resistant to carbapenems.[17] Optimization of antimicrobial use is an essential component for an approach in the prevention of antimicrobial resistance. The quality of antimicrobial administration involves selecting the appropriate medication, always optimizing your dose and duration of treatment. What favors the reduction of toxicity and conditions for selection of resistant bacterial strains, ensuring the success of therapy.[10]

In the hospital environment, the antimicrobial can affect not only the user of the drug, but also the microflora of the hospital. Use without an effective control of this kind of medicine contributes to increased mortality, morbidity, prolonged hospitalization time and higher costs of treatment.[18] In this context, the optimization of the use of antimicrobials through the Antimicrobial Stewardship, aims to reduce the selective pressure for organisms resistant to multiple drugs (MDR), in order to preserve the usefulness of currently available drugs. In short, the implementation of the program promotes better results and greater safety for patients and reduce the risk of infection by Clostridium difficile.[19,20]

The use of antimicrobial broad-spectrum is often the initial scheme adopted for most infections with risk of death. Thus, to ensure the most appropriate empiric treatment is a major focus of Antimicrobial Stewardship interventions in this scenario.[21] Therefore, several strategies that optimize the use of antimicrobials should be implemented: medical education; setting clinical guidelines and protocols; incorporation of clinical pharmacist on the team; support systems for clinical decision; alteration of the dosage form and administration routes of antimicrobials; adequacy of dosages; or simplification escalation therapy; shortening the duration of treatment; review of the prescription; determining the etiologic agents and the susceptibility profile ably.[22]

Tasks of microbiology laboratories programs in Antimicrobial Stewardship

Although infectious disease physicians and clinical pharmacists are considered the main leaders of Antimicrobial Stewardship, clinical microbiologists can play a key role in these programs.[23] From this perspective, microbiologists in microbiology laboratories have several tools to support the diagnosis, the prognosis and the program's actions, actively integrating its multidisciplinary team. The clinical microbiology laboratory has several pespectivas for subsequent correct prescription of antibiotics. For has the following isolation, identification and determination of antimicrobial susceptibility profile of specific pathogens causing infections each particular hospital. Furthermore, antibiograms are used in the construction of therapeutic guides the local Antimicrobial Stewardship programs for empiric therapy.[17]

These efforts are important so that the data of antimicrobial susceptibility testing provided by the microbiology laboratory as a basis for clinical decision-making, are accurate and delivered on time, in about an hour. However, these data are often not available until two to three days after the collection of the clinical sample for microbial culture.[24] The use of rapid molecular diagnostics in hospitals has shown lead to a more targeted use of narrow antimicrobial spectrum, the earliest changes in therapy and reduce the overall use of antibiotics.[25] Many of these rapid tests are already or can be made available in hospitals, but not all, especially in low-income countries.[26] Rapid tests streptococcal antigens and rapid molecular tests for molecular screening for colonization and infection by Staphylococcus aureus, Clostridium difficile and respiratory viral pathogens including influenza and pneumococcal among others are widely available.[27]

Moreover the technique for microbial identification using Matrix Assisted Laser Desorption / Ionization whith Time of Flight Mass Spectrometry (MALDI-TOF MS) and rapid susceptibility testing accelerated prescribing of antimicrobial treatment directed, potentially improving the clinical outcome of the patients, but it has high costs.[25,28] The Verigene Gram-negative blood culture test nucleic acid test (BC-GN) is an automated molecular diagnostic test for identifying multiplexed eight gram-negative organisms and blood cultures resistance markers with a two-hour approximate time for the response. The BC-GN with intervention within the antimicrobials programs could potentially reduce the time for effective and optimal antibiotic therapy.[29] Nevertheless, the molecular test still lacks relevant aspects of bacteriological routine. This includes testing antimicrobial susceptibility profiles, allocation of patients with resistance genes of a given species from mobile genetic elements and serum biochemical markers.[30] Therefore monitoring of serum antibiotic levels and serum monitoring biomarkers related to their use are important responsibilities of clinical laboratories.

A meta-analysis of thirteen clinical trials totaling 5136 patients showed that decisions guided by serum determination of procalcitonin reduced the overall use of antimicrobials in those hospitalized patients with various bacterial infections, without leading to losses in their predictions. procalcitonin levels may reflect bacterial replication and have been tested extensively to guide decisions on whether to use or stop the use of antimicrobials.[31] To summarize the duties of microbiology laboratories in Antimicrobial Stewardship program was elaborated in Table 1. In this table there is a description of the main laboratory techniques currently available as well as the objectives and specifics of each assignment or laboratory technique.

Table 1 Objectives and characteristics of assignments and laboratory techniques performed by microbiology laboratories in Antimicrobial Stewardship program

Objectives and techniques performed by microbiology laboratories	Goals and specificities
Realization of classical microbiological and biochemical tests	Perform microbial identification tests and antimicrobial susceptibility testing by disk diffusion and classical biochemical tests.
Determination of serum procalcitonin	Stratify the risk for generalized infections and guiding systems for administration of antimicrobial agents in cases of sepsis.
Methods of implementation for rapid diagnosis	Deploy Reaction Polymerase Chain tests (PCR) and Fluorescence In Situ Hybridization with Nucleic Acid (PNA-FISH) platforms for rapid microbial identification and accurate.
Determination of genotype group and phylogenetic analysis	Implement microbiological enrichment methods and genetic and chromosomal extraction for elucidation of microorganisms and antimicrobial resistance mechanisms.
Identification by Mass Spectrometry Ionisation with assisted laser desorption matrix and by time-of-flight (MALDI-TOF MS).	To implement this new technique which has high sensitivity for microbial identification.
Participation in the clinical guides and protocols and pharmacotherapeutic	Participate in the development and implementation of guidelines and clinical protocols for safe and rational use of antimicrobials.

Discussion

The review found that the programs of the Antimicrobial Stewardship are already well implanted in developed countries, but a novelty in developing countries or low income. For the vast majority of articles was carried out in countries with higher incomes. Moreover, few studies that specifically address the duties of microbiology laboratories in these programs. There is also lack of original articles that controllably evaluated the financial impact and developments in the prognosis of infection from these types of programs to promote the rational use of antimicrobials in the hospital. However, the studied articles make clear the need to implement these programs in an attempt to reduce cases of microorganisms caused infections resistant to multiple drugs. Therefore, if a joint action with cross support of all professionals in health institutions is necessary. Microbiology laboratories have important duties to perform tests that evaluate the microbial and antimicrobial sensitivity profiles and serum biochemical tests, for example procalcitonin. These actions provide subsidies for guidelines aimed at listing the antimicrobials that should have restricted its use in clinical trials. Microbiologist also must also integrate the various hospital committees within the Antimicrobial Stewardship program, working in matrix for the rational use and antimicrobial insurance with a view to reduce the serious problem of microbial multidrug resistance.

Conclusion

This review concludes that the perspectives, roles and insights for microbiology laboratories in Antimicrobial Stewardship programs range from making laboratory tests for detection, microbial identification, determination of the sensitivity profile to in ensuring the rational management of these antimicrobials. This, from the following guidelines and protocols for directed therapy. And it must be done within an interprofessional team of integrated and continuous way in the pursuit of rational prescription and ensuring the safe and rational use of antimicrobials. Articles that effectively evaluated the role of microbiology laboratories without methodological biases were rare. What stresses the importance of implementing these programs evaluating the clinical and financial outcomes of their deployments. Be necessary, therefore, more studies identifying the real impacts of the assignments and new insights for microbiology laboratories in Antimicrobial Stewardship programs.

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Conflicts of interest

Authors declare that there is no conflicts of interest.

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