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(Review)

Antimicrobial Stewardship and the role of Microbiology Laboratory, and Pharmacists.

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ABSTRACT

Antimicrobial resistance of pathogenic microorganisms may be the cause of severe infections and complications of diseases, high cost, and high morbidity and mortality of the infected patients. Antibiotic overprescribing is a particular problem in primary care, community pharmacies, outpatient clinics, and hospital settings, where the unnecessary prescriptions of antibiotics are most common in low and middle-income countries. In the intensive care units, where there are severe infections and high antibiotic pressure, the management of such severe infections and rapid correct diagnosis is of paramount importance. So, the rapid increase of emergence of antibiotic resistance, and the failure and or delayed treatment of severe infections with high mortality cases, increases the importance of the management of prescription of antibiotics. The role of a microbiology laboratory in providing rapid microbiological diagnosis and antimicrobial susceptibility tests to broaden the choice of the suitable antibiotic and on survival of the patient is necessary. Pharmacists are considered to be experts in medicines and probably the ideal choice to oversee antimicrobial stewardship programs within hospitals and in primary care.. The aim of this review is to reveal the importance of the management of antibiotic prescriptions and the important role of microbiology laboratories and pharmacists.

Keywords: antimicrobial stewardship, Antimicrobial resistance, pharmacist roles

1-Introduction

The problem of antibiotic resistance of microorganisms had been recognized for some time before the end of the 20th century.

Microbial resistance to antibiotics is a growing threat that causes over 700,000 deaths per year worldwide[1]. The cost of antibiotic resistance should of course be measured primarily in terms of the suffering that results from the failure of antibiotics to cure infections against which they were formerly effective. The antibiotic resistance crisis has been attributed to the overuse, and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry. Antibiotic policies designed to improve the quality of antibiotic prescribing and restrict resistance in hospitals become essential. Another, challenge of infections due to the so-called "ESKAPE" pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella species, Acinetobacter baumannii, Pseudomonas aeruginosa, and* extended-spectrum beta-lactamase-producing strains of *E. coli* and *Enterobacter species*) together with the low number of antibiotics from the pharmaceutical industry has further increased the pressure to the importance of management of antimicrobial prescriptions (antimicrobial stewardship) [1].

There are less obvious consequences of resistance too: when the first-line drugs cease to be effective it is sometimes necessary to revert to alternatives that are more toxic. *Acinetobacter* infection is a good example of this situation because the organism is naturally multidrug-resistant and the incidence of isolates resistant to all first-line antibiotics has risen from 5% to 40% in ten years, so now colistin, a drug that became virtually obsolete in the 1960s because of significant risk of kidney damage is, for many patients, the most likely antibiotic choice.

There is widespread agreement that greater use of antibiotics predisposes to the development of resistance. According to WHO reports, more than 50% of all antibiotics are prescribed, sold or dispensed incorrectly; in addition, 50% of patients do not take antibiotics properly [2]. Inappropriate prescribing and consumption, together with the fact antibiotics can represent up to 30% of a hospital pharmacy budget, have provided further impetus for measures designed to achieve more prudent prescribing and avoiding the unnecessary medicines . Some reports have estimated a reduction in antimicrobial use by 22 to 36% with antimicrobial stewardship programs.

Misuse of antibiotics

Under use, this is quite frequent in low and middle-income countries due to a lack of access to healthcare services. Unnecessary use, where an antimicrobial is not indicated and there is no health benefit for the patient (e.g. treatment of an upper respiratory tract infection caused by a virus or an antibiotic is not recommended). Inappropriate (or suboptimal) use, where timing antimicrobial choice, dose, route, frequency of administration or duration of treatment is incorrect. For example: delayed administration in a critically ill patient, choice of an antibiotic with an unnecessary broad-spectrum or too narrow spectrum, also, prescription of two drugs incompatible with each other. Prescription of I.V drug while one oral drug is possible. Prescription of antibiotic with too high dose or too low dose compared to what is indicated for that patient. Prescription of antibiotic of long duration or short duration without necessity. Duration is > 24 hrs for surgical prophylaxis, except when guidelines endorse longer duration. Treatment is not streamlined or changed when microbiological culture data becomes available. Poor patient adherence to the prescribed treatment.

Antibiotic misuse in the community setting [3]

The majority of antibiotic use, around 80% occurs in the community, prescribed in settings such as outpatient clinics, health posts and general practice. The prevalence of antibiotic use in the community varies between countries from less than 20% to over 40% of the population dispensed at least one antibiotic each year. Much of the inappropriate prescribing of antibiotics in the community is for infections not caused by bacteria such as colds and influenza and other viral infection and in low income countries for diarrhea and malaria. Over 50% of antibiotics may be prescribed unnecessarily in the community for upper respiratory tract infections. As many as 30% of residents in aged care facilities are prescribed antibiotics when not indicated for asymptomatic UTI. A need for educational programs for management of antibiotic prescriptions (Antimicrobial stewardship) and the role of healthcare professionals for appropriate use of antibiotics to prevent the rapid microbial resistance to antibiotics should be introduced early in medical curricula.

Antimicrobial stewardship [4]

It can be defined as “The optimal selection, dosage, and duration of antimicrobials that result in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance”.

From the clinical point of view, it can be defined as: “The right antibiotic for the right patient, at the right time, with the right dose, and the right route, causing the least harm to the patient and future patients.”

The principal goal of antimicrobial stewardship programs is the appropriate use of antimicrobial agents to improve patient outcomes, lessen the risk of adverse effects, reduce resistance levels or at least slow the rate of resistance development, and improve cost-effectiveness through: the appropriate use of specific antibiotic avoiding the patient from the morbidity and may be mortality due to the resistant pathogenic microorganism to antibiotics. Reducing long-stay in hospitals and cost effectiveness. Protect and preserve the potential antibiotics many years of life for many people by reducing the emergence of microbial resistance to antibiotics.

Components of antimicrobial stewardship programs [5]

There are no nationally or internationally accepted guidelines on the structure of a stewardship program, so they vary from country to country and even from one hospital to another in a geographical region. Indeed, even the title varies so terms like “good antimicrobial practice programs”, antibiotic management programs”, and “antibiotic control programs” have been used. However, there is agreement on the personnel comprising an antimicrobial stewardship team, and usually consists of:

1-An infectious disease physician

2-A clinical pharmacist with infectious disease training

3-A medical microbiologist

3-An infectious control professional

4-A hospital epidemiologist

5-An information technology specialist

Most hospitals have drugs and therapeutic committee (DTC), also known as a pharmacy and therapeutics committee, whose function is to evaluate drugs for inclusion in a hospital formulary on the basis of their efficacy, toxicity, and cost. The intention is to avoid the unnecessary stoking of multiple drugs from the same class which has similar or identical property few hospitals stock every available aminoglycoside or third-generation cephalosporin for example. A recommendation or even written approval of senior clinical staff when prescribing antibiotics in a restricted category usually those drugs whose effectiveness needs to

be preserved because of their value in treating infection for which few drugs are effective e.g. linezolid or daptomycin, or antibiotics which may predispose to other problems, e.g. clindamycin because of its link to *Clostridium difficile outbreaks.*

The effectiveness of stewardship strategies

The use of a clinical pathway that includes a specified antibiotic regimen in the treatment of community-acquired pneumonia, for example, has been shown to be capable of reducing the duration of hospital stay and duration of antibiotic therapy and there is strong evidence that practice guidelines and clinical pathways incorporating local resistance patterns can generally improve antimicrobial utilization.

Four other elements of the Infectious Disease Society of America (IDSA) that has been shown to afford clear benefits are the use of antimicrobial order forms, de-escalation of therapy, parenteral to oral conversion, and optimized dosing. Order forms are particularly useful when antibiotics are prescribed for prophylactic purposes to reduce the incidence of infection following surgery. In this situation, there is a tendency to continue the course of treatment for an unnecessarily long period after the operation, and studies have shown that order forms with a default stop date have diminished drug consumption with no adverse effect.

When hospital treatment for infection begins, it is often the case that the organism responsible has not been identified, so initial treatment is empirical or "blind" and in order to maximize the probability of inhibiting the pathogen, it may involve the use of either a broad-spectrum antibiotic or of two or more different drugs. Once the organism has been identified, it is good practice to replace broad-spectrum antibiotics (or redundant components of combination) with a drug having more specific activity because the continued unnecessary use of a broad-spectrum therapy contributes to the selection of resistant pathogens.

Converting from intravenous to oral therapy affords a benefit primarily in terms of cost reduction but may also permit earlier removal of intravenous lines which facilitate the establishment of infections by skin pathogens like *Staphylococcus epidermidis.* Oral antibiotics are usually cheaper than intravenous ones, quite simply because the use of the latter is largely restricted to the hospital anyway, so their manufacturers have to recover the development costs from lower lifetime sales. Optimizing dosing is as the name implies, modifying the antibiotic dose to suit an individual patient's circumstances. Factors that may influence the dose, and hence the effectiveness of the therapy include the patient's physical characteristics (weight, age,

immune status, renal function), the site of infection, and the pharmacokinetics of the drug which determine its access and concentration at that infection site.

Antimicrobial stewardship in long-term care facilities [6]

The number of elderly people living in long-term care facilities (LTCFs) is increasing worldwide. Antibiotic use is high in LTCFs compared with the primary care setting, and bacterial resistance prevalence is also much higher. About 80% of residents with a suspected infection are prescribed antibiotics, and receive at least one antibiotic course per year. The main motives for antibiotic use are suspected urinary tract infections (32%-66%), respiratory tract infections (15%-36%), and skin and soft tissue infections (13%-18%). As in any other setting, around one-third of antibiotic prescriptions are appropriate, one-third are unnecessary and one-third are inappropriate.

Excessive durations of treatment are the leading cause of inappropriate prescriptions in LTCFs, with treatment longer than 7 days in half of the cases. The prevalence of multidrug-resistant bacteria in LTCFs is very high and sometimes higher than in hospitals. Residents are often colonized for several months since they accumulate many risk factors (high level of transmission, antibiotic use, wounds, catheters, etc.). LTCFs are therefore considered as multidrug-resistant bacteria (reservoir).

Antimicrobial stewardship in ICU [7]

Management of infections in ICU is important, where severe infections are most prevalent and antimicrobial use is most important. Antimicrobial resistance emerges primarily in the intensive care setting where there are high antibiotic pressure, loss physiological barriers, and high transmission risk. The ICU is a place where specialists work together to provide the most optimal patient care. Microbiologists and clinical pharmacists, relying on their own expertise, all advise the ICU physician on the optimal use of antibiotics.

Correct diagnosing of the infection is essential for the appropriate use of antibiotics. Clinical diagnosing of infection depending only on signs and symptoms may not be enough for a perfect diagnosis of infection and so, for a perfect prescription of antibiotics. Because of this, it is evident that signs of inflammation cannot be the only tools to guide antibiotic decision-making, and specific signs and symptoms of the infection, such as pneumonia or abdominal infection should be sought after.

Microbiology diagnosis is crucial, in some cases with rapid techniques. However, usually microbiological confirmation will generally come late and has only a limited role at the start of antibiotic therapy. The threshold to initiate therapy is often low, as there is pressure on clinicians not to delay antibiotic therapy in order to improve outcomes. As a result, many patients receive antibiotic therapy for noninfectious causes, apart from the futility of the treatment and the impact on the microbiome of the patient, this may also delay establishing an accurate diagnosis and appropriate therapy. Initial appropriate antibiotic therapy is highly describable, yet challenging as the microbiology results will only become available at a later stage.

Empirical therapy should therefore cover the expected pathogens in a particular patient. This may be determined by many factors such as the site of infection, local ecology, previous antibiotic exposure, length of stay in the hospital, and known colonization status with multidrug-resistant pathogens can aid in determining the appropriate empirical choice of therapy.

Traditionally, the focus of initial antibiotic therapy has been on timing and spectrum, and guidelines advocate the initiation of broad-spectrum antibiotic therapy within the hour of hypotension in patients with septic shock. Whereas the latter is indeed crucial, the role of delays in antibiotic therapy is more debated. Whereas several studies have suggested that mortality increases with the hour that antibiotics are delayed.

The role of Microbiology Laboratory in promoting Antimicrobial Stewardship

Microbiology laboratories play an important role in guidelines to clinicians for appropriate prescription of antimicrobial therapy. Inappropriate antibiotic prescribing results in poor patient outcomes increased treatment costs, and increased risk of super-infection by multi-resistant organisms with the selection of resistant clones. However, the results of the microbiology laboratory of the causative agents and antibiotic susceptibility tests may take a long time.

Introducing rapid diagnostic tests (RDTs) provided new opportunities for diagnosis of infections. These methods significantly reduce the time for pathogen identification and antimicrobial susceptibility from days to hours compared with conventional techniques. Time for targeted treatment by conventional tests takes at least 4 days, while rapid diagnostic tests may take 2 days. Numerous studies have shown the impact of early antimicrobial therapy on the

survival of the patient. Early results from microbiology laboratories by using rapid tests allow physicians to start life-saving therapy for the patient with serious infections.

The rapid tests not only benefit the individual patient but also improve AMS by decreasing antibiotic use, time to optimal antimicrobial therapy, length of stay, and cost[8][9].

Some most commonly used RDTs are: matrix-assisted laser desorption-ionization time of flight (MALDI-TOF), quantitative polymerase chain reaction (qPCR) assays, peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) assays, and multiplex nucleic acid assays.

Real-time PCR assays are usually developed for the diagnosis of bloodstream infections. They accurately detect methicillin resistance in Staphylococcal bacteria after the detection of Gram-positive cocci in blood culture, thereby improving early targeted antibiotic prescribing. In a recent randomized clinical study, diagnosis by real-time PCR assay revealed a decrease in the median time of reporting for methicillin resistance by 21.5 h, a decrease in the time to targeted antibiotic therapy by 20.5 h, and a decrease in unnecessary exposure to vancomycin in the patient with *S .aureus* bacteremia.

Multiplex PCR can detect multiple pathogens in specimens. These systems identify the bacteria and some yeasts within 1.5 h from positive signaling in the blood culture bottle. They also detect several resistance genes including CTX-M, VIM, IMP, OXA, KPC, NDM, Van A, and mec A. Several studies demonstrated the benefits of adding rapid multiplex PCR-based identification systems to antimicrobial stewardship programs. In patients with bacteremia and fungemia, a decrease in time to specific antimicrobial therapy and a decrease in duration of broad-spectrum therapy were reported[10]. They also significantly enhance antimicrobial de-escalation (with multiplex PCR 21h versus control34 h) [11].

PAN-FISH is another promising diagnostic technique that yields the results within 4h after blood culture bottle growth signal. Pathogen-specific RNA-targeted fluorescein-labeled probes are used. The PAN-FISH assay has a good performance in the accurate identification of *S. aureus, Enterococci,* Gram-negative rods, and *Candida species* from blood cultures and cerebrospinal fluid cultures.

These assays can provide the results at least one work day before MALDI-TOF mass spectrometry-based identification [12].

The role of pharmacists

Pharmacists are considered to be experts in medicines and are probably the ideal choice to oversee antimicrobial stewardship programs within hospitals and in primary care[13]. They oversee medicine optimization in all healthcare sectors. Clinical pharmacists review the prescribing of doctors to ensure safety and efficacy and optimize long-term medicines that patients are taking prior to admission. Medicines optimization: the safe and effective use of medicines to enable the best possible outcomes. Manchester 2015, most hospitals have a policy for the use of medicines, so the AMS policy can be written by the AMS pharmacist as part of the hospitals overarching medicine policies. Within the AMS program, the AMS pharmacist often leads the development of systems for the control of antimicrobial supply such as restricted or protected antibiotics and intravenous to oral switch guidance. The introduction of new antimicrobials into a hospital or local health economy formulary is through the Drug and Therapeutics Committee (DTC) process. The AMS pharmacist can work with infectious disease specialists to identify the potential place in therapy within both its licensed indications and potential off-label uses. The AMS pharmacist will usually produce a review of the evidence to support the introduction of the new antimicrobial, including its cost-effectiveness and advantages over existing therapies.

Many hospitals rely on clinical pharmacists to review antimicrobial prescribing against local guidelines and to confirm with prescribers where this is not a justified reason. Compliance to antimicrobial guidelines can reduce patient mortality [14].

De-escalation based on culture results can reduce patient mortality and is a key activity of the non-specialist clinical pharmacist. A switch from IV to oral therapy can decrease inpatient length of stay, save money (as IV antibiotics are usually more expensive than oral) and save nursing time [15].

The monitoring of blood levels for antimicrobials with narrow-therapeutic spectrum has been shown to reduce the risk of nephrotoxicity, and this should be a key activity of the clinical pharmacist or the AMS pharmacist at the ward level [16].

The role of the pharmacist in ICU or other high-risk populations is especially as important in optimizing antimicrobial therapy based on organ dysfunction, obesity, and cystic fibrosis [17].

Primary care pharmacy

The role of the AMS pharmacist in primary care is growing and includes the localization of national guidelines, delivering education and training to doctors and prescribing nurses and pharmacists, academic detailing of general practitioners or family practices, and coordination of public health campaigns for world antibiotic awareness week.

Community pharmacy

Community pharmacies are often the first point of call for patients seeking advice for infections or self-care treatment for minor ailments. They can perform the triage role and direct patients to their family doctor or to an urgent care facility. Importantly, community pharmacists should say: “I am sending you to the doctor for a further opinion” but not mention antibiotics, as this generates expectation in the patient and make it difficult for the doctor not to prescribe them. Community pharmacists can check prescribing against local guidelines by asking the patient what type of infection there are for. They can also play an important role in counseling the patient to complete the course and return any unused antibiotics back for destruction and warn of the dangers of sharing antibiotics. Community pharmacies run health promotion campaigns to reduce the need for antibiotics by promoting good hygiene, vaccination, and self-care of viral infections. They can also raise awareness of sepsis and the benefits of early treatment.

Some countries run minor ailment schemes where community pharmacies can provide symptomatic relief for no change, thereby avoiding opportunities for patients to ask for antibiotics. Targeted point-of-care group A streptococcus antigen in testing in community pharmacies has demonstrated opportunities for decreasing antibiotic prescribing rates for sore throats [18].

2. Conclusion

The problem of resistance of microorganisms to antimicrobial agents is growing dramatically worldwide. The massive use of antibiotics in community-acquired infections and in hospital settings and also in long-term care aged care home settings consumes big amounts of medicine improperly and unnecessarily. Over 50% of antibiotics may be prescribed unnecessarily or inappropriate for community-acquired infections. In hospitals, about 25-50% of inpatient use of antibiotics is unnecessary or inappropriate. The non-adherence to guidelines is similarly high.

In low-income countries, antibiotics are often prescribed after surgical procedures using 7 times more antibiotics. From 30% to 60% of antibiotic prescribing in ICU is unnecessary or inappropriate. Suboptimal prescribing I ICU such as poor choice of antibiotic use of a redundant combination of agents, failure to de-escalate therapy, and excessive duration of therapy. A rate of 75% of antibiotic use in long-term care aged care home is estimated to be inappropriate.

We need to control the process of antibiotic prescriptions everywhere for outpatients or inpatient settings and for healthcare services. Prescription of antibiotics should be based on correct diagnosis and through a team of clinical pharmacists, infectious disease physicians, and medical microbiologists. Obtaining the correct samples for microbiological diagnosis of infections is crucial as the use of rapid techniques of diagnosis and antimicrobial susceptibility tests. Accurate antibiograms that are specific to the local community (for community-acquired infections) and in hospitals (for nosocomial infections). In hospitals and primary-care health settings, full data about the most common pathogens and the resistant pattern of microorganisms to antibiotics and guidelines to suitable antibiotic administration and in stock in different hospitals in different regions. Restrictions of antibiotic prescriptions in community pharmacies, nurses, dentists, and general practitioners should be undertaken.

The mandatory regular and continued teaching and training of pharmacists, physicians, dentists, and nurses on prudent antibiotic use and infection management. Teaching courses in microbial resistance and training in the management of antibiotic use for undergraduate clinical pharmacists.

- **Conflict of Interest**

There are no conflicts of interest.

3. References

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