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MINIREVIEWS

Methodology in improving antibiotic implementation policies

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Abstract

The basic requirements of antibiotic prescribing are components of methodology; knowledge, logical reasoning, and analysis. Antimicrobial drugs are valuable but limited resources, different from other drugs and they are among the most commonly prescribed drugs all over the world. They are the only drugs which do not intentionally affect the patient. They affect the pathogens which invade the host. The emergence and spread of antibiotic-resistant pathogens are accelerated by heavy antibiotic usage. The effective antimicrobial stewardship and infection control program have been shown to limit the emergence of antimicrobial-resistant bacteria. In this respect, education for antibiotic prescribing could be designed by going through the steps of scientific methodology. A defined leadership and a coordinated multidisciplinary approach are necessary for optimizing the indication, selection, dosing, route of administration, and duration of antimicrobial therapy. In scenarios, knowledge is also as important as experience for critical decision making as is designated. In this setting, the prevalence and resistance mechanisms of antimicrobials, and their interactions with other drugs need to be observed. In this respect, infectious disease service should play an important role in improving antimicrobial use by giving advice on the appropriate use of antimicrobial agents, and implementing evidence-based guidelines.

Key words: Antibiotics; Infection; Antibiotic resistance; Therapy; Medical informatic applications

Core tip: Treatment of infections has become problematic because of increasing global antimicrobial resistance. One of the major reasons of this is antibiotic misuse and over use. In order to make antibiotic therapy more effective, some guidelines are used. Although guidelines lead to improvements in clinical practice, no guideline can be sufficiently specific that can be applied to all clinical situations. For improving antibiotic implementation strategies, not only consensus-based but also evidence-based scientific methods are needed. This review highlights the knowledge and experimentation of expert physicians under the supervision of antibiotic stewardship.

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INTRODUCTION

The implementation of antibiotics in cancer chemotherapy and organ transplant patients, make the serious lethal complications of diseases likely treatable. Therefore parallel to medical advances, practice of medicine have changed greatly through antibiotic usage. The early initiation of antibiotics to treat infections reduce morbidity[1]. However, 20%-50% of the prescribed antibiotics in hospitals are either unnecessary or inappropriate[1-3]. Unnecessary antibiotic using patients are candidates for serious adverse effects even without any effective clinical cure. The misuse of antibiotics also contributes to the growing problem of antibiotic resistance. In the twenty-first century, because antibiotic resistance has become a serious issue for patient safety, improving the use of antibiotics is an important public health problem[1,4,5].

Therefore, antibiotic prescribing should be based on a prudent, well-thought, and rational process. The basic requirement for this is knowledge, logical reasoning and analysis. Meanwhile, the system of rules and procedures for interventions to improve antibiotic use is constantly being updated as scientists and physicians look for new and better ways of making observations, analysis and synthesis[6]. For implementation strategies we may need evidence-based methodology. Thus, the below stated steps of a scientific method can be applied for improving antibiotic implementation policies[7]: (1) Asking a question; (2) Carrying out background research; (3) Constructing a hypothesis; (4) Testing the hypothesis through an experiment; (5) Analyzing data and drawing a conclusion; and (6) Communicating the results.

A PRAGMATIC APPROACH TO THE METHODOLOGY OF ANTIBIOTIC IMPLEMENTATION POLICIES

In 2015 Center's for Disease Control and Prevention (CDC) published a report about core elements of hospital antibiotic stewardship programs[1]. According to CDC "there is no single template to optimize antibiotic usage". The medical decision is complex and the antibiotic implementation policies should be flexible. Therefore, there is need for defined leadership and coordinated multidisciplinary approach[1]. Although the relevant guidelines for antibiotic usage and expert opinions steer and shape the author's vision for judicious antibiotic use in writing this review, the methodology used in this manuscript highlights the author's own ideas.

WHY ARE ANTIMICROBIAL AGENTS DIFFERENT FROM OTHER DRUGS?

Antimicrobial drugs are valuable but limited resources, and they are different from other drugs. Why are antibiotics different from other drugs?[8] The three factors which differ antimicrobials from other drugs, compose the important components of antimicrobial therapy[9]:

First, antibiotics are among the most prescribed drugs all over the world. Antimicrobials account more than of 30% of hospital pharmacy budgets[4]. In developing countries one third of the budget reserved for health care is also spent for antibiotics[10]. Therefore the cost effectiveness of antimicrobial treatment of bacterial infections is important[11]. The excessive consumption and prescription of antibiotics ended up with high costs; so the "the Ministry of Health in Turkey" restricted the prescription of excessively used expensive antibiotics nationwide[10]. With this new policy the responsibility of the prescription of antimicrobials is given to the infectious disease (ID) specialist physicians. Nevertheless, the comparative cost of antibiotics is only one of the factors in determining the physicians' antibiotic choice, and it should never be the most important factor[11].

Second, antimicrobials are the only drugs which do not intentionally affect the patient; this feature differs antibiotics from other drugs. Antibiotics can affect both the pathogen and the colonizing flora[8,9]. Antimicrobial therapy is based on the characteristics of a patient and a drug, as well on the characteristics of the microorganisms[8]. This complex relationship between the patient, antimicrobial, and microorganism is defined as the cornerstones of a triangle[8], as shown in Figure 1. In this concept host presents the antimicrobial agent to the pathogen[9,12].

The selection of an antibiotic for the appropriate empirical antimicrobial therapy has become increasingly difficult. Physician has to know many different aspects of IDs; such as immunological and genetic host factors, microbial virulence, pharmacokinetics (PKs) and pharmacodynamics (PDs) of drugs[8]. PKs describes the action of drugs in tissues and body fluids over a period of time, including the processes of absorption, distribution, and excretion[13]. PDs studies the relationship between the biochemical and physiological interactions of drugs on the body or on microorganisms. Physiological effects are associated with primary and underlying disorders, aging, interactions with other drugs, *etc*. Meanwhile, the time course and the concentration of the therapeutic agent at the infection site, and its adverse effects have to be concerned[13]. PDs, with PKs, explains the relationship between the dose and response. The postantibiotic and bactericidal action of antimicrobials related to drug's PD effects, have to be known for optimal dose regimens. In addition, the optimal dose and dosing intervals have also to be determined according to the minimal inhibitory concentrations (MICs) and minimal bactericidal concentrations of the antimicrobials against microorganism groups[13].

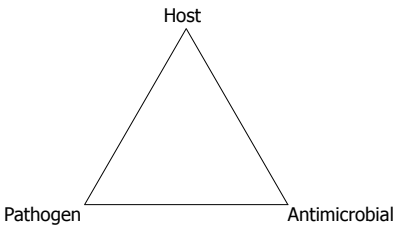

Figure 1 The relationship between the patient, antimicrobial and microorganism.

Some drugs, such as the β-lactams, exert their maximal effect when antibiotic load exceed the MIC of the microorganism for a certain period of time between doses. Such agents are known as "time-dependent" antibiotics and they are also recognized with the PD indices as "time above MIC"[4,14]. For time-dependent antibiotics during the dosing interval, the serum drug concentrations should achieve at least 40% to 50% of the MIC of the causative pathogen[13]. These studies support the concept of administering β-lactam antibiotics at shorter intervals, prolonging the infusion time, or even administering by continuous infusion for serious systemic infections[4,14]. Beta-lactam antibiotics show an inoculum effect. When the bacterial density is low, the concentration of the required β-lactam could be low, and vice versa[13]. The aminoglycosides and fluoroquinolones, on the other hand, exhibit "concentration-dependent" killing. For these and similar agents, the PD indices are determined as "peak/MIC" (peak serum concentrations divided by the MIC) and as "24-h area under curve/MIC". These ratios show that giving the fluoroquinolones and aminoglycosides by once daily dose are encouraging from a PD point of view[4,14]. Thus the high peak levels obtained after short infusion dosing or high exposures during 24 h, cause the most rapid killing of the infecting pathogen[4,14]. In most clinical settings, administering aminoglycosides as a total single daily dose are recommended and have become the standard of application. On the other hand, the glycopeptides exhibit time-dependent killing. They also show slow bactericidal activity and a short post-antibiotic effect *in vitro*[13]. Studies of PK and PD account for the basis of dose optimization[4].

Third, the overuse of antibiotics in human health care and animal feeds, the increased use of invasive devices and procedures, and invalid infection control practices have resulted in antibiotic resistance. The resistance is acquired by mutational change or by transfer and acquisition of resistance-encoding genetic material in health care settings[15]. So, multidrug resistant bacteria is the major cause of failure of the treatment of IDs which the clinician has to deal with[15]. The overuse of other drugs does not introduce any negative effect to other medications as antimicrobials do. Therefore, to limit the transmission of emerging multidrug-resistant organisms, implementation of regional antibiotic usage data has to be developed[5].

It is known that changing the attitude of the professional who is prescribing an antibiotic, is not easy. So, to aide the physicians attitude for antibiotic usage, early antimicrobial stewardship interventions have been practiced at the postgraduate level[3,16]. The IDs Society of America (IDSA) has defined the antimicrobial stewardship. With this, IDSA stated that for maximum clinical cure, the indication, selection, dosing, route of administration and duration of antimicrobial therapy have to be optimized. In addition while selecting antimicrobials, it should be taken into account that they will produce no damage; including toxicity, selection of pathogenic organisms, such as *Clostridium difficile*, and emergence of resistance[4,5,8,16]. To avoide resistance selecting pressure, the antibiotics have to be given for the shortest possible duration, in adequate doses, and with the least broad-spectrum[8].

The systematic ways of doing, teaching, and studying antibiotic implementation strategies constitute the main issue of this manuscript. In other words the question of what could be the system of methods and principles used in improving antibiotic implementation practices, should be answered. James Bach states that "there is no consensus about what practices are the best, unless consensus means; people I respect also say they like it. There are practices that are more likely to be considered good and useful than others, within a certain community". But… so what? "Good practice is not a matter of popularity. It's a matter of skill and context" (James Bach; founder and operator of exploratory software company Satisfice, Inc.).

INFECTIONS AND ANTI-INFECTIVE THERAPY

The IDSA and the Society for Healthcare Epidemiology of America (SHEA) published Guidelines for Antimicrobial Stewardship Programs in 2007[4]. These guidelines do not pose as a substitute for clinical judgement[4,16]. In selecting the appropriate antimicrobial agent for therapy of an infection, some important factors should be kept in mind[14]. First, the identification and the source of infecting organism must be known or, at the very least, it must be possible to arrive at a statistically reasonable guess as to its identity on the basis of clinical information[14]. Also, the environment where the infecting organism is contracted (community or hospital) should be questioned. Second, information about the susceptibility of the infecting organism, or likely susceptibility, must be as accurate as possible[14]. Finally, a series of factors specific to the patient who is being treated must be considered to arrive at the optimal choice of antimicrobial agent[14].

Today most antibiotic treatment is empirical. In 2012 as stated by Livermore[17], "in general most diagnostic microbiology laboratory practice moves at the speed it did in Fleming's time: 1 d from specimen to culture and another from culture to identification and susceptibility

data". In practice, for critically ill patient empirical therapy is started as early as possible when evidence of infection is observed[18]. The antibiotic guidelines combined with the physician's experience shape the therapeutic choices for empirical antimicrobial usage[18]. Meanwhile, several methods for the rapid identification of pathogenic bacteria are available in clinical specimens. A Gram stain-preparation is perhaps the simplest and least expensive method to determine the presence of bacterial and some fungal pathogens. Final and definitive identification of pathogenic organisms still often require a culture technique. It is extremely important that appropriate specimens be obtained for culture before beginning antimicrobial therapy, to test the susceptibility of agents that may be used in therapy[14]. Once anti-infective therapy starts, cultures often become sterile, even though viable organisms remain in the host. So samples taken before starting antimicrobic therapy is important for the identification and antimicrobial susceptibility of the organisms causing an infection[14]. If fast usage of molecular microbiology techniques to identify pathogens and fast detection of their resistances in primary clinical specimens could be achieved, the individual patient may benefit from early use of the most powerful antimicrobial[17].

For optimal therapy, a number of host factors that may influence the efficacy and toxicity of antimicrobial agents should be considered. The age of the patient, the presence of genetic and metabolic abnormalities, pregnancy, renal and hepatic function all have significant effect on the toxicity of a given antimicrobial agent[14,19,20]. Another consideration in selection of an appropriate antimicrobial is the site of infection. The concentration of the antibiotic at the site of infection should be $\geqslant$ the MIC of the infecting organism for the antimicrobial therapy to be effective[14,19,20].

For judgement of the effectiveness of therapy, clinical improvement is the best directory; although it is not always easy to observe objectively[21]. As stated by Paterson *et al*[21], "culture results are sometimes negative, yet an infection is clinically present, or culture results are positive, but indicate the presence of colonization rather than true infection". In such situations, switching an antimicrobial agent has to be questioned in detail; "Don't change a winning team"[21]. Besides, for serious infections such as endocarditis long-trerm therapy is needed, so for monitoring clinical improvement physician has to observe the patient for a longer period of time. Another point is that fever should not always be the only factor to judge the success of antimicrobial therapy. Altough a febrile patient under antimicrobial therapy could be related to treatment failure, there are also other factors which have to be considered; such as, drug fever, abscess formation, or other infection with an opportunistic pathogen[14]. Some surgical interventions in such occasions, like abscess formation drainage, could be as important as anti-infective therapy and should be considered by the ID specialist and by the surgean[19].

ANTIMICROBIAL STEWARDSHIP PROGRAM

Antibiotic implementation policies should be flexible[1]. Meanwhile, the success depends on a defined leadership and a coordinated multidisciplinary approach[1]. For optimum decision making in prescribing antibiotics, physicians have to have sufficient knowledge of IDs, infecting pathogens, and antimicrobials. So the director of the program should be ID specialist, or ID specialist should co-direct the program with a clinical pharmacist. Thus, the key members of an antimicrobial stewardship team is constituted[4,5]. For antimicrobial resistance surveillance a clinical microbiologist, and for the computer support an information system specialist are also needed[4,5]. The IDs physician or a clinical pharmacist with IDs training has to have interactions with the prescriber physicians. They should perform a prospective audit and a feedback system, serving to reduce the inappropriate use of antimicrobials[4,5].

What could be done for to avoid antimicrobial resistance? Many investigators in nowadays try to figure out inappropriate antibiotic use and they use this figure as a surrogate marker[4,5]. For effective antimicrobial stewardship many interventions are recommended such as; formulary restriction and preauthorization, antimicrobial order forms, antimicrobial cycling[4,5]. However, the formulary restriction should be dynamic. The recommendation rules of the routine uses of these basic implementation procedures are not based on sufficient data. Therefore, to increase the acceptance of stewardship strategies, continuous education programs have to be considered[4,5,8]. In addition, local microbiology laboratories' antibiotic sensitivity results and resistance patterns, and infection control programs should be taken into account to improve antimicrobial utilization[4,5].

Interaction between inappropriate antibiotic use and antimicrobial resistance

Although, antibiotic resistance is caused by mutations in bacteria's genes, inappropriate use of antibiotics accelerates the emergence of antibiotic-resistant bacteria[15]. However, antibiotics kill susceptible bacteria but resistant bacteria can overgo to grow and multiply. The people who have not taken antibiotics are also under risk of getting infected with antibiotic resistant bacteria strains. In this respect, there seems to be a complex relationship between antibiotic use and antimicrobial resistance[15,22]. The relationship is affected by antimicrobial PDs, mutant selection windows (MSWs), the mutational or acquired resistance[15,22].

The MSW is a novel *in vitro* concept. It is defined as "the zone between MIC and mutant prevention concentration"[23]. In other words, it means "the ability of antibiotics to prevent the emergence of mutant"[23]. Becauce antibiotic susceptibilities of different bacteria strains may differ, they might have different selective

windows, depending on the MIC of a given antibiotic. When resistance to antibiotics has reached high levels, it is difficult to prevent new mutants[24].

Another interaction between antibiotic usage and antimicrobial resistance can be MIC creep[25]. To explain this phenomenon for at least last 20 years, vancomycin has been used as the cornerstone for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA)[25]. In healthcare settings, very small percent of *S. aureus* isolates (< 1%) select resistance to vancomycin. There are also very rare vancomycin-resistant *S. aureus* and vancomycin intermediate-resistant *S. aureus* strains. "Vancomycin MIC creep" is the rising of vancomycin MICs among vancomycin susceptible *S. aureus* (vancomycin MIC $\geqslant$ 2 μg/mL). Vancomycin MIC creep is seen in patients with recent vancomycin use. This situation causes difficulty in the treatment of complicated staphylococcal infections like bacteremia, pneumonia, *etc*[25]. Various poor clinical outcomes and increased costs of hospitalization have shown to be associated with infections caused by *S. aureus* isolates with higher vancomycin MICs[25].

Although, for successful empirical therapy broad-spectrum coverage is necessary, excessive aggressive therapy may cause the emergence of antibiotic resistance[21]. After getting antibiotic sensitivity results, the sectrum of therapy should be narrowed. The value of such streamlining and de-escalation therapy, have to be evaluated fully by the IDs physicians[21].

Formats of educational curricula

For antibiotic prescribing behavior of hospital programs, education is an essential element[8]. According to Pulcini *et al*[8] "targeted antibiotic sessions in the format of problem-based learning are absolutely necessary. It is important to identify the topics or concepts that benefit from a disease- (*e.g.*, acute bronchitis) or problem- (*e.g.*, antimicrobial resistance) oriented, rather than a pathogen- (*e.g.*, MRSA) oriented, or a drug- (*e.g.*, antibiotic classes) oriented approach". In the United Kingdom, for the same purpose a website is performed as "the Prudent Antibiotic User" (PAUSE, www.pause-online.org.uk). It is aimed to be used in the undergraduate medical curriculum. PAUSE has provided standardized teaching aides for all educators of antibiotic prescribing that have based on cases[8]. Meanwhile, "the European Society of Clinical Microbiology and IDs study group for Antibiotic Policies" (available at www.escmid.org/esgap) has performed postgraduate education courses; "Antimicrobial Stewardship: Measuring, auditing and improving", held bi-annually before "the European Conference on Clinical Microbiology and IDs", internationally[8]. It is pointed out that antimicrobial stewardship programs have mainly been implemented at the postgraduate level. Instead, it seems antimicrobial stewardship is likely to be more successful if started earlier with undergraduate programs, "at the time when knowledge, attitude, and behavior of professionals are being shaped" as stated by Pulcini *et al*[8].

For improving antibiotic usage educational programs should be based on the needs of the hospitals[1]. The effective element in one hospital may not be effective in another[8]. To optimize antibiotic selection and duration, there are written national guidelines. These guidelines cover systemic infections such as respiratory tract, urinary tract, intra-abdominal, skin and soft tissue infections, and as well, documentations for surgical prophylaxis[1]. The Cleveland Clinic published a guideline booklet (2012-2013) for antimicrobial usage[26]. The information given in the introduction section of that booklet was striking; in that the authors underlined that the materials were subject to change and appropriate medical judgements were necessary relative to individual patient's needs[5,26]. Meanwhile to improve antibiotic usage, Fishman in CDC's safe Healthcare Blog proposed some simple steps that could be overviewed for antimicrobial therapy[16]: (1) "Never treat viral syndromes such as acute bronchitis with antibiotics, even when patients demand therapy; (2) Use fluoroquinolones cautiously. Not only fluoroquinolone resistance is rising at an alarming rate, but this group of drugs causes resistance to many other antibiotics and is associated with the new more virulent strain of *C. difficile*; (3) Antibiotics used for surgical prophylaxis should rarely be given for more than 24 h; post-operative doses are not required in many cases; (4) Refine your antibiotic choice once culture data is available and always use the drug with the narrowest spectrum; and (5) Double coverage is rarely necessary once antimicrobial susceptibilities are known".

Empirical therapy is being started at the first visit of the patient. Soon after the hospitalization of the patient some additional laboratory data are also available. Bacterial culture and susceptibility test results are achieved in 48 h. So, all clinicians should review their initial antibiotic choises after sufficient laboratory data are in hand[1]. According to CDC (2015) for the management of antimicrobial therapy, below key questions have to be answered[1]: (1) "Does this patient have an infection that will respond to antibiotics? (2) If so, is the patient on the right antibiotic(s), dose, and route of administration? (3) How long should the patient receive the antibiotic(s)? and (4) Can a more targeted antibiotic be used to treat the infection (de-escalate)"?

At the beginning of therapy, broad-spectrum antibiotics which are effective to the most likely pathogens are started. The de-escalation means; knowing and collecting bacterial culture results of the organisms for later microbiological judgement while targeting streamlining to a more narrow-spectrum antimicrobial regimen 2-3 d later. This intervention is performed by the means of clinical status and culture results of the patient[27]. Thus, by definite or pre-emptive approaches to the pathogen, a decrease in antimicrobial resistance pressure and antibiotic costs could be achieved by de-escalation strategies[27].

Guidelines for antimicrobial usage

The guidelines for antimicrobial usage aim to encourage prudent prescribing of antimicrobials for empirical treatment of infections, and thereby improve the results of treatment, reduce drug related toxicities, and limit the emergence of resistant strains[28,29]. They contain advice on the appropriate initial management of common conditions and include route of administration, dose, and duration of treatment. Where a dose range is recommended, the patient's status should be considered to define the need for using higher doses in more severe infections and considering lower doses for certain patients' groups such as the elderly, those with a low body mass index, and those with liver and kidney failures[28,29]. Recommendations for antibiotics in medical prophylaxis are also given. Surgical prophylaxis documents are available separately[28,29].

Essentials of antimicrobial use guidelines

Dose optimization: Optimal dosing of antimicrobials depends on patient's age, renal function, weight, *etc*., and causative organism. Site of infections (endocarditis, meningitis, osteomyelitis, *etc*.), and PK and PD parameters are also have to be taken in account.

Continuous infusion of β-lactams, once-daily dosing of aminoglycosides, and increased dosing of fluoroquinolones for *Streptococcus pneumoniae* and for *Pseudomonas aeruginosa* in nosocomial pneumonia are good examples depending on PK and PD parameters[4,30].

Parenteral to oral conversion: To reduce the length of hospitalization and to lower the costs of antibiotics, switching from intravenous (IV) to oral (PO) therapy is recommended when patients become stable. Generally IV forms of antimicrobials are more bioavailable and have greater effects, meanwhile some oral forms of antibiotics provide high serum levels as comparable as parenteral forms[31,32]. Some antibiotics don't have an oral form, in such situations an oral antibiotic from a different class with similar spectrum of activity is adviced[33].

Combination therapy: Combination therapy is unnecessary when the pathogen and the susceptibility are known. Combination therapy is recommended for the prevention of resistance. When an organism load is heavy and when there is a high probability of mutational resistance during therapy, combination of antimicrobials are to be considered. Good examples which are supporting the combined anti-infective therapy are tuberculosis or HIV infection[4]. Other indication of combined antibiotic therapy is enterococcal endocarditis. Combination drug therapy in some situations may prevent or delay the emergence of resistance during exposures within the MSW[14].

Rifampin has good CSF penetration but selects resistant mutants when used alone, so its combined use with other antimicrobials is recommended. Rifampin with vancomycin combination in staphylococcal CSF shunt infections is accepted as the best choice[34].

Besides, some medications penetrate tissues better than others. For example, if the primary focus of *Pseudomonas* meningitis treated with meropenem is mastoiditis, it is advised to combine meropenem with an aminoglycoside antibiotic which penetrates to the skeletal system better.

Microbiology laboratory: For the identification of microorganisms and for the determination of bacterial susceptibilities, the clinical microbiology laboratory plays an important role. For qualitative susceptibility testing principles, national and international guidelines are used. Using disk-diffusion (Kirby-Bauer) techniques by measuring zone diameters, or by calculating MICs, ESBLs can be detected. For inducible clindamycin resistance of *S. aureus* D test is also performed with disk-diffusion method[4]. The detection of such parameters regarding resistance leads to the selection of appropriate antimicrobials.

Duration of therapy: To control the bacterial infection and prevent relapse, the duration of antibiotic therapy is to be sufficient. When optimizing therapy for an infection, one should consider the person's immune status, the infecting agent and the focus of infection. In most clinical scenarios, because the recommended duration of therapy depanding on the clinical situation is flexible, it is usually based on expert opinions[35]. To base the clinical decision on laboratory data, some biomarkers such as C-reactive protein or procalcitonin (PCT) have been increasingly studied[35]. Today, PCT is the only biomarker which has been generally accepted to help the decision-making in discontinuing antibiotic therapy in sepsis and pneumonia of adults. In clinical practice the advised use of PCT levels are the 1st day, 2nd or 3rd days, and every 48 h of antibiotic commencement until antibiotic discontinuation[36]. Meanwhile, the use of procalcitonin levels has not been excessively studied in all infection types. Besides, the high cost in determining procalcitonin level can limit its use[35].

Longer antibiotic therapy encourages the development or acquisition of antibiotic-resistant organisms. Ventilator-associated pneumonia has traditionally been treated for a long course (14-21-d). However, prolonged antibiotic therapy has caused the emergence of multidrug-resistant strains. It is also associated with high toxicity and high costs. In patient groups who are receiving antibiotics for shorter periods of time (8 d) antibiotic resistance is less common. The studies support that if the choise for initial antibiotic therapy is prudent, 8-d duration of therapy for ventilator-associated pneumonia may be appropriate, and the clinical course seems to be favorable after stopping antibiotics[37].

Emerging developments in antibiotic stewardship

In antibiotic stewardship programs the commonly used diagnostic test is PCT. There are also novel tests which are not used frequently, such as fluorescence *in situ*

hybridization and matrix-assisted laser desorption/ionization time of flight mass spectrometric analysis[1].

Recently, measuring antibiotic use as either days of therapy, or defined daily dose (DDD) is becoming favorable. With the use of DDD hospitals may have the opportunity to compare their antimicrobial consumptions with that of other similar hospitals[1,4].

DECISION MAKING IN CLINICAL PRACTICE

Study (clinical practice)[2]

The Center of Disease Control (CDC) evaluated hospitalized patients with the aim of improving inpatient antibiotic prescribing. They used a national administrative database, "MarketScan Hospital Drug Database", and CDC's "Emerging Infections Program" for the study[2]. First, judicious antibiotic usage was described. Second, the principles of improving antibiotic prescribing data were illustrated in selected clinical cases. Third, when antibiotic usage had been improved, the decrease in *Clostridium difficile* infections were estimated. The results of the study had been reported to the "National Healthcare Safety Network" with the findings of using selected antibiotics in variable lengths of time[2].

Scenario (decision making-1)[38]

An 83-year-old man with fever (38.7 ℃), dysuria, and chills is admitted to the ward. The patient's medical history and clinical examination findings are recorded. On the basis of symptoms and signs of the patient, the urine examination is found to be necessary. After observing urine microscopy, the physician has to decide starting IV antibiotic treatment with the diagnosis of severe urinary tract infection[38].

The most common pathogens of urinary tract infection are reviewed as *Escherichia coli* (*E. coli*) (60%), *Proteus mirabilis* (10%), and *Klebsiella pneumoniae* (10%) in people of that age. It is known that the microbiology laboratory of the hospital reports the susceptibility of common pathogens yearly. From those datas the physician can estimate that the sensitivity of the mostly used antibiotics will be as follows: Imipenem 100% third generation cephalosporins 95%, gentamicin 92%, second generation cephalosporins 75%, and ampicillin 40%[38]. The clinician wants to choose the antibiotic which is supposed to be matching with the *in vitro* susceptibility of the pathogen, to give the patient the best chance of recovery. However, you have been told by the head of the administration that third generation cephalosporins and imipenem are expensive, and they should rather not be the first choice if patient's clinical status is affordable[38]. With gentamicin treatment nephrotoxicity and ototoxicity develop in the ratio of 10%. In addition, there can be more severe side effects, and because of the patient's advanced age, the risk of nephrotoxicity can be high. On the other hand, the *in vitro* susceptibility pattern of the pathogen will be announced within 48 h, so that the clinician can change the antibiotic with the susceptible one[38]. According to Leibovici *et al*[38], "the thought that a healthy and active 83-year-old man will need hemodialysis because of a drug that you have prescribed is frightening; so the physician decide to order a second generation cephalosporin. Still, the clinician are not altogether satisfied with the fact that he has reduced the antibiotic coverage by 7%-15% because of his concern about the high costs and fear of side effects associated with other antibiotics[38]. He wishes that the balance of benefits and detriments of antibiotic drugs could have been weighed at leisure somewhere else and that you had evidence based guidelines to help him make a choice"[38].

Two days after admission, the *E. coli* isolate identified from urine sample of the patient is informed as susceptible to second generation cephalosporins and the patient is doing well as expected with the result. "But still the physician wonders whether prescribing a drug that affords less than the maximum coverage is the right thing to do", as Leibovici *et al*[38] emphasize. The authors also highlight that, "this may well slow down the development of resistance and give future patients (to whom you have a duty too) a better chance for an uneventful recovery but your main duty is to your present patient[38]. How do you balance the two duties? The important decision in antibiotic treatment turns out to be a choice between present and future patients"[38].

As antibiotic resistance increases, chosing prudent antibiotics for the empirical treatment of serious infections become even more difficult[39]. As stated by Retamar *et al*[39] "in such situations, physicians face a dilemma: To provide a very-broad-spectrum empirical coverage, accepting that on many occasions it will be excessive and might contribute to further resistance selection, or to use a narrower-spectrum empirical regimen, accepting that it may not cover the causative pathogen and might require correction once the susceptibility results are known".

Scenario (decision making-2)

A 52-year-old male was admitted to the emergency room at the fifth day of right inguinal hernia operation. He had 39.2 ℃ fever, erythematous rash on the right lower extremity and systemic signs of toxicity (tachycardia and hypotension). The surgeon learned that the patient became erythematous at the site of the surgical wound the third day. He examined the patient; opened the incision and observed the wound as deceptively benign in appearance and obtained culture specimen from the wound. The ID specialist diagnosed the patient as septic shock and moved the patient to the intensive care unit (Özgenç O; unpublished data).

In patients with clean extra-abdominal operations, surgical site infections (SSIs) are generally seen in the ratio of 2%-5%. This ratio can reach up to 20% in abdominal surgery[28]. Surgical complications associated with infection at the site of incision generally are not

visible till two weeks. Some small portion can be apparent in five days after the operation. Late infections are less probable but 30 d period of following-up of infectious complications are recommended[40].

In this situation, how could the surgeon evaluate the patient? (1) Not all postoperative fevers are related to SSIs and there could also be non-infectious erythematous signs around the surgical incision; (2) Soft-tissue infection within the 48-72 h after an operation is not common and an infection can rarely cause fever; and (3) In this respect, could the surgeon exclude the possibility of SSI for this case? The answer is no. After two days the microbiology laboratory reported that *S. aureus* has grown from the culture of the above mentioned patient's wound specimen.

Early post-SSIs are due to *Streptococcus pyogenes* or *Clostridium* species[40]. When high fever is measured or systemic signs of infection are observed in few days after surgery, direct examination of the wound is necessary[40]. Toxic shock syndrome is another rare cause of early SSI due to staphylococci[40]. In such cases the wound misleads to benign appearance, although there is serious infection beneath the incision site. Erythroderma may be seen early in the course of the infection. Fever, hypotension, hepatic and renal impairment, and sometimes diarrhea may also be the early findings. Before beginning antistaphylococcal therapy, the incision should be opened and specimen for culture should be obtained[40].

This presented scenario highlights that knowledge is as important as experience. The physician has to know all the clinical aspects of surgical manipulations which may lead to early or late SSIs, or to some other complications. "The devil is hidden in the individual details" as stated by Fishman[41]. These hidden details could be lightened by the experienced and well-informed ID specialists.

OVERWHELMING ANTIBIOTIC RESISTANCE - KNOWLEDGE AND EXPERIMENTATION

"The Antibiotic Resistance Monitoring and Reference Laboratory" have shown that during the last decades, resistance to antibiotics have shifted from Gram-positive to Gram-negative bacteria. With the development of new antimicrobials and with strict infection control policies, resistance to MRSA has fell down. New antibiotics; daptomycin, linezolid, and tigecycline, active against MRSA have been discovered[42]. After the development of conjugate vaccine, the resistance problem to pneumococci has seemed to be declined. The problem with enterococci is greater. In serious manifestations with enterococci such as in endocarditis, high-level aminoglycoside resistance is great concern since bactericidal activity is needed. In this situation, the clinician refers to daptomycin's bactericidal effect with its high activity[42].

With Gram-negative pathogens the resistance rate is twice that of Gram-positive bacteria[17]. The spread of extended spectrum β-lactamases (ESBLs) in Enterobacteriaceae have resulted cephalosporin resistance to go up[43]. In severe infections with ESBL-positive bacteria cephalosporins have not shown good clinical outcomes. Moreover, in the last decade there have rosen a problem with the striking emerging of CTX-M ESBLs. Although TEM and SHV ESBLs have associated with *Klebsiella* spp., CTX-M types confine to *E. coli.* The CTX-M ESBLs have both spread amongst hospital and community patients. They are mostly isolated from elderly patients and from patients who have hospital contacts[17].

The most CTX-M positive *E. coli* is resistant not only to cephalosporins, but also to quinolones and trimethoprim-sulfamethoxazole which are commonly used antimicrobials for the treatment of urinary tract infections[44]. Instead, susceptibility rates indicate that fosfomycin and nitrofurantoin can be considered as important oral treatment options for the treatment of uncomplicated urinary tract infections[44]. By the way, there is concern about the rise of rapid and disturbing spread of ESBLs, Amp C enzymes, and quinolone resistance against Enterobacteriaceae. Carbapenem resistance, caused by *Klebsiella pneumoniae* carbapenemases, metallo-β-lactamases, and OXA-48 is decreasing reliance on carbapenems[17,42]. Last, the gonococcus is also developing resistance to most antibiotics (fluoroquinolones and cefixime) wich can easly be used orally[17].

In the last decades third-generation cephalosporins and fluoroquinolones were used alone for urinary infections in many hospitals. This phenomenon has also resulted in selection of resistant mutants such as *C. difficile*[17]. Thus, the use of β-lactamase inhibitor combinations has been increased; principally piperacillin/tazobactam and amoxicillin/clavulanic acid 3-4 fold[17]. Piperacillin/tazobactam shows less selective pressure than cephalosporins for *C. difficile,* and also produces less selective pressure for vancomycin-resistant enterococci, and for some ESBL-producers, than cephalosporins do[17].

On the other hand, another important antimicrobial resistance mechanism is the expression of chromosomally encoded multidrug efflux pumps[45]. During fluoroquinolone monotherapy of *P. aeruginosa* infections, these efflux producing mutants can be selected and especially if the given drug dosages are not adequate, fluoroquinolones can select multidrug-resistant organisms. Therefore, in the treatment of serious infections among hospital patients, the usage of fluoroqinolones can be limited[46].

For the treatment of serious infections by ESBL-producer microorganisms, carbapenems remain as almost only active drug choise[42]. Because of the fact that cephalosporin resistance in Enterobacteriaceae has risen, carbapenem use has increased[43]. This increased use of carbapenems has resulted in carbapenemase

enzymes selection which are much more commoner in non-fermenters than in the Enterobacteriaceae. The carbapenemases are mostly produced by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, due to OXA carbapenemases and to chrosomal mutations in the non-fermenters, respectively[42]. Meanwhile, against carbapenemase-producers, colistin, tigecycline, and fosfomycin are the treatment options with some adverse effects such as toxicity and resistance[17].

To delay antibiotic resistance, heterogenous use of different antimicrobial classes within a period, can be preferred. Prescribing antibiotics from different groups in equal proportions are shown to be effective for preventing the dissemination of multi-drug resistant pathogens[47,48].

Antibiotic resistance has become a major public health priority[42]. In this respect, Australian Government has announced "the first National Antimicrobial Resistance Strategy for the years of 2015-2019", for "antibiotic misuse and resistance" (AMR)[49]. Because the prevalence of AMR is increasing all over the world, there is a great concern that we will be out of treatable antibiotics. The World Health Organization and other authorities are aware of the fact that pharmaceutical industry is far beyond the increasing resistance pace of microorganisms for to develop new anti-infective drugs against them[49]. So, the physicians should achieve wide knowledge and experience regarding multidrug-resistant bacteria, to prevent the failure of treatment of IDs both in the hospital and in the community.

IMPORTANCE OF ANTIMICROBIAL SURVEILLANCE PROGRAMS

Antimicrobial surveillance programs (SENTRY, MYSTIC, European Antimicrobial Resistance Surveillance System, *etc*.) have become necessary for to control antimicrobial resistance and to guide appropriate clinical decisions for anti-infective therapy[50]. From antimicrobial surveillance studies there can be obtained many information serving for antimicrobial resistance data. These programs detect emerging and changing resistance problems and patterns, as well guide appropriate antimicrobial therapy, based on antibiotic susceptibility data. These findings and results will help to the progress of the development of new antibiotic compounds[50].

CONCLUSION

In summary, selection of the appropriate antimicrobial depends on understanding of the likely pathogens and local susceptibility patterns. In choosing the right antibiotics, the properties of the antimicrobials; such as PK and PD profiles, activity and potency, tolerability and safety, are all important factors[51]. For the treatment of serious infections, the prudent antibiotic with the narrowest spectrum should be started early with the right dose, and should be given for an adequate duration. These antibiotic implementation principles early in the ID course, play the key role in initial appropriate antibiotic prescribing[19,51]. By the way, initial appropriate antibiotic treatment has been shown to reduce mortality, length of stay in intensive care unit and hospital. Early correct antibiotic choses have also served to the reduction in antimicrobial costs[19,51]. In this respect, it is underlined that ID service being an expert in the field, plays an important role in improving antimicrobial usage, by giving advice on the judicious use of antimicrobial agents and by developing evidence-based guidelines under the light of antibiotic implementation policies[50,52]. The ID specialist in his tough way can adopt antibiotic resistance as a "chronic disease", instead of trying to overwhelm it[53].

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