Facets for the Relevance, Prevention and Resistance of Antibiotics, albeit it’s the Foremost Confrontation for the Heath Care Professionals

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Abstract

Anti-biotics are not quite the same as different medications in a way that when they are administered to human, they kill bacteria. Antibiotics also seems to produce its action against normal flora which are very necessary for the physiological function of skin, mucosa, digestive system, vagina etc. The use of antibiotics and evolution of bacterial resistance are interconnected, and it has been demonstrated at various occasions, therefore it should be taken into account. The research projects proposed are ranked to favor those with clinical and epidemiological goals. They can be divided into 2 classes: (1) analytical studies of available data and (2) trials providing an answer to a specific public health problem. This project deals with the brief knowledge about development of antibiotics resistance and how resistance develop by various factors and thoroughly analyzing populations that are exposed to antibiotics, also it covers all the possible aspects for controlling the development of antibiotics resistance and to prevent irrational use of antibiotics.

Keywords: Antibiotic Resistance; Overview; Control Of Antibiotic Resistance; Mechanism of Resistance

Introduction

The emergence of antibiotic-resistant organisms is a main public health concern, more specifically in hospitals and other health care services [1,2]. Antibiotic-resistant organisms are capable of causing serious or fatal infections which are difficult to treat because of limited choice of antibiotics. This raise in the frequency of drug-resistant pathogens while at the same time, the detection and development of new anti-infective agents is declining unexpectedly [2]. Consequently, there is concern that in foreseeable future, we may be exposed with a growing number of potentially fatal infections. In the past several years, various antibiotic resistant bacteria species have been documented as causes of severe life-threatening infections in the hospitalized patients.

The Genetics of Antibiotic Resistance

The genetic encoding of proteins and ribosomal RNA, empowers pathogenic bacteria to overcome antimicrobial therapies. Such antibiotic resistance may either be intrinsic or acquired [3]. Intrinsic resistance is directly linked with the determinants of the organism’s characteristics or with the “usual” chromosomal genes. However, due to the alteration in the genetic composition of organism antibiotic opposition occurs. This could be due to 1 of 2 mechanisms: there may be mutation in the bacterial chromosomal DNA, or it could be due to attainment of new genetic information. Mutations are frequently rare events, which may occur at a frequency of 1 event per 107–1010 bacteria, but it may lead to the emergence of resistance during antibiotic therapy in organisms which were previously susceptible [3].

This type of antibiotic resistance is more clearly understood by ionized resistance which is develop by Mycobacterium Tuberculosis. This sort of resistance is unmovable to other organisms. The probability of multiple resistance mutations occurring in a single organism is equal to the product of their individual probabilities. This is the explanation for the subsequent benefit of combination therapy for the treatment of tuberculosis. Likely, the superior concern is the emergence of resistance because of the addition of new genetic material. Genes intervening antimicrobial resistance may originate on interchangeable portions of DNA such as plasmids, transposons or integrons [3]. Plasmids are transmissible between organisms and it may provide survival benefits to an...
organism. There are few plasmids which carry genetic information that permits an organism to attain a new antibiotic-resistance mechanism. Transposon is a DNA sequence which is capable of being transported from one bacteria to another. Integron is a huge mobile genetic element that can be transported from one organism to another. Integrons are often consist of large number of gene clusters, which often include multiple factors of antibiotic resistance. Intrinsic resistance is mainly an antibiotic resistance in an organism whose innate chromosomal (genetic) constitution probably specifies resistance. Intrinsic resistance happens in an organism for the reason of mutation in its genetic composition or because of the attainment of a new genetic information leading to the emergence of a new means of resistance [3].

**Mechanisms of Antibiotic Resistance**

Antibiotic achieve its action by interacting with certain special bacterial targets, inhibiting bacterial cell-wall synthesis, protein production or nucleic acid replication. Antibiotics must bind to its specific bacterial target site for the destruction of bacteria. The occurrence antibiotic resistance is either intrinsic or acquired, there is encoding of specific biochemical resistance mechanism on the genetic code of bacteria which may include inactivation of antibiotics by enzyme or changes in the configuration of antibiotic binding locations, and alterations that does not allow the entree of satisfactory concentration of the antimicrobials to the target site (Table 1) [3].

**Antibiotic inactivation by Enzyme**

Bacteria produce enzyme that destroy the activity of antibiotic which renders antibiotics ineffective. The enzymatic drug inactivation mechanism is best understood by the β-lactamase group of enzymes. The enzyme, β-lactamase leads to the hydrolysis of the β-lactam ring of penicillins, cephalosporins and carbapenems. There are hundreds of β-lactamase enzymes depending upon the substrate they bind and response they produce. Some β-lactamase genes are chromosomal, while others are positioned on plasmids or transposons. Production of β-lactamases enzyme in bacteria results in emergence of Penicillin resistance in S. aureus and Neisseria gonorrhoeae, ampicillin resistance in Haemophilus influenzae, and resistance to extended-spectrum cephalosporins in E. coli and Enterobacter species. Resistance to extended-spectrum cephalosporins (e.g., cefotaxime, ceftriaxone, and ceftazidime) has been evolved primarily by1 of 2 mechanisms, both of these mechanism involve the synthesis of β-lactamases [4]. Plasmid mediated extended-spectrum β-lactamases are synthesized by E. coli and Klebsiella species, and it is for the reason of the mutations in the TEM, SHV or CTX-M genes(Ambler class A β-lactamases). AmpC cephalosporinases is responsible for this emergence of resistance, in other gram-negative bacilli, such as Enterobacter, Citrobacter or Serratia species [5]. Both resistance mediated by Ambler class A extended-spectrum β-lactamases and AmpC are linked with cross-resistance to penicillins and

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<thead>
<tr>
<th>Mechanism</th>
<th>Resistant Organism</th>
<th>Antibiotic affected by resistant organism.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Antimicrobial inactivation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a- Beta-Lactamase</td>
<td>• Staphylococcus aureus.</td>
<td>• Penicillin.</td>
</tr>
<tr>
<td></td>
<td>• Haemophilus Influenzae.</td>
<td>• Cephalosporin.</td>
</tr>
<tr>
<td></td>
<td>• Enterobacteriaceae.</td>
<td></td>
</tr>
<tr>
<td>b- Aminoglycoside inactivating enzyme.</td>
<td>• Enterobacteriaceae.</td>
<td>• Gentamycin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tobramycin.</td>
</tr>
<tr>
<td>2-Altered Target Site:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a-Altered penicillin binding protein.</td>
<td>• Streptococcus pneumonia</td>
<td>• Penicillin.</td>
</tr>
<tr>
<td></td>
<td>• Methicillin resistant staphylococcus</td>
<td>• Methicillin.</td>
</tr>
<tr>
<td></td>
<td>aureus.</td>
<td>• Cloxacillin.</td>
</tr>
<tr>
<td></td>
<td>• Enterobacteriaceae.</td>
<td></td>
</tr>
<tr>
<td>b-Altered DNA gyrase or topoisomerase.</td>
<td>• Streptococcus pneumonia</td>
<td>• Ciprofloxacin.</td>
</tr>
<tr>
<td></td>
<td>• Enterobacteriaceae.</td>
<td>• Levofloxacin.</td>
</tr>
<tr>
<td></td>
<td>• Pseudomonas aeruginosa.</td>
<td>• Moxifloxacin.</td>
</tr>
<tr>
<td>3-Decreased Access To the Target Site:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a-Change in the outer membrane protein.</td>
<td>• Enterobacteriaceae.</td>
<td>• Gentamycin.</td>
</tr>
<tr>
<td></td>
<td>• Pseudomonas aeruginosa.</td>
<td>• Tobramycin.</td>
</tr>
<tr>
<td>b- Efflux Pump</td>
<td>• Staphylococcus aureus.</td>
<td>• Tetracyclin.</td>
</tr>
<tr>
<td></td>
<td>• Streptococcus</td>
<td>• Clindamycin.</td>
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<td></td>
<td>• Erythromycin.</td>
</tr>
</tbody>
</table>

Alteration of the Antibiotic Target Site

Antibiotic produce its action by binding to its specific bacterial target site. An alteration in the structure of the target of the bacterial cell prevent the binding of antibiotic to its desired location. For instance, the β-lactam antibiotic agents like the effect of penicillin rises when it joins with the penicillin binding protein, located on bacterial cell wall. Methicillin resistant strains of S. aureus (MRSA) contains different genetic constituent called as staphylococcal cassette chromosome mec (SCCmec), having the mecA gene that programs the synthesis of an altered penicillin-binding protein (PBP2a). This altered penicillin-binding protein (PBP2a) never binds successfully with β-lactam antibiotics [7]. And due to this reason, there is development of resistance by the MRSA to currently available penicilins, cephalosporins and carbapenems [8]. One more example of resistance to antibiotic triggered by a change in the target site is the ineffectiveness to the fluoroquinolones (e.g. levofloxacin and moxifloxacin). Fluoroquinolones overcome the bacterial infection by hindering proteins called DNA gyrase (encoded by gyrA and gyrB genes) and topoisomerases (encoded by parC and parE), which are essential for bacterial DNA replication. Mutations in particular areas of the gyrA or parC genes (recognized as the quinolone-resistance determinant region) result in alterations to DNA gyrase or topoisomerase, and subsequently leads to alteration to the binding site [9].

Prevention of Antibiotic Access to the Target Site

Antibiotics work when they bind to its target site with satisfactory concentration. Bacteria develop resistance also by efflux pump mechanism or because of a permeability barrier which hinders the entry of appropriate concentration of antibiotic to its target site which renders the antibiotic ineffective. The cell wall of gram-negative bacteria is made of internal and external membranes, and these membranes act as a permeability barrier. Gram negative bacteria are provided with some special protein (porins) present in their cell wall, which permits the movement of necessary molecules inside in the cytoplasm including antibiotics by the process of diffusion. Transformations in the structure of outer membrane proteins can give rise to permeability barrier that hinders the access of antimicrobial agents to their active site. This process may describe for resistance to β-lactams and aminoglycosides in P. aeruginosa and other gram-negative bacilli [10]. Instead of blocking the penetration of antibiotics to the active site, some organisms have developed an active efflux apparatus which expel out antibiotics from the cytoplasm of the bacterial cell before they attach to their target binding site [11]. These efflux apparatus or efflux pumps are seen in both gram-positive and gram negative organisms. These pumps are involved in emergence of resistance to clindamycin, aminoglycosides, macrolides (e.g., erythromycin), tetracyclines and fluoroquinolones. Certain pumps could be specific for just 1 class of antibiotics, while others could work against multiple drugs.

Selective Antibiotic Pressure

Selective antibiotic pressure involves the environmental settings which permit the organism with certain attributes to proliferate and remain alive. Subjection to an antibiotic may kill or inhibit the large number of the bacterial population which are vulnerable. However, a resistant group of microorganisms may remain alive or they aren't inhibited by antibiotics. That group of bacteria may have acquired resistance, or they may be inherently resistant to the antibiotic. Thus, the usage of antimicrobial, depends on the appearance of resistant strains of organisms which may then proliferate and turn out to be predominant. As a matter of fact, the emergence of antimicrobial resistance in community and health care area is predominantly determined and exaggerated by the selective pressure of antimicrobial use [12]. There are countless examples which demonstrate the direct relationship between antimicrobial use, both appropriate and inappropriate, and antimicrobial resistance at both the individual patient level and population.

Selected Antibiotic-Resistant Organisms in Hospitals

Multidrug-resistant gram-negative bacilli

Mostly the multidrug-resistant gram-negative organisms are inactive to penicillins (including those combined with a β-lactamase inhibitor), cephalosporins, trimethoprim-sulfamethoxazole, aminoglycosides and fluoroquinolones. Few of the strains are also resistant to the carbapenems, usually leaving colistin as only choice of antibiotic for the treatment of the infections [13]. Acinetobacter is usually resistant to majority of antibiotic classes, leaving carbapenems, and possibly glycylcyclines (tetracycline derivatives such as tigecycline), as the only useful antimicrobial agents [14].

Vancomycin-resistant Enterococcus

The emergence of resistance by enterococci against Vancomycin is due to addition of a plasmid-associated gene cluster, mostly the vanA or vanB genes. These genes are responsible for the synthesis of altered cell-wall precursors which are unable to bind glycopeptide antimicrobial agents [15]. These genes are also exchangeable and even can extend from enterococci to MRSA, as a result of which they can further complicate the treatment of infectious disease caused by this microorganism [16].
Methicillin-resistant Staphylococcus aureus

At present, MRSA is the frequently recognized antibiotic-resistant bacteria in the patients admitted to the hospital [17]. Until recently, MRSA was considered to be primarily a nosocomial pathogen, affecting older adults with comorbidities in long term care settings or hospitals. Community associated-MRSA may cause infections at any site but are most frequently linked with soft tissue and skin infections, including furunculosis, pustulosis, and abscesses.

Clostridium difficile

C. difficile is the most common infectious cause of nosocomial diarrhea. Noticeably increased disease rates (as high as 156 cases per10,0000 people) and severity occurred, especially among elderly people. In this outbreak, there was often a poor response to metronidazole therapy [18,19]. The appearance of such several disease is thought to have occurred because of the presence of a hyper virulent epidemic strain of C. difficile, known as PCR ribotype [20], or North America pulso-type 1 (NAP1) [21].

Analysis of Population Exposure to Antibiotics

Regardless of inter country discrepancy in the amount of antibiotics used, increase in the utilization of antimicrobials has been pragmatic in several developed countries during the past 20 years [22-24]. For example, it has been discovered that at day 200 after birth, 70% of children have received at least 1 antibiotic [25]. Additionally, both in the hospitals and in community, there is communal indication that the main factors responsible for promoting acquired resistance is antibiotic exposure to populations [26-28]. It is therefore expected that resistances to antibiotic that will emerge and spread tomorrow is due to the current revelation of populations to antibiotics [28,29]. Therefore, although descriptive studies are not proposed to confirm scientific hypotheses, so the first step should be the clarification and monitoring over time of antibiotic exposure to population and of bacterial resistance. Such investigations should approximate the exposure quantitatively, focusing on aspects such as classes of antibiotic, dosage form, dosages, durations of treatment and administration protocols. This requires the extension of standardized measures for expressing qualitative and quantitative exposures of antimicrobial agents to humans and animals, thus enabling us comparisons over time as well as geographic comparisons. Additionally, the reasons for and modalities of exposure in the particular population (e.g., children in day-care centers, elderly in nursing homes, agricultural animals or hospitalized patients) should be recognized. Resistance monitoring of bacteria should be done both for samples from infected individuals as well as the commensal bacterial flora (pathogenic or nonpathogenic), which could characterize a pool of resistance genes. To case the ecological impact of a particular class of antibiotics, it might be wise to generate model systems of populations exposed to the antibiotics (e.g., patients with sickle cell anemia [penicillins], cystic fibrosis [macrolides], HIV infection [cotrimoxazole] or acne [tetracyclines]) by initiating standardized, prospective monitoring of population. It would be advantageous to encourage monitoring of antibiotic use, combined resistance, and reasons for prescription with use of standardized observation units (region wide, nationwide, institutions or individuals , or countywide). The data generated after monitoring should be collected and validated regularly in order to create linkage between antibiotics prescription, clinical databases and bacterial resistance [30]. Although it has been claimed that resistance to antibiotic increases financial costs of treatment, mortality and morbidity [31,32], probable effects remain inadequately documented. For that reason, it seems essential to promote research in these areas. Nosocomial bacteremia, Pulmonary infections, infections of prosthetic devices and acute middle-ear infections would be pertinent for such studies. Moreover, with regard to alterations in usage of antibiotic, it would be advantageous to have a better understanding and awareness of the behavioral motivations of the different persons involved (patients and their relatives, practitioners, animal breeders, farmers and veterinarians) in connection with a change in prescription pattern of antibiotics [33-38].

Understanding and Quantifying Risk of Emergence and Dynamics of Transmission of Resistance

The progression of bacterial resistance to antibiotics in animals, humans and the environment is the consequence of the interaction between antibiotics exposure and resistance genes transmission between bacteria, but also between exposure to antibiotics and direct or indirect conduction of resistant bacteria between individuals. This progression depends on the social habits and on environment [39] and for that reason requires an epidemiological approach, as for any community health related problem. Resistance should be viewed from a risk point of view and analyzed crucially in terms of probabilities within populations. Studies planned to elucidate the dynamics of transmission of resistance should travel around not only inter human or to-human transmission but also animal-to-animal, human-to-plant, animal-to-plant and human-to-animal dissemination, with particular prominence on environmental pathways. In particular, they should deal with the following issues. (1) The factors influencing the transmission of resistant bacteria extrinsic [e.g., lifestyle], (intrinsic [e.g., virulence] [40] or environmental [hospital, day-care center, etc.]) should be recognized [41], as should ecological advantage (s), in terms of dissemination, that resistant strains might have in comparison with their susceptible counterparts [40,42] and the host–bacteria relationships (e.g., factors affecting bacterial carriage) [39]. For example, research into the resistant bacteria transmission from hospital-to-community should be encouraged. (2) The reservoirs (animals, plants, humans and the environment, including water and soil) of resistance genes and of resistant bacteria should be identified [43]. (3) The cost to the survival of bacteria in a unfriendly environment (fitness), i.e., the biological cost of acquirement of resistance to antibiotics [44,45] The very confined knowledge we have about development of bacterial resistance in their natural environment requires the expansion of research programs on the transmission of resistance within a given environment.
and similar ecosystem in animals and humans (airways, digestive tract etc.). Additionally, epidemiological studies of animals and humans should be encouraged to analyze, qualify and quantify the risk factors related with spread and emergence of resistant bacteria and to develop models mathematically for these phenomena that take into account both exposure to antibiotics and inter individual transmission [46-50]. These investigations should reflect on the various levels of selective antibiotic pressure (cellular, individual, population and genetic).

Best Strategies in Antibiotic Use to Slow Development of Resistance

Regardless of the perceptible steadiness of resistance genes’ prevalence even in the absence of exposure to antibiotics, some studies advocate that decreasing usage of antibiotic to overturn bacterial resistance in human populations is attainable, both in the hospitals and in community [28-32]. Because of the requirement to treat infections caused by bacteria, diminishing antibiotic use to zero is neither practical nor enviable. The goal of this approach is to achieve desirable outcome for the patient with the minimalization of the resistance development. Commercially available antibiotics and reversibility of resistance. It is desirable to conduct studies, such as pharmaco epidemiological trials, that will try to exhibit and estimate the opportunity of delaying appearance of resistance, restrictive its spread, and reversing its increase [51]. Only this sort of approach can distinguish between occurrence of a particular phenomenon (e.g., an epidemic) and natural evolution and disclose the impact of modification of antibiotic use. By modification of use of antibiotic resistance rate is going to be decrease [50-54]. It is essential to assess very early the potential for selection of resistance of new molecules in comparison with the potential for members of the same class that are already available, as well as to describe and better forecast therapeutic schemes that, at the same efficiency, will be less selective. This requires the development of experimental animal models so that all these questions can be answered at a preclinical phase of a drug’s development. An excellent example of a therapeutic class of antibiotics “at risk” is the fluoroquinolones [28,55]. A quite large number of new fluoroquinolones with superior activity against gram-positive cocci are striking the market simultaneously. Because of this reason they will be overprescribed in the coming years which will results in a very high selective pressure toward resistance in both gram-positive and gram-negative bacteria. Clinical trials should be considered that take into deliberation both bacterial ecology and clinical efficacy as criteria for comparison of therapeutic strategies.

Promoting Research on Diagnostic Tests

One of the major factor that need to be modified in order to better control resistance is use of antibiotics irrationally. This requires the provision to prescribers of tools that allow fast distinction between viral and bacterial infections. To provide prescribers with routine diagnostic tools for detection of bacterial infection qualitatively and quantitatively with optimal predictive values would definitely improve the adequacy of prescribed antibiotics for valid bacterial infection. Therefore for appropriate prescribing of antibiotics these tools i.e. research, development, and improvement of tests for the rapid diagnosis of bacterial infections and detection of resistance to antibiotics are recommended [56].

Promoting Research on New Anti-Infective Agents

There are various strategy to prevent increasing resistance to antibiotics. One of them is the development of novel anti-infectious approaches to prevent increasing resistance to antibiotics. However, it is crucial to investigate original and new anti-infectious approaches-for example, to promote research on vaccines [57]. One should also focus on antibiotic therapy to address specifically the micro-organism responsible for causing infection rather than to effect normal flora of the patient. This allows the advantage of the “barrier effect” exerted by the resident indigenous bacteria that oppose colonization and invasion by exogenous microorganisms. It can be estimated that antipathogenicity drugs that convert pathogenic and harmful bacteria into nonpathogenic microorganisms may well turn out to be the most narrow-spectrum antimicrobial agents. These drugs are not lethal and should also be less subject to resistance but these drugs simply limit the growth in certain mammalian ecosystem. Another need is new classes of antibiotics with new mechanisms of action that are not subject to cross-resistance with molecules that are already in use [58]. The discovery of such drugs should be facilitated by the accessibility of the sequences of entire bacterial genomes, which provide new targets, and of a series of powerful techniques such as virtual screening, computer-assisted drug design, high-throughput screening of in vitro activity and combinatorial chemistry. Finally, delivery of antibiotics to the target site or targeted delivery of antibiotics that acts on the pathogenic and virulent bacteria at the site of infection, while sparing the microbial ecology strategies (barrier flora, “probiotics”) and commensal flora can also contribute to a decrease in the use of antibiotics [59].

Summary

The burden of antibiotic resistance continues to increase drastically and is recognized to be a major threat to the treatment of infectious diseases, mostly among patients in hospital. The reasons for the variability in resistance rates around the world is unknown but may be related to differences in diagnostic procedures, patterns of antimicrobial use or infection prevention and control practices. Other important gaps in our knowledge include uncertainty about how understanding specific mechanisms of resistance may lead to the identification of novel targets for new antimicrobial drug development. A better understanding of the relative importance of selective pressure related to antibiotic use compared to cross-infection as mechanisms for emergence and spread of antimicrobial resistance would also be important to design and evaluate effective infection prevention and control strategies. Infections caused by antimicrobial-resistant organisms are almost always related with prolonged hospital stays, increased attributable mortality and excess costs [60]. These interventions must include attention to hand hygiene, enhanced surveillance of antibiotic resistance and...
other standard infection prevention and control measures, and antibiotic stewardship to ensure appropriate use of antimicrobial agents [61,62]. Several articles on the control of bacterial resistance have been published during the past 5 years. Research should not delay action but rather should be associated with action. On the one hand, there is a gap between the theoretical models and fundamental data and, on the other hand, the hard facts of bacterial resistance in populations. That's why the expert panel insisted on the need for clinical and epidemiological research. We suggest that the consequences of bacterial resistance need additional analysis and efforts. Since the appearance of various publications on the alarming aspects of resistance, which echoed widely in the media [60,61], the scientific and medical communities have become mobilized. Despite these efforts, new resistances have emerged and known resistances have spread [62]. Since the determinants of the evolution of resistance to antimicrobial agents and the possibility for reversing this evolution are not completely understood, any public health policy on this matter must be associated with active promotion of research. The results of various fields of investigation could have a direct impact on the mastering of bacterial resistance or could contribute to rapid decision-making. As a result of which an active multidisciplinary approach, the return to the “pre-antibiotic era,” which means no antibiotic use but no resistant bacteria, could be delayed.

References