ijmps

Vol 04 issue 04
Section: Healthcare
Category: Review
Received on: 17/10/13
Revised on: 15/11/13
Accepted on: 18/12/13

ANTIBIOTIC DRUG RESISTANCE: CURRENT GLOBAL ISSUE

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ABSTRACT

Life-threatening infections caused by microorganisms (Bacteria) that have become resistant to commonly used antibiotics have become the most important universal healthcare problem in 21st century. It is more severe, need longer and more complex treatments, but is also extensively more expensive to diagnose and treat. Antibiotic resistance, a major problem of hospital acquired infections generally in immunosuppressed and seriously ill patients, has now spread into the community causing severe infections difficulty to detect and treat. In the year 2011 approximately 630 000 cases of MDR-TB were predicted. Worldwide, 3.7% of new cases and 20% of formerly treated cases are estimated to have MDR-TB, with large differences in the incidence of MDR-TB between countries. The fourth generation antibiotics are resistant to nearly 70% of the community-acquired infections which is a dangerous trend. The most frequent type of resistance is conjugation of a plasmid and enzymatic inactivation of the antibiotic. There is a chance that more new biological mechanisms of resistance will develop in the future. Thus there is a need for the pharmaceutical companies and researchers to develop new antibiotics that shows a long-term extent of activity against bacteria.

Keywords: Antibiotic resistance, Epidemiology, conjugation, receptor modification, Antibiotic research

INTRODUCTION

Antibiotic: Antibiotics constitutes one of the most significant contributions of modern science. The discovery of these life-saving drugs transformed the health-care scene during the last century. The ability to treat bacterial infection is critical in modern medicine, starting from abdominal surgery to transplantations, cancer management etc. Without antibiotics, these treatments are impossible owing to the infection risk. Selman Waksman (1942) defined antibiotics as low molecular weight chemical substances produced by microorganisms, having growth-inhibitory activity on other microorganisms in high dilution. However in the present context, any chemical substance either of microbial, synthetic or semi-synthetic origin, used in the clinical treatment of infections, is called antibiotic. The antibiotics field was initiated when Paul Ehrlich first coined the term ‘magic bullet’, or chemotherapy, to designate the use of antimicrobial compounds to treat microbial infections. In 1910, the first antibiotic drug “Salvarsan” was discovered by Paul Ehrlich, which was used against syphilis.

In the last 60 years, a major progress in the early detection and the treatment of infectious disease has resulted in a notable decline in the morbidity and mortality associated with these illnesses. This has been due, in part, to our improved understanding of the mechanisms of fine molecular biology and to our better understanding of their pathophysiology and epidemiology of

these diseases but, most prominent, to the fast development of secure and effective new anti microbial treatments that have been able to attack the specific agent causing the infection, thus helping the infected host to remove the infection being treated. [1]

This review tries to provide an outline of the serious problem of antibiotic resistance in the 21st century and to open a new casement into the complex challenges of new antibiotic development in the future. The first cases of antimicrobial resistance (Antibiotics Resistance is the reduction in effectiveness of a drug such as an antimicrobial or an antineoplastic in curing a disease or condition. When the drug is not intended to kill or inhibit a pathogen, then the term is equivalent to dosage failure or drug tolerance) [1] occurred in the late 1930's and in the 1940's, soon after the introduction of the first antibiotic classes, sulfonamide and penicillin. Within a very short span of time, the strains of staphylococcus aureus became resistant to these classes of antibiotics. After the introduction of the first antibiotics, throughout the first 25 years, resistance was one of the major problems for the hospitalized patients.

The list of bacteria developing resistance is significant, from sulfonamide and penicillin-resistant Staphylococcus aureus in the 1930's and 1940's [2] to penicillin resistant Neisseria gonorrhoeae (PPNG), and β-lactamase producing Haemophilus influenzae in the 1970's, [4][5] methicillin- resistance Staphylococcus aureus (MRSA) and the renaissance of Multi-Drug Resistance (MDR) Mycobacterium tuberculosis in the late 1970's and 1980's,[6][8] and numerous resistant strains of general enteric and non-enteric gram–negative bacteria such as Shigella sp., Salmonella sp.,Vibrio cholera, Acinetobacter baumannii, Pseudomonas aeruginosa, E. Coli, Klebsiella pneumoniae.

Recently we have also witnessed the report of very difficult cases of formerly unthinkable resistance as well as the spread of resistant bacteria outside the hospital causing community-acquired infections. Such is the case for the strains of Group A Streptococcus becoming resistant to macrolides antibiotics,[9][10] Streptococcus pneumoniae developing resistant to different antibiotic classes, including penicillin, and causing serious infections [11][12] and more virulent strains of MRSA (due to the appearance of certain toxins such as the so-called Panton-Valentine leukocidin) spreading to the community [6][7][13][14]as well as staphylococcus aureus and Enterococci becoming resistant to vancomycin.[15][16] One of the last resorts in the clinical management of infections was caused by multidrug-resistant organisms. The organisms were believed to be originated from India. That is why the enzyme was named New Delhi Metallo β-lactamase (NDM-1). Some of the other most important types of multiple drug-resistant organisms include extended-spectrum beta-lactamase producers (which are resistant to cephalosporins and monobactams) and penicillin-resistant *Streptococcus pneumoniae*. Studies on resistance in soil bacteria have shown that these organisms serve as a reservoir for multiple antibiotic resistances.

Epidemiology of antibiotic resistance

The frequency of methicillin-resistant *Staphylococcus* increased from 2% in 1975 to 32% in 1992. By this time, resistance to virtually all the therapeutically useful antibiotics had been evidenced. Emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) have raised serious concern all over the world since these two antibiotics were believed to be invincible when they were released in the market. An incredible 150% increase in the occurrence of drug-resistant *Pneumococci* was noted between 1987 and 1994. A 20-fold increase in the frequency of hospital-acquired *Enterococci*, resistant to vancomycin, was seen between 1989 and 1993. According to an estimate by The Centers for Disease Control and Prevention (USA), 13,300 patients died of antibiotic-resistant bacterial infection in the US

during 1992. In 2011 there were an estimated 630 000 cases of MDR-TB among the world's 12 million cases of TB. Worldwide, 3.7% of novel cases and 20% of formerly treated cases are estimated to have MDR-TB.

Mechanism of Antibiotic Resistance

Gaining an excellent understanding of the molecular basis for the growth of resistance is important because it allows us to build up new approaches to handle the infections caused by these bacteria and to create new strategies for the development of novel treatments against these bacteria. In general, it can be said that bacterial resistance changes in the genetic make-up of the formerly susceptible takes place either via mutations or by the introduction of new genetic information. [17][18]

For developing antibiotic resistance, it is essential that two key elements combine: the presence of an antibiotic in a colony and a heterogeneous colony of bacteria, capable of inhibiting the majority of bacteria, where the genetic determinant capable of expressing resistance to the antibiotic is carried by at least one of this bacterium. [17] Once this happens, the resistant strains will stay alive where as susceptible bacteria in the colony will die.

Resistance to antibiotics can be intrinsic (natural) or acquired and can be transmitted horizontally or vertically.

Natural (Inherent) resistance: Bacteria may be inherently resistant to an antibiotic. For example, an antibiotic not having a transport system to enter into the organism; or an antibiotic molecule not having a target site on the micro organism; or, the cell wall of the micro organism is enclosed with an outer membrane that establishes a permeability barrier against the antibiotic in the case of Gram-negative bacteria.

Acquired resistance: Bacteria shows resistance to different antibiotics due to the change of existing genetic material or the acquisition of new genetic material from another source.

Adaptive resistance: Adaptive resistance is defined as a reduction in the susceptibility of the bacteria to an antibiotic as a result of exposure if a sub-inhibiting concentration of the antibiotic. [24]

Genetic Basis (Genetic mechanism) of Antibiotic Resistance

The growth of antibiotic resistance tends to be related to the degree of simplicity of the DNA present in the microorganism becoming resistant and to the ease with which it can acquire DNA from other microorganism.

The genes that codify this resistance (the "resistant genes") are normally situated in specialized fragments of DNA known as transposons (sections of DNA containing "sticky endings"), which allows the resistant genes to move from one plasmid to another without any difficulty. [18]Some transposons may have a special, more complex DNA fragment called "integron", a site capable of integrating different antibiotic resistance genes and thus able to give multiple antibiotic resistance to a bacteria. Integrons have been recognized in both gram – positive and gram- negative bacteria and they seem to give high level multiple drug resistance to the bacteria that carry and express them. Once a genetic mutation occurs and causes a change in the bacteria DNA, genetic material can be transferred among bacteria by number or times. [18]

Spontaneous Mutation and Gene Transfer: Antibiotic tolerance in bacteria emerges as a result of error in DNA replication, a phenomenon known as spontaneous mutation having a frequency of one in 107 cells. During the epidemic of *Shigella* infections in Japan during 1950s, it was observed that bacteria could transfer copies of antibiotic resistance genes to susceptible bacteria thus making the latter antibiotic-tolerant.

Conjugation: It is the most common and important mechanism of transmission of resistance in bacteria. This mechanism is usually mediated by plasmids (circular fragments of DNA) that are simpler than chromosomal DNA and can replicate independently of the chromosome. The plasmids in the bacteria forms a "pilus" between bacteria when they are next to each other, thus linking

them for a moment and making it possible for the passage of these DNA fragments. (Figure 1)

Transformation: Transformation takes place naturally in some species and can also be attained by artificial means. The process of transmission of bacterial resistance genes is takes place when there is direct passage of free DNA (also called as "naked DNA") from one cell to another. The receiving bacteria then simply introduction the free DNA into their cytoplasm and incorporate it into their own DNA. This process is known to occur in several bacterial species such as *Salmonella, Escherichia, and Micrococcus* etc.This technique is being used very frequently in the field of biotechnology for the purpose of cloning. Transformation is a powerful gene-mobilizing mechanism. (Figure 1)

Transduction: Transduction occurs via the use of a "vector", most frequently viruses capable of infecting bacteria also known as "bacteriophages" (or simply "phages").The virus containing the bacterial genes that codifies antibiotic resistance (the "resistant DNA") infects the new bacterial cell and introduces this genetic material into the recipient bacteria. In a number of cases, the infecting bacteriophage also introduce to the receiving bacteria its own viral DNA, which then takes over the bacterial replication system forcing the cell to produces more copies of the infecting virus until the bacteria cells dies and liberates these new bacteriophages, which then go on the infect other cells. Transduction also plays some role in dissemination of antibiotic resistance. (Figure1)

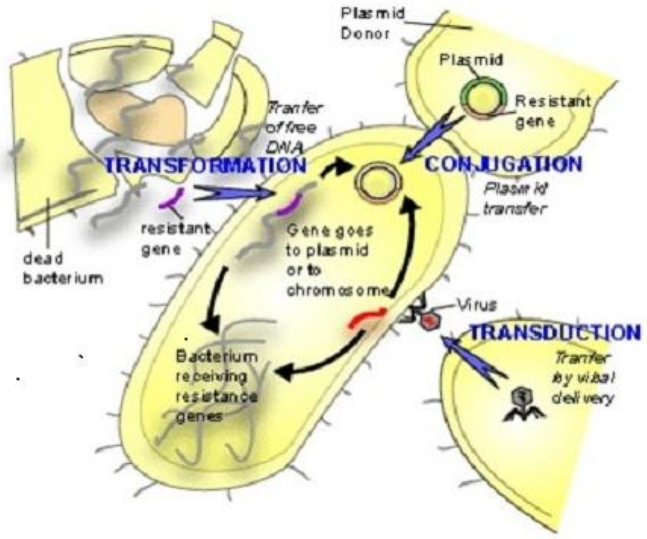

Figure 1: Shows conjugation, transformation and transduction

Horizontal gene transfer: The movement of genetic material between unrelated species of bacteria. This can happen through direct incorporation of free DNA by bacterial cells. This direct form of gene transfer, for instance in the soil or in the digestive tract of animals, is the most common mode for the transfer of genetic material. It fosters rapid dissemination of antibiotic resistance in the bacterial community. Horizontal gene transfer can happen either through transformation, transduction or conjugation), enables bacteria to transfer copies of antibiotic resistant genes even to the distantly related species in their neighborhood and thus contributes significantly in dissemination of resistance. Different types of such resistant genes, when

accumulated in a single cell, result in multi-resistant phenotype.

Biological Basis (Biological mechanism) of Antibiotic Resistance

The biological mechanisms are several and different but they can be summarized as follows.

Drug Inactivation by Microbial Enzymes: Among a number of mechanisms involved in the development of antibiotic resistance, drug modification plays a most important role in rendering a lot of therapeutically useful drugs futile. For example chloramphenicol is converted to the therapeutically inactive compound 1, 3-Diacetoxychloramphenicol by chloramphenicol acetyl transferase (CAT), produced by some resistant bacteria. Likewise, β-lactamase, an enzyme elaborated by many Gram-positive and some Gramnegative bacteria, converts penicillin into penicilloic acid, which is therapeutically inactive. The following examples are drugs inactivation by microbial enzymes.

- Antibiotic inactivation (aminoglycoside phosphoryl transferase, aminoglycoside acetyltransferase,aminoglycoside nucleotidyltransferase)
- Streptogramin Antibiotic inactivation (streptogramin acetyltransferases inactivate type A streptogramins by O-acetylation; C-O lyases inactivate Streptogramin B.

Exclusion of Antibiotics from the cell: There are many examples of exclusion of antibiotics from the cell. The mechanisms involved in the resistance of bacteria to tetracycline, energy mediated efflux is a powerful strategy, which does not allow the drug to accumulate in sufficient concentration to exert its inhibitory effect. It is mediated by a trans-membrane export protein that functions as an elctroneutral antiport system. [19] Efflux was first described for tetracycline and macrolides antibiotics. The protein catalyzes the exchange of a tetracycline-divalent metal cation complex for a proton [20][21] but is now general for several other antibiotics such as fluoroquinolones. [18][19] (Figure 2)

Reduction in Permeability or uptake to Antibiotics: In some cases, emergence of mutants with reduced permeability of the cell membrane to antibiotics compared to that of the wild-type strain, leads to tolerance to the antibiotic. For example *Neisseria gonorrhoea*, the causative organism of gonorrhea (one of the most common sexually transmitted disease (STD)), can gain antibiotic resistance by acquiring a mutation in the gene encoding the membrane protein 'porin', thus inhibiting the transport of the antibiotics penicillin and tetracycline (into the periplasmic in Gram-negative bacteria cell) and rendering the cells immune to the effect of drugs. Another example is Enterobacter aerogenes porin, which can acquire mutations that cause cephalosporin resistance. (Figure 2)

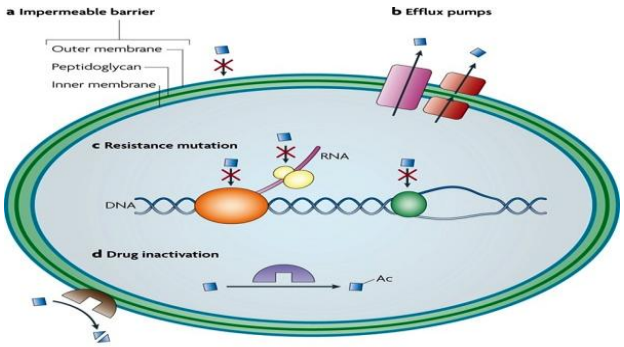

Figure 2: Shows membrane impermeability and efflux mechanism

Alteration of Drug Target Site: The other mechanisms of antibiotic-resistance an example close to home to the alteration or over-expression of the drug target is InhA, which has a -15C to T promoter mutation. This mutation causes over-expression of the drug target InhA, and lead to a low-level Isoniazid (INH) resistance in *M. tuberculosis*. Likewise, modification of the target is best exemplified by streptomycin and erythromycin resistance of Both of these antibiotics act by ribosomal binding thereby inhibiting bacterial protein synthesis. Modification of the S12 protein of the 30S subunit of the ribosome makes the ribosome insensitive to streptomycin. Under susceptible conditions, vancomycin inhibits cross-linking of peptidoglycan by binding to D-Ala-D-Ala dipeptide of the muramyl peptide. Final example is the modification of the β-subunit of RNA polymerase of *Mycobacterium* leading to the failure of the antitubercular drug rifampicin to bind the subunit and inactivate the enzyme. A third example is vancomycin resistance.

Overproduction of a Target Metabolite: In some cases, the molecule, which is competitively antagonized by the antibiotic, is overproduced. For example, sulphonamides act by competitively inhibiting the enzyme dihydropteroate synthetase, which plays a crucial role in the synthesis of folate. Sulfonamides (or sulfa drugs) are structural analogs of p-aminobenzoic acid (PABA), the substrate of this enzyme. The indispensable role of folate in the synthesis of nucleic acids viz., DNA and RNA is well-known. In some PABA-overproducing mutants of *Staphylococcus aureus*, sulfonamide molecules are outnumbered by the substrate and therefore the activity of the enzyme is not inhibited even in the presence of the drug.

Receptor modification: Receptor modification generally happens when the intracellular target or receptor of the antibiotic drug is changed by the bacteria, resulting in the lack of binding and the lack of antibacterial effect. Examples if this mechanism includes modification in the structural conformation of penicillin-binding protein (PBPs) observed in certain types of penicillin resistant, ribosomal modifications that can cause aminoglycosides, macrolides or tetracyclines inactive, and DNA-gyrase modifications resulting in resistance to fluoroquinones. [17][18]

Risk factors for the development of antibiotic resistance:

- In outpatient practice antibiotics are used irrationally, excessively.
- Over utilization of antibiotics in hospitalized patients either therapeutically or prophylactically.
- Now a day's the use of antibiotics in agriculture industry, mainly in the production of food.
- Lack of use of good and effective preventive infection control measures such as antibiotic usage restriction, proper hand washing and proper isolation of patients with resistant infections.
- Increased use of invasive producers
- Increased use of foreign bodies and prosthetic devices amenable to super infection with resistant bacteria

The use of antibiotics in human results in "selective pressure" in the host receiving the antibiotic. The chance to develop resistance for bacteria becomes higher with broad spectrum antibiotics. [22][23] Fluoroquinolones and more recently Azithromycin have been connected to these problems. 70% of the community-acquired infections are resistant to the fourth generation antibiotics which show a very dangerous trend. Thus the use of antibiotics should be carefully monitored and should be prescribed only to those individuals who needed.

In the past two decades we have witnessed

- Fluoroquinolone antibiotics get resistance by plasmid-mediated (and thus horizontally disseminated) mechanisms.
- Virulent MRSA (methicillin - resistant Staphylococcus aureus) is spreading extensively in the community.

- Neisseria gonorrhoea shows multi-drug resistance.
- The appearance and worldwide distribution of multi-drug resistant microorganisms Klebsiella pneumoniae, Enterobacteriaceae and Pseudomonas aeruginosa, Acinetobacter baumannii.
- Mycobacterium tuberculosis shows and spreads drug resistance extensively.
- Daptomycin and Linezolid are two newest antibiotics to be approved for clinical purpose but these drugs also developed resistance.

CONCLUSION

In the final analysis, however, the problem of antibiotic resistance will not be solved with the creation of many more of stronger, bactericidal antimicrobes.If past history is in any way a good predicator of future history, microorganisms will consistently continue to adapt to their environment by developing resistance to newer antibiotics and serious infections caused by these bacteria will continue to pose a major challenge to the practicing clinician.

Collaborative effort among industry, academia and government is required to strike a "balance" in the war against pathogenic bacteria. This effort will include the implementation of numerous strategies and at the same time preventive measures to avoid infections. The efforts will also include better infection control practices, better availability of diagnostic tools that allow us to more clearly and rapidly distinguish those patients, especially those in the outpatient community, who truly need an antibiotic prescription. All these requirements should be done at a reasonable cost.

It will also take a distant rational use of antibiotics emphasizing the need to use narrow-spectrum agents while saving the broad-spectrum ones for special circumstances. Finally, it will also take the creation and broader use of vaccines capable of preventing infections with some of these multi-resistant bacteria.

It is likely that number of newer biological mechanisms of resistance will develop in the future. One can only hope that as these appear, we will be able to use these new targets as new mechanisms for the development of novel, effective and successful antibiotics. Better design of innovative antibiotics that shows a long-term degree of activity against bacteria is the need of the hour.

ACKNOWLEDGEMENTS

Authors are greatful to the Mrs. Nijara Sarmah and Mr. Venu Gopal Jonnalagadda for their support in proofreading of the manuscript.

CONFLICTS OF INTERESTS: None

REFERENCES

1. Drug Resistance at the US National Library of Medicine Medical Subject Headings (MeSH).
2. Levy SB. From tragedy the antibiotic era is born. In: Levy SB, ed. The Antibiotic paradox: How the Misuse of Antibiotics Destroy Their Curative Power, 2nd ed. Cambridge, MA: Perseus Publishing: 2002.pp.1-14.
3. Rammelkamp M. Resistances of Staphylococcus aureus to the action of penicillin.Proc R Soc Exp Biol Med 1942:51:386-389.
4. Jaffe HW. Biddle JW. Johnson SR. Wiesner PJ. Infections due to penicillinases-producing Neisseria gonorrhoeae in the United States: 1976-1980. J Infect Dis 1981; 144:191-197.
5. Jorgensen JH. Update on mechanisms and prevalence of antimicrobial resistance in Haemophilus influenzae. Clin Infect Dis 1993; 17:1078-1079.
6. Lowy FD. Medical progress: Staphylococcus aureus infections. N Engl J Med 1998; 339:520-532.
7. Foster TJ, The Staphylococcus aureus "Superbug". J Clin Invest 2004; 114:1693-1696.
8. Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, Hoffner S,

Rieder H, Binkin N, Dye C, Williams R, and Raviglione M. Global trends in resistance to antituberculosis drugs. N Engl J Med 2001; 344:1294-1303.

9. Seppala H, Klaukka T, Lehtonen R, Nenonen E, Huovinen P. Outpatient use of erythromycin: link to introduced erythromycin resistance in Group A streptococci. Clin Infect Dis 1995; 21:1378-1385.
10. Huovinen P. Macrolide-resistance Group A streptococcus now in the United States. N Engl J Med 2002; 346:1243-1244.
11. Nuorti JP, Butler JC, Crutcher JM, Guevara R, Welch D, Holder P, Elliot JA. An outbreak of multidrug-resistant pneumococcal pneumonia and bacteremia among unvaccinated nursing home residents. N Engl J Med 1998; 338:1861-1868.
12. Jacobs MR. Streptococcus pneumoniae: epidemiology and patient of resistance. Am J Med 2004: 117(Suppl 3A):3S:15S.
13. Saravolatz LD, Markowitz N, Arking L, Pohlod D, Fischer E. Methicillin resistant staphylococcus aureus, Epidemiologic observation during a community –acquired outbreak. Ann Intern Med 1982; 96:11-16.
14. Kalpan SL, Hulten KG, Gonzalez BE, Hammerman WA, Lamberth L, Versalovic j, Mason EO Jr. Three-year surveillance of community –acquired Staphylococcus aureus infections in children. Clin Infect Dis 2005; 40:1785-1791.
15. Robinson DA, Keams AM. Holmes A, Morrison D, Grundmann H, Edwards G, O' Brien FG, Tenover FC, McDougal LK, Monk AB, Enright MC, re-emergence of early pandemic Staphylococcus aureus as a community acquired methicillin- resistant clone. Lancet 2005; 365:1256-1258.
16. Sorensen TL, Blom M, Monnet DL, Frimodt-Moller N, Poulsen RL, Espersen F, Transient intestinal carriage after ingestion of antibiotic –resistant Enterococcus faecium from chicken and pork. N Engl J Med 2001; 345; 1161-1166
17. Levy SB, Marshall B, Antibiotic resistance worldwide: cause, challenges and response. Nat Med 2004; 10(Suppl):S122-S129.
18. Sefton AM. Mechanism of antimicrobial resistance. Drugs 2002; 62:557-566.
19. Jacoby GA, Munoz-price Ls. The new β-lactamases. N Engl J Med 2005; 352:380-391.
20. Roberts MC, Tetracycline resistance determinants: mechanism of action, regulation of expression, genetic mobility, and distribution. FEMS Microbiol Rev 1996; 19:1-24.
21. Leclercq R, Mechanisms of resistance to macrolides and Lincosamides: nature of the resistance elements and their clinical implication. Clin Infect Dis 2002; 34:482-492.
22. Vanderkooi O, Low D, Green K, Powis J, Mc Geer A. Predicting antimicrobial resistance in invasive pneumococcal infections. Toronto invasive bacterial disease network. Clin Infect Dis 2005; 40:1288-1297.
23. Pantosai A, Moro ML, Antibiotic use: The crystal ball for predicting antibiotic resistant. Clin Infect Dis 2005; 40:1298-1300.
24. Karlowsky JA, Zelenitsky SA, Zhanel GG. 2012. Aminoglycoside adaptive resistance. Pharmacother. 17:549-555.