

Review

Issues of resistance of pathogens to antimicrobial agents

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Antimicrobial resistance among pathogenic organisms is now a persistent problem and of tremendous public health care concern around the globe. These pathogens are able to develop mechanisms of resistance, the antimicrobial agents that were at one time the drug of choice. They continue to develop various mechanisms of resistance either by intrinsic or acquired, and have been able to transfer and accept different resistance genes, given rise to multi-drugs resistance bacteria called superbugs. This new phenomenon has caused an increase in the incidence of nosocomial infections making the treatment problematic for the health care providers. Resistance to antimicrobial agents is fast becoming a norm and is an enormous challenge worldwide.

Key words: Antimicrobial resistance, antimicrobial agent, pathogen, mechanism, superbug.

INTRODUCTION

Antimicrobial resistance developed by pathogenic organisms is a global menace and has escalated over the years by the emergence of multi-drug resistant strains among these pathogens (Gould et al., 2010; Lister et al., 2009). Development of resistance to antimicrobial agents by pathogens is a fitness trait acquired to survive in whatever environment they find themselves (Koskella et al., 2011). This evolution trait (survival of the fittest) has accounted for the unparalleled success of microbial existence in any part of the earth irrespective of the extreme conditions (Babalola et al., 2009).

Bacteria may possess intrinsic resistance that protect them from a particular antibiotic; or acquire resistance through chromosomal mutation or acquisition of genetic materials from other bacteria either through vertical or horizontal transfer of genes (Périchon et al., 2009). This has led to some strains being called superbugs due to acquisition of resistant genes to different classes of antibiotics, making their treatment highly problematic for

both the clinicians and patients (Kelland, 2011).

Antimicrobial resistant infections can be acquired in health care facilities, in the community or through food supply (Bester and Essack, 2010; Calfee and Jenkins, 2008; Miller and Die, 2008). Globalization also makes possible the easy spread of these pathogenic organisms from one country to other countries (Dhanji et al., 2010). Examples of clinically important pathogens that are increasingly becoming multi-drug resistance to antibiotics in use are *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Enterococcus faecalis*.

This review article will focus on the survey of microbial resistance to antibiotics in use; examine mechanisms of action of antimicrobial agents and the mechanisms of antimicrobial resistances. Additionally, the issue of multi-drug resistance that is fast becoming norms among these pathogens will be discussed.

MICRO-ORGANISMS AS CAUSATIVE AGENTS OF DISEASES

The major causes of human diseases are the

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micro-organisms and they (bacteria, fungi and viruses) have been the greatest burden to mankind. Throughout the history of mankind, there has been a continuous war between humans and the pathogenic organisms (Tenover, 2006). The infectious diseases caused by micro-organisms range from tonsillitis to pneumonia, osteomyelitis, cough, diarrhea, measles, acquired immune deficiency syndrome (AIDS), plague, tuberculosis, septicemia, candidiasis, malaria, influenza and many other diseases (Willey et al., 2010). Many people have lost their lives due to these infectious diseases, which at times reach epidemic rates (Gerberding, 2003; Jones et al., 2008).

For a disease to be established in a host, some factors have to be fulfilled by the disease causing organism. For example, the pathogen has to fight the defensive mechanisms of the host and overcome them before disease can become established (Harvey et al., 2007). The pathogens do this by secreting enzymes and spreading factors, for example strains of *S. aureus* secrete an enzyme coagulase, which aids the transformation of fibrinogen into fibrin, thus allowing the clotting of human and rabbit plasma (Todar, 2011). This creates a barrier between the pathogen and the leucocyte. *Streptococci* and *Staphylococci* produce a substance called fibrinolysin, which is similar to coagulase. Fibrin dissolves only human fibrin and not animal fibrin (Todar, 2011).

Streptococci are among the most common disease-causing bacteria responsible for infections of the throat, middle ear, scarlet fever, rheumatic heart disease, gangrene, glomerulonephritis and tooth decay (Willey et al., 2010). Worldwide *Streptococcus pneumoniae* causes one million fatal pneumonia infections a year in children (O'Brien et al., 2009). *Streptococci* have become resistant to many antibiotics for over thirty years (Phares et al., 2008; Rubinstein et al., 2011). *Staphylococci*, which can contribute to wound or burn infections, endocarditis, mastitis, toxic shock syndrome, osteomyelitis and other serious disorders, have developed resistance to many antibiotics (Waters et al., 2011). Infections due to *S. aureus* have continued to be a major source of morbidity and mortality in hospitals and hence a significant cause of concern among the physicians (Adaleti et al., 2010; DeLeo and Chambers, 2009). *Enterococci* contribute to some of the most common infections acquired in the hospitals (McBride et al., 2007) causing intra-abdominal abscesses, meningitis, endocarditis and infections of the urinary tract and soft tissues. Usually, infections resulting from strains resistant to many groups of antibiotics like the beta-lactams and aminoglycosides are treatable with vancomycin, chloramphenicol or other antibiotics (Jones et al., 1995). But resistance has developed to these drugs within the last two decades (Biendo et al., 2010). Enterococci have gained notoriety over the past decades as frequent causes of multiple antibiotic resistant, hospital-acquired

bloodstream, urinary tract and surgical wound infections; and because of their capacity to transfer antibiotic resistance to other microbes (Arias et al., 2010).

Shigellae are the major cause of diarrhea and dysentery throughout the world (Golberg, 2009). The frequency of strain's multiple resistances to ampicillin, trimethoprim-sulfonamide, streptomycin, chloramphenicol, tetracycline and even third generation cephalosporin is a cause of growing concern (Bhattacharya et al., 2011; Folster et al., 2011). Epidemic dysentery caused by these strains result in the death of most people infected due to resistance to antibiotics (Ahmed et al., 2006; Schroeder and Hilbi, 2008). *Salmonellae* are known to cause disease in human, animals and birds. The two major diseases caused by *Salmonellae* are gastroenteritis and typhoid fever. *Salmonella typhi*, the bacterium responsible for typhoid fever also joined the class of antibiotic resistant bacteria making treatment of the infection more problematic (Ray et al., 2006). The most common infections associated with *Pseudomonades* include skin infections, urinary tract infections, bronchitis, pneumonia, meningitis, otitis media, endocarditis, bacteremia, mastoiditis and corneal ulcers (Willey et al., 2010). *P. aeruginosa* infections are the frequent cause of morbidity and mortality in hospitalized patients (Fortaleza et al., 2011; Lanini et al., 2009). Treatment of these infections is complicated by the intrinsic and acquired resistant of the organism to many commonly used antimicrobial agents (Feliziani et al., 2010; Mandsberg et al., 2009).

Human diseases caused by Clostridia include tetanus, pseudomembranous colitis, botulism and gas gangrene. *Clostridium difficile* is called the hospital superbug because of its ability to resistant different types of antibiotics and is the leading cause of infectious diarrhea in hospitals worldwide (Rupnik et al., 2009). Some strains of the bacterium like *E. coli* O157:H7 are the emerging cause of food borne and water borne diseases (Currie et al., 2007). Pathogenic strains of *E. coli* are responsible for infections such as urinary tract infection, neonatal meningitis, mastitis, haemolytic uremic syndrome, septicemia, peritonitis, and gastroenteritis (Olaniran et al., 2011). *Klebsiella* are human pathogens causing pneumonia, urinary tract infections, ankylosing spondylitis, septicemia and soft body infections (Sandhyarani, 2011). *Klebsiella* are resistant to quite a number of antibiotics including aminoglycosides, fluoroquinolones, sulfonamides and even carbapenems that used to be antibiotic of choice for serious infections (Song et al., 2009). *Vibrios* are important causes of diarrhea worldwide. *Vibrio cholera* 01 is the most important since is associated with pandemic and epidemic diarrhea in many countries (Olaniran et al., 2011). Multi-drug resistant *V. cholera* strains was reported making the treatment of the infection problematic especially in developing countries (Das et al., 2011). Protein cause urinary tract infections, meningitis in

children, wound infections, rheumatoid arthritis, gastroenteritis, otitis media and pneumonia (Harvey et al., 2007). Apart from food poisoning, *Listeria monocytogenes* may cause meningitis, meningoencephalitis, septicemia or spontaneous abortion in pregnant women (Yin et al., 2011).

The last few decades have witnessed emergence of many new diseases and resurrection/re-emergence of previously eradicated diseases. For many of these diseases there is no treatment or cure and the possibility of controlling them is limited. For example, the emergence of multidrug-resistant strains of *Mycobacterium tuberculosis* is an increasing problem for populations and tuberculosis control programs in developed and developing countries alike. The pathogens are now found in what used to be safe zones is highly a worldwide concern (Wright et al., 2009).

MECHANISMS OF ACTION OF ANTIMICROBIAL AGENTS

Antimicrobial agents are compounds that destroy pathogenic microorganisms or inhibit their growth and are used in the treatment of diseases. Most of them are antibiotics, microbial products or their derivatives that can kill susceptible microorganisms or inhibit their growth. An effective chemotherapeutic agent must have selective toxicity. A drug with selective toxicity has a high therapeutic index and usually disrupts a structure or process unique to the pathogens and has fewer side effects (Todar, 2011). Antimicrobial agents may be grouped into two categories; cidal or static. Examples of bacteriocidal agents includes; bacitracin, ciprofloxacin, gentamicin, streptomycin, ampicillin, cephalosporins, vancomycin, carbenicillin, etc, while bacteriostatic agents include; rifampin, chloramphenicol, chydramycin, dapson, erythromycin, tetracyclines, sulfonamides, etc. Antimicrobial agents are more effective against actively growing bacteria, than against non-growing persisters or spores.

Antimicrobial agents have diverse chemical structures and differ in their range of action (Moore and Payne, 2008). Some act on both Gram-positive and Gram-negative bacteria, and are said to have broad spectrum of action, for example, ampicillin, carbenicillin, rifampin, cephalosporins and streptomycin while some are only potent to either Gram-positive or Gram-negative bacteria and are said to be of narrow spectrum, for example, erythromycin, penicillin, polymycin B, dapson, bacitracin and vancomycin (Todar 2011).

Antimicrobial agents injure microbes through several different mechanisms. Below are reviews of some of the major modes of action of antimicrobial agents.

Inhibition of cell-wall synthesis

Component of the cell wall provides rigid mechanical

stability by virtue of its highly cross linked lattice work structure (Willey et al., 2010). Peptidoglycan is made up of polysaccharide chains containing alternating residues of N-acetylmuramic acid and N-acetylglucosamine (Todar, 2011). Peptide units cross-link extending from the N-acetylmuramic acid and during bacterial wall synthesis these linkages are caused by precursors which are catalysed by specific enzymes e.g. transpeptidases, endopeptidases and carboxypeptidases. These enzymes are called penicillin binding proteins (PBPs) because they can be bound by beta-lactam antibiotics (Kashyap et al., 2011).

The cell wall, which is many layers thick in Gram-positive organisms and quite thin in Gram-negative ones, protects the cell against rupture from hypotonic environments (Scheurwater and Burrows, 2011). Penicillin and certain other antibiotics prevent the synthesis of intact peptidoglycan; by irreversibly binding to and deactivating enzymes involved in cross-linkage of peptide chains, the cell-wall is greatly weakened, and the cell undergoes lysis (Drawz and Bonomo, 2010). Because penicillin targets the synthesis process, only actively growing cells are affected by these antibiotics. And, because human cells do not have peptidoglycan cell walls, penicillin has very little toxicity for host cells (Drawz and Bonomo, 2010).

Bacitracin and vancomycin interfere with the synthesis of the linear strands of peptidoglycan. Penicillin and cephalosporins prevent the final cross linkage of the peptidoglycans, which interferes with the construction of the macromolecular cell wall (Todar, 2011). Examples of other drugs that inhibit the synthesis of peptidoglycan are cycloserine, phosphomycin, isoniazid, carbapenems, cephamycins, monobactams and mersacidin.

Inhibition of protein synthesis

Protein synthesis as a common feature of all cells, whether prokaryotes or eukaryotes, it would seem an unlikely target for selective toxicity (Willey et al., 2010). One notable difference between prokaryotes and eukaryotes is the structure of their ribosomes. The difference in ribosomal structure accounts for the selective toxicity of antibiotics that affects protein synthesis (Willey et al., 2010). Among the antibiotics that interfere with protein synthesis are chloramphenicol, linezolid, erythromycin, streptomycin, clindamycin, fusidic acid and tetracyclines. These drugs discriminate between prokaryotic and eukaryotic ribosomes; hence their therapeutic index is fairly high (McKee et al., 2006).

Protein synthesis inhibitors work at different stages of prokaryotic mRNA translation into proteins, like initiation, elongation (including aminoacyl tRNA entry, proofreading, peptidyl transfer and ribosomal translocation) and termination (Kohanski et al., 2010). Rifampicin inhibits DNA-dependant RNA polymerase in bacterial cells by binding its beta-subunit, thus preventing

transcription to RNA and subsequent translation to protein (Osburne et al., 2006). Tetracyclines inhibit cell growth by inhibiting translation. It binds to the 16S part of the 30S ribosomal subunit and prevents the amino-acyl tRNA from binding to the A site of the ribosome (Griffin et al., 2010). Chloramphenicol inhibits the formation of peptide bonds in the growing polypeptide chain by blocking peptidyl transfer step of elongation on the 50S ribosomal unit (Kostopoulou et al., 2011). Fusidic acids bind to elongation factor G (EF-G) and block translocation, thus preventing protein synthesis (Farrell et al., 2011).

Some antibiotics bind to the 30S or 50S ribosomal subunit. Erythromycin also reacts with 50S portion of the 70S prokaryotic ribosome. Some other antibiotics react with the 30S portion of the 70S prokaryotic ribosome for example, tetracyclines. Aminoglycoside antibiotics, such as streptomycin and gentamicin, interfere with the initial steps of protein synthesis by changing the shape of the 30S portion of the 70S prokaryotic ribosome. These interferences cause the genetic code on the mRNA to be read incorrectly (Gorgani et al., 2009).

Injury to the plasma membrane

The membranes of all cells are quite similar; those of bacteria and fungi differ from eukaryotic cells. These differences allow for selective action of antimicrobial agents (Willey et al., 2010). Certain antibiotics, especially polypeptide antibiotics, bring about changes in the permeability of the plasma membrane, these changes result in the loss of important metabolites from the microbial cell. For example, polymyxin B causes disruption of the plasma membrane by attaching to the phospholipids of the membrane (Cardoso et al., 2007). Amphotericin B and nystatin selectively inhibits microorganisms that possess ergosterol in their cell membrane and produce pores on the membrane through which ions and small molecules are lost (Palacios et al., 2010).

Inhibition of nucleic acid synthesis

A number of antibiotics interfere with nucleic acid synthesis by blocking synthesis of nucleotides, inhibiting replication, or stopping transcription (Todar, 2011). Some drugs with this mode of action have an extremely limited usefulness because they interfere with mammalian DNA and RNA as well. Examples of drugs that inhibit nucleic acid synthesis are rifampin, quinolones, norfloxacin, ciprofloxacin and actinomycin D. Ciprofloxacin and other quinolones bind to the β subunit of DNA gyrase and prevent supercoiling of DNA, thereby inhibiting DNA synthesis (Oliphant and Green, 2002). Rifampin inhibits synthesis of mRNA by binding to DNA-dependent RNA polymerase (Hartmann et al., 1967). Actinomycin D

inhibits both DNA and RNA synthesis by binding strongly to duplex DNA and interfering with the passage of DNA and RNA polymerase (Vekshin, 2011).

Inhibition of essential metabolites synthesis

Anti-metabolites are substances that affect utilization of metabolites and therefore prevent a cell from carrying out necessary metabolic reactions. Several antibiotics acts as anti-metabolites; they block the functioning of metabolic pathways by competitively inhibiting the use of metabolites by key enzymes (Lamichhane et al., 2011). Sulfonamides and several other drugs inhibit folic acid metabolism by competing with para-aminobenzoic acid (PABA). In many microorganisms, PABA is the substrate for an enzymatic reaction leading to the synthesis of folic acids, a vitamin that functions as a co-enzyme for the synthesis of the purine and pyrimidine bases of nucleic acids and many amino acids. In the presence of sulfanilamide, the enzyme that normally converts PABA to folic acid combines with the drug instead of PABA (Focks et al., 2010; Proctor, 2008). This combination prevents folic acid synthesis and stops the growth of the microorganisms. Examples are, trimethoprim, sulfa drug (sulfanilamide and sulfamethoxazole), they have a high therapeutic index because humans do not produce folic acid, therefore exhibits selective toxicity (Willey et al., 2010).

MECHANISMS OF ANTIMICROMIBIAL RESISTANCE

The treatment of infectious diseases caused by microorganisms that have become resistant to commonly used antibiotics has become a major global health care problem in the 21st century (Luzhetskyy et al., 2007; Woolhouse, 2008). Microbial resistance to drugs was recorded early in the history of chemotherapy and post introduction of penicillin into medical practice; resistant bacteria emerged rendering the "magic drug" ineffective, a pattern the microbes maintained for many years (Arias and Murray, 2009; WHO, 2011). However, over the past decades microbes have proved themselves to be adapted at becoming resistant to each new antimicrobial agent produced by man (Bergstrom, 2011). Just as it has been possible to develop antibacterial agents to interfere with each critical step in the growth mechanism or in the production of the protective walls of bacteria, they have evolved novel mechanisms of resistance to thwart the antimicrobial attack. There are many different mechanisms by which microorganisms' exhibits resistance to antimicrobial agents.

Resistance based on altered receptors for a drug

Because most drugs act on a specific target such as

protein, RNA, DNA, or membrane structure, microbes can circumvent drugs by altering the nature of this target, penicillin resistance is due to alterations in penicillin binding proteins (Arias and Murray, 2009). Resistance of bacteria to rifampin (Jassal and Bishai, 2009) develops because of altered DNA-directed RNA polymerase. A change of one amino acid in the beta subunit of DNA-directed RNA polymerase alters binding of rifampin. Usually the degree of resistance is related to the degree that the enzyme is changed but does not correlate strictly with enzyme inhibition. This form of resistance which exists at a low level in any microbial population develops during treatment (Olofsson and Cars, 2007). Appearance of such resistance is not due to mutation event but rather to selection of a few that possess an RNA polymerase with poor affinity for rifampin. Such microorganisms are common among the enterobacteriaceae, which explains why urinary tract infection pathogens easily become resistance to rifampin (Jassal and Bishai, 2009).

Erythromycin and clindamycin resistance is associated with an alteration on the 50S ribosomal binding site (Dunkle et al., 2010). Sulfonamide-trimethoprim resistance among microbial pathogens was based on altered receptors for the drug (Jensen and Lyon, 2009). The presence of an altered or new dihydropyrimidin synthetase with poor affinity for sulfonamides will preferentially bind para-aminobenzoic acid and preclude a block of the folate synthesis cycle. Sulfonamide resistance of this type can be due to point mutation or plasma derived causing synthesis of a new enzyme (Jensen and Lyon, 2009). A serious problem is the increase in resistance to trimethoprim and its analogue, which is plasmid and transposons-mediated and due to production of an altered dehydrofolate reductase (Wagenlehner et al., 2008). Vancomycin resistance mostly in Gram positive bacteria is due to changes in the binding sites of vancomycin from D-Ala-D-Ala to D-Ala-D-lactate dipeptide of the muramyl peptide in their peptidoglycan (Sieradzki and Markiewicz, 2004).

Decreased entry of antibiotics

The main target of most antibiotics lies in the cytoplasmic membrane or in the cytoplasm hence drugs must penetrate the outer layer of the cell envelope for activity. The resistance of some bacteria can be due to a mechanism that prevents the drug from entering the cell and acting on its target. The plasmid encoded multi-drug resistance gene, *qacB* from *S. aureus* mediates resistance to a number of classes of antimicrobial organic cations (Nakaminami et al., 2010; Pantosti and Venditti, 2009). The gene has shown to encode a protein qac BIII with 25 transmembrane segments (Nakaminami et al., 2010) that confers resistance via export of the antimicrobial agent thus preventing their cytoplasmic accumulation. Basically

tetracycline resistance is due to a decrease in drug accumulation, a drug efflux mechanism in which decrease uptake and efflux occur simultaneously probably influences its development as well (Poole, 2007). Resistant free milieu loses the tetracycline they do accumulate.

Resistance by drug inactivation or destruction

Many microorganisms confer resistance by their ability to produce enzyme that inactivates or destroy action of antimicrobial agents. Many Gram-positive and Gram negative bacteria are resistant to chloramphenicol because they have chloramphenicol-transacetylase that acetylates hydroxyl groups of the antibiotic structure thereby inactivating it. The best known mechanism of bacterial resistance is that of penicillinase (Pantosti and Venditti, 2009). Subsequent resistance of staphylococci to penicillin was confirmed to be due to penicillinase. With the production of β -lactam antibiotics, it became more appropriate to designate these enzymes as β -lactamase since their attack on the β -lactam ring leads to drug destruction (Moya et al., 2009). Chromosomal mediated β -lactamase is present in many *Enterobacter*, *Citrobacter*, *Klebsiella* and *Pseudomonas*. Aminoglycoside-inactivating enzymes are able to add acetyl, adenylyl and phosphoryl groups to inactivate the antibiotic (Boehr et al., 2003).

Synthesis of resistance or alternative pathways

The action of anti-metabolites can be circumvented if a microbe develops an alternative metabolic pathway or enzyme. Antibiotic resistance by way of alternative metabolic pathway is not uncommon with *Pseudomonas* and fungi. Koser et al. (2010) showed that the target enzymes produced by a mutant organism might change in respect to its sensitivity to the inhibitor while still functioning as the unchanged enzyme. Some thymidine-requiring streptococci failed to be inhibited by trimethoprim and sulfonamides. These organisms cause some urinary tract infections but fail to undergo the thymineless-death that occurs normally with bacteria exposed to these agents (Koser et al., 2010). Other bacteria produce adequate dTMP by alternative methods, and as a result survive exposure to the folic acid inhibitors (Willey et al., 2010). Sulfonamide and Trimethoprim resistance develops when microbes deviate from the usual patterns of folic acid synthesis.

SUPERBUGS

The emergence and reemergence of antimicrobial resistance among bacterial pathogens has a global

negative impact on public health (Vila and Pal, 2010). Upon the introduction of a new antibiotic into the market the development of resistant is simply a matter of time (Newman and G.M.C., 2007). Antibiotics use in clinical practices has been the major selective force for emergence and spreading of resistance gene (Edoh and Alomatu, 2007). Several other factors also contribute to this emergence and dissemination of antimicrobial resistance; among these are abuse of antibiotics, inadequate access to all antimicrobial agents, health care system, malnutrition and poverty (Caron and Mousa, 2010).

The development of resistant to more than one antibiotics is a major problem in the treatment of infectious diseases caused by pathogenic microorganisms (Mindlin et al., 2008; Nikaido, 2009). Over the past few decades, bacterial resistance to multiple antibiotics has become widely recognized as serious problem. These resistances make many diseases increasingly difficult if not impossible to treat. The rate at which the microorganisms are now developing resistance to the available antimicrobial agents is getting to an alarming rate.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Methicillin resistant *S. aureus* (MRSA) is a bacterium that causes different types of infections that are very difficult to treat in humans. This is because this bacterium has developed the mechanism to resist the action of antimicrobial agents such as penicillin, methicillin and cephalosporin (Klevens et al., 2006; Sakoulas and Moellering, 2008). *S. aureus* is a virulent pathogen that is responsible for a wide range of infectious diseases like bacteremia, endocarditis, osteomyelitis, meningitis, septicemia and pneumonia; has developed resistance to most common antibiotics in use especially that of the beta lactam class (Gould et al., 2010). Strains of *S. aureus* that are resistant to multiple antimicrobial compounds are major threat to public health care system (Jensen and Lyon, 2009). For many years, clinicians and public health officials have faced methicillin resistance *S. aureus* to many antibiotics in use (Baltz, 2009; Gould et al., 2010). MRSA infections are among the most virulent infections known; the superbug causes nearly 500,000 hospitalizations and 19,000 deaths in the United States each year, more deaths than caused by AIDS (Klein et al., 2007). The bug can be acquired in the community or in hospitals (Naimi et al., 2003).

Most MRSA infections occur in people who have been in hospitals or other health care facilities, such as nursing homes and dialysis centers. When it occurs in these settings, it is known as Health Acquired MRSA (HA-MRSA). HA-MRSA infections typically are associated with invasive procedures or devices, such as surgeries, intravenous tubing or artificial joints (Maree et al., 2007;

Zell and Goldmann, 2007). However, people who have an open wound, abscess, boil or other type of puss-filled lesion are also susceptible to this pathogen. Communities Acquired MRSA (CA-MRSA) occurred in the wider community among healthy people, who are not immune compromised and have not had any medical procedure or stay in health care facility within the last year. It can be spread by skin to skin contact with infected person especially among groups such as wrestlers, high school students, child care workers and people who live in crowded conditions; or sharing of things such as towel and razor (Davis et al., 2007; Wang et al., 2008). Strains of MRSA had been reported to have developed resistance to vancomycin that was regarded as the last resort (Arias and Murray, 2009).

Mechanisms of resistance in MRSA may be acquired or produces through mutations in genes or integration of certain genes (Ito et al., 2007). The presence of the plasmid gene (*blaZ*) that is able to produce β -lactamase enzyme confer resistant in *S. aureus*. This enzyme is able to hydrolyze the peptide bond in the β -lactam ring in the penicillin drugs, rendering the drug useless by not been able to bind to the transpeptidases which play important role in the cross-linking of the peptidoglycan subunits (Milheirigo et al., 2011). The emergence of MRSA is due to the acquisition of staphylococcal cassette chromosome *mec* element which carry a gene (*mecA*) which encodes a penicillin binding protein (PBP2a) with low affinity for β -lactam antibiotics (Abd El-Moez et al., 2011; García-Álvarez et al., 2011). MRSA resistant to antimicrobial agent quinolones is due to mutation, in either the *GyrA* subunit of gyrase or *GrlA* subunit of topoisomerases IV, this reduce quinolone affinity for its targets (Strahilevitz et al., 2009). Another mechanism of resistance is the presence of efflux pump which enables the bacteria to pump out the antibiotics from the cell (Poole, 2005). Strains of MRSA called Vancomycin Resistant *S. aureus* (VRSA) are able to resist due to the acquisition of the *vanA* gene cluster (Perichon and Courvalin, 2009).

Vancomycin-resistant *Enterococcus species* (VRE)

Vancomycin resistant *Enterococci* are of major health care concern due to their prevalence and ability to transfer resistance to other bacteria like in the case of Vancomycin resistant *S. aureus* (Zirakzadeh and Patel, 2006). *Enterococci* are normal flora of the gastrointestinal tract and the two major pathogenic *Enterococci* are *E. faecalis* and *E. faecium* (Chlebicki and Kurup, 2008). They have gained recognition as nosocomial pathogens and have developed resistance to many commonly used antibiotics like penicillin, cephalosporins, aminoglycosides, fluoroquinolones, lincosamide and many others (Deshpande et al., 2007; Kuzucu et al., 2005; Rice, 2001). Among these resistances, the emergence of

resistant against glycopeptides is of major clinical concern. Vancomycin resistance among *Enterococci* (VRE) was first recorded in England in 1988, and subsequent development arise worldwide (Uttley et al., 1988). Reports on VRE colonization and infections in hospitalized patients have tragically increased in countries all over the world (Huh et al., 2006; Kosack et al., 2009; Yilmaz et al., 2009). Retrospective study has suggested that the major carrier for VRE is the healthy population within a community (Robredo et al., 2000).

The reasons why *Enterococci* have become established in health care facilities is their intrinsic resistance to several commonly used antibiotics and their ability to acquire resistance either by mutation or acceptance of foreign genetic material through the transfer of plasmids and transposons (Qu et al., 2007). There are seven identified phenotypes of vancomycin resistance: vanA, vanB, vanC, vanD, vanE, vanG and vanL (Boyd et al., 2008; Cetinkaya et al., 2000). The phenotypical naming of these *Enterococci* strains is based on their resistance to vancomycin and teicoplanin, the inductivity capacity of the resistance and the ability to transfer resistance to other organisms (Aznar et al., 2004). VanA and vanB have been seen in health facilities and have been major cause of serious infections (Kirdar et al., 2010; Sakka et al., 2008).

Mechanism of resistance of VRE: the *vanA* and other genes involved in the resistance (*vanR*, *vanS*, *vanH*, *vanX* and *VanZ*) reside on 10,581-bp transposon (Tn1546), which is found on a plasmid (Vilela et al., 2006). Regulation and expression of these genes results in the synthesis of abnormal peptidoglycan precursors terminating in D-alanine-D-lactate instead of D-alanine-D-alanine that contain pentapeptide intermediate structure and thus eliminate the glycopeptides target which was suppose to block the transglycosylation and transpeptidation reactions in the cell wall synthesis (Tenover, 2006).

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP)

Carbapenem Resistant *K. pneumoniae* is an emerging nosocomial pathogenic organisms and infections cause by this organism is of serious public health care concern (Falagas et al., 2007; Schwaber et al., 2008). *K. pneumoniae* is a Gram negative pathogenic bacterium causing urinary tract infections, cholecystitis, pneumonia, osteomyelitis, wound infections, thrombophlebitis, septicemia and many others. This organism has gotten recognition worldwide due to its ability to produce extended-spectrum β -lactamases (ESBLs). CRKP is resistant to almost all available antibiotics and infections have caused high morbidity and mortality especially among hospitalized patients who are seriously ill and exposed to invasive device (Goren et al., 2010; Lledo et al., 2009; Schwaber et al., 2008).

Carbapenems has been the drug of choice used to

treat serious infectious caused by *K. pneumoniae* producing ESBLs (Song et al., 2009a). Carbapenem resistance in *K. pneumoniae* has been ascribed to enzymatic activities by plasmid borne carbapenemases (Queenan and Bush, 2007). In addition to signifying resistance to carbapenems by *K. pneumoniae*, is also associated with additional mechanisms of resistance to other antibiotics like cephalosporins and monobactams, this leads to the emergence of multi-drug resistance bug (Leavitt et al., 2007; Schwaber et al., 2008).

The resistance mechanism of Carbapenem Resistant *K. pneumoniae* is the production of carbapenemase enzyme, *bla_{KPC}* (Sidjabat et al., 2011). This gene that encodes the *bla_{KPC}* resides on transposon which is mobile; this increases the risk for dissemination (Lledo et al., 2009).

Fluoroquinolone-resistant *Pseudomonas aeruginosa* (FRPA)

Fluoroquinolone-Resistant *Pseudomonas aeruginosa* is a leading cause of nosocomial infections in health care facilities worldwide (Lee et al., 2010; Zhanel et al., 2010). The spread of this organism in health care facilities is often difficult to control due to its ability to develop resistant to multiple classes of antibiotics, even during the course of treatment (Lister et al., 2009). *P. aeruginosa* is an opportunistic organism with high virulent index causing infections such as pneumonia, bacteremia, urinary tract infection, and wound infection especially among immunocompromised patients (Shams-Eldin et al., 2011). Both community acquired and hospital acquired infections caused by *P. aeruginosa* are of serious therapeutic challenge for treatment associated with high morbidity and mortality rates (Lambert et al., 2011; Shorr, 2009).

Fluoroquinolones show potency against a broad range of pathogens responsible for community-and hospital-acquired infections (Hooper, 2001; Polk et al., 2004). Broad use of these antibiotics had lead to the emergence of resistance organisms especially among Gram-negative bacteria (Zervos et al., 2003). Mechanism of resistance of *P. aeruginosa* to fluoroquinolones is predominantly due to point mutation in the DNA gyrase (*gyrA* and *gyrB*) and topoisomerases IV (*parC* and *parE*) genes (Maeda et al., 2011; Poole, 2011). This mutation makes it impossible for the fluoroquinolones to form complex with the DNA, thus not been able to block DNA replication (Poole, 2011; Tam et al., 2010). Plasmid resistance and efflux systems have also been reported in *P. aeruginosa* (Poole, 2005; Strahilevitz et al., 2009).

Cephalosporin-resistant *Escherichia coli* (CREC)

Pathogenic *Escherichia coli* are one of the leading causes of diarrhea and extraintestinal infections in

humans with high morbidity and mortality rates due to outbreaks (Flock, 2011). The emergence of a new *E. coli* strain (*E. coli* 025:H4-ST131) have been reported in Europe, this superbug is been found to be resistant to eight different classes of antibiotics including cephalosporin (Woodford et al., 2009). Recently a new superbug *E. coli* 0104:H21 emerge in Germany causing hemolytic-uremic syndrome that result in epidemic (Gallagher, 2011).

The major mechanisms of resistance of cephalosporin-resistant *E. coli* is the production of extended-spectrum β -lactamases (ESBLs) which are synthesized by the presence of plasmid genes encoding for TEM-1, TEM-2, SHV-1 or SHV-8; they are able to hydrolyze the antimicrobial agent cephalosporin (Dhanji et al., 2010; Liu et al., 2007; Livermore et al., 2007).

CONCLUSION

The emergence of antimicrobial resistance by pathogenic organisms to some extent is inevitable because of the ability to adapt and survival as a living organism. One of their mechanisms of survival is antimicrobial resistance. But it is sadden that antimicrobial resistance by pathogenic organisms is spreading at astronomical rate even to once susceptible pathogen either through new mutations or the acquisition of new genetic materials from other organisms.

The challenges presented by these resistant pathogenic organisms can be effectively tackle by molecular epidemiology and molecular analyses of mechanisms of antimicrobial resistance; these will greatly help in developing new antimicrobial agents with different mechanism of action against the pathogenic organisms.

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REFERENCES

- Abd El-Moez SI, Dorgham SM, Abd El-Aziz E (2011). Methicillin resistant *Staphylococcus aureus* - post surgical infections in Egyptian hospital. *Life Sci. J.* 8: 520-526.
- Adaleti R, Nakipoglu Y, Ceran N, Tasdemir C, Kaya F, Tasdemir S (2010). Prevalence of phenotypic resistance of *Staphylococcus aureus* isolates to macrolide, lincosamide, streptogramin B, ketolid and linezolid antibiotics in Turkey. *Braz. J. Infect. Dis.* 14: 11-14.
- Ahmed AM, Furuta K, Shimomura K, Kasama Y, Shimamoto T (2006). Genetic characterization of multidrug resistance in *Shigella* spp. from Japan. *J. Med. Microbiol.* 55: 1685-1691.
- Arias CA, Contreras GA, Murray BE (2010). Management of multidrug-resistant enterococcal infections. *Clin. Microbiol. Infect.* 16: 555-562.
- Arias CA, Murray BE (2009). Antibiotic-resistant bugs in the 21st century - A clinical super challenge. *N. Engl. J. Med.* 360: 439-443.
- Aznar E, Buendía B, García-Peñuela E, Escudero E, Alarcón T, López-Brea M (2004). Community-acquired urinary tract infection caused by vancomycin-resistant *Enterococcus faecalis* clinical isolate. *Rev. Esp. Quimioter.* 17: 263-265.
- Babalola OO, Kirby BM, Le Roes-Hill M, Cook AE, Cary SC, Burton SG, Cowan DA (2009). Phylogenetic analysis of actinobacterial populations associated with Antarctic dry valley mineral soils. *Environ. Microbiol.* 11: 566-576.
- Baltz RH (2009). Daptomycin: Mechanisms of actions, resistance, and biosynthetic engineering. *Curr. Opin. Chem. Biol.* 13: 144-151.
- Bergstrom R (2011). The role of the pharmaceutical industry in meeting the public health threat of antibacterial resistance. *Drug Resist. Updat.* 14: 77-78.
- Bester LA, Essack SY (2010). Antibiotic resistance via the food chain: Fact or fiction? *S. Afr. J. Sci.* 106: 1-5.
- Bhattacharya D, Purushottaman SA, Bhattacharjee H, Thamizhmani R, Sudharama SD, Manimunda SP, Bharadwaj AP, Singhanian M, Roy S (2011). Rapid emergence of third-generation cephalosporin resistance in *Shigella* sp. Isolated in Andaman and Nicobar Islands, India. *Microb. Drug Resist.* 17: 329-332.
- Biendo M, Adjid'e C, Castelain S, Belmekki M, Rousseau F, Slama M, Ganry O, Schmit JL, Eb F (2010). Molecular characterization of glycopeptide-resistant enterococci from hospitals of the Picardy Region (France). *Int. J. Microbiol.* :doi:10.1155/2010/150464.
- Boehr DD, Draker K, Kalinka K, Bains M, Hancock RE, Wright GD (2003). Broad-spectrum peptide inhibitors of aminoglycoside antibiotic resistance enzymes. *Chem. Biol.* 10: 189-196.
- Boyd DA, Willey BM, Fawcett D, Gillani N, Mulvey MR (2008). Molecular characterization of *Enterococcus faecalis* N06-0364 with low-level vancomycin resistance harboring a novel d-Ala-d-Ser gene cluster, vanL. *Antimicrob. Agents Chemother.* 52: 2667-2672.
- Calfee D, Jenkins SG (2008). Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant *Klebsiella pneumoniae* in intensive care unit patients. *Infect. Control Hosp. Epidemiol.* 29: 966-968.
- Cardoso LS, Araujo MI, Góes AM, Pacífico LG, Oliveira RR, Oliveira SC (2007). Polymyxin B as inhibitor of LPS contamination of *Schistosoma mansoni* recombinant proteins in human cytokine analysis. *Microb. Cell Fact.* 6:doi: 10.1186/1475-2859-1186-1181.
- Caron WP, Mousa SA (2010). Prevention strategies for antimicrobial resistance: A systematic review of the literature. *Infect. Drug Resist.* 3: 25-33.
- Cetinkaya Y, Falk P, Mayhal CG (2000). Vancomycin-resistant enterococci. *Clin. Microbiol. Rev.* 13: 686-707.
- Chlebicki MP, Kurup A (2008). Vancomycin-resistant enterococcus: A review from Singapore perspective. *Ann. Acad. Med. Singapore* 37: 861-869.
- Currie A, MacDonald J, Ellis A, Siushansian J, Chui L, Charlebois M, Peermohamed M, Everett D, Fehr M, Lai-King NG (2007). Outbreak of *Escherichia coli* O157:H7 infections associated with consumption of beef donair. *J. Food Prot.* 70: 1483-1488.
- Das S, Choudhry S, Saha R, Ramachandran VG, Kaur K, Sarkar BL (2011). Emergence of multiple drug resistance *Vibrio cholerae* O1 in East Delhi. *J. Infect. Dev. Countries* 5: 294-298.
- Davis SL, Perri MB, Donabedian SM, Manierski C, Singh A, Vager D, Haque NZ, Speirs K, Muder RR, Robinson-Dunn B, Hayden MK, Zervos MJ (2007). Epidemiology and outcomes of community-associated methicillin-resistant *Staphylococcus aureus* infection. *J. Clin. Microbiol.* 45: 1705-1711.
- DeLeo FR, Chambers HF (2009). Reemergence of antibiotic-resistant *Staphylococcus aureus* in the genomics era. *J. Clin. Investig.* 119: 2464-2474.
- Deshpande LM, Fritsche TR, Moet GJ, Biedenbach DJ, Jones RN (2007). Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: A report from the SENTRY antimicrobial surveillance program. *Diagn. Microbiol. Infect. Dis.* 58: 163-170.
- Dhanji H, Murphy NM, Doumith M, Durmus S, Surman Lee S, Hope R, Woodford N, Livermore DM (2010). Cephalosporin resistance mechanisms in *Escherichia coli* isolated from raw chicken imported into the UK. *J. Antimicrob. Chemother.*:doi: 10.1093/jac/dkq1376.
- Drawz SM, Bonomo RA (2010). Three decades of β -lactamase

- inhibitors. *Clin. Microbiol. Rev.* 23: 160-201.
- Dunkle JA, Xiong L, Mankin AS, Cate JHD (2010). Structures of the *Escherichia coli* ribosome with antibiotics bound near the peptidyl transferase center explain spectra of drug action. *PNAS* 107: 17152-17157.
- Edoh D, Alomatu B (2007). Comparison of antibiotic resistance patterns between laboratories in Accra East, Ghana. *AJST*, 8: 1-7.
- Falagas ME, Rafailidis PI, Kofleridis D, Vartzili S, Chelvatoglou FC, Papaioannou V, Maraki S, Samonis G, Michalopoulos A (2007). Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: A matched case-control study. *J. Antimicrob. Chemother.* 60: 1124-1130.
- Farrell DJ, Castanheira M, Chopra I (2011). Characterization of global patterns and the genetics of fusidic acid resistance. *Clin. Infect. Dis.* 52: S487-S492.
- Feliziani S, Luján AM, Moyano AJ, Sola C, Bocco JL, Montanaro P, Canigia LF, Argaraña CE, Smania AM (2010). Mucoicid, quorum sensing, mismatch repair and antibiotic resistance in *Pseudomonas aeruginosa* from cystic fibrosis chronic airways infections. *PLoS ONE*, 5: e12669.
- Flock E (2011). *E. coli* outbreak not from cucumbers: *E. coli* explained. The Washington post. Washington. Online at: www.washingtonpost.com/blogs/blogpost/post/e-coli-outbreaks-and-cucumber-victims-e-coli-explained/2011/05/2011/AGzbzOFH_blog.html. (June 10, 2011).
- Focks A, Klasmeier J, Matthies M (2010). Mechanistic link between uptake of sulfonamides and bacteriostatic effect: Model development and application to experimental data from two soil microorganisms. *Environ. Toxicol. Chem.* 29: 1445-1452.
- Folster JP, Pecic G, Bowen A, Rickert R, Carattoli A, Whichard JM (2011). Decreased susceptibility to ciprofloxacin among *Shigella* Isolates in the United States, 2006 to 2009. *Antimicrob. Agents Chemother.* 55: 1758-1760.
- Fortaleza CMCB, Bacchi CE, Oliveira DE, Ramos MC (2011). Polyclonal endemicity of *Pseudomonas aeruginosa* in a teaching hospital from Brazil: Molecular typing of decade-old strains. *J. Venom. Anim. Toxins Incl. Trop.* 17: 176-183.
- Gallagher J (2011). Outbreak is new form of *E. coli* London. Online at: www.bbc.co.uk/news/health_13626499. (June 13, 2011).
- García-Álvarez L, Holden MTG, Lindsay H, Webb CR, Brown DFJ, Curran MD, Walpole E, Brooks K, Pickard DJ, Teale C, Parkhill J, Bentley SD, Edwards GF, Girvan EK, Kearns AM, Pichon B, Hill RLR, Larsen AR, Skov RL, Peacock SJ, Maskell DJ, Holmes MA (2011). Meticillin-resistant *Staphylococcus aureus* with a novel *mecA* homologue in human and bovine populations in the UK and Denmark: A descriptive study. *Lancet Infect. Dis.* doi:10.1616/S1473-3099(1011)70126-70128.
- Gerberding JL (2003). Faster, but fast enough? Responding to the epidemic of severe acute respiratory syndrome. *N. Engl. J. Med.* 348: 2030-2031.
- Golberg MB (2009). Pathogenesis of *Shigella* infection. Online at: www.uptodate.com/contents/pathogenesis-of-shigella-infection.
- Goren MG, Carmeli Y, Schwaber MJ, Chmelnitsky I, Schechner V, Navon-Venezia S (2010). Transfer of carbapenem-resistant plasmid from *Klebsiella pneumoniae* ST258 to *Escherichia coli* in patient. *Emerg. Infect. Dis.* 16: 1014-1017.
- Gorgani N, Ahlbrand S, Patterson A, Pourmand N (2009). Detection of point mutations associated with antibiotic resistance in *Pseudomonas aeruginosa*. *Int. J. Antimicrob. Agents*, 34: 414-418.
- Gould SWJ, Cuschieri P, Rollason J, Hilton AC, Easmon S, Fielder MD (2010). The need for continued monitoring of antibiotic resistance patterns in clinical isolates of *Staphylococcus aureus* from London and Malta. *Ann. Clin. Microbiol. Antimicrob.* 9. <http://www.annclinmicrob.com/content/9/1/20>.
- Griffin MO, Fricovsky E, Ceballos G, Villarreal F (2010). Tetracyclines: A pleiotropic family of compounds with promising therapeutic properties. Review of the literature. *Am. J. Physiol. Cell Physiol.* 299: C539-C548.
- Hartmann G, Honikel K, Knüsel F, Nüesch J (1967). The specific inhibition of the DNA-directed RNA synthesis by rifamycin. *Biochem. Biophys. Acta*, 145: 843-844.
- Harvey RA, Champe PC, Fisher BD (2007). Lippincott's Illustrated Reviews: Microbiology. Lippincott' Williams and Wilkins, Baltimore. pp. 11-18.
- Hooper DC (2001). Emerging mechanisms of fluoroquinolone resistance. *Emerg. Infect. Dis.* 7: 337.
- Huh JY, Lee WG, Jin HY (2006). Molecular characterization of vancomycin-resistant enterococci from clinical and surveillance specimens. *Infect. Control Hosp. Epidemiol.* 27: 1076-1080.
- Ito T, Kuwahara K, Hiramatsu K (2007). Staphylococcal cassette chromosome mec (SCC mec) analysis of MRSA. *Methods Mol. Biol.* 391: 87-102.
- Jassal M, Bishai WR (2009). Extensively drug-resistant tuberculosis. *Lancet Infect. Dis.* 9: 19-30.
- Jensen SO, Lyon BR (2009). Genetics of antimicrobial resistance in *Staphylococcus aureus*. *Future Microbiol.* 4: 565-582.
- Jones KE, Patel NG, Levy MA, Storegard A, Balk D, Guttelman JL, Daszal L (2008). Global trends in emerging infectious diseases. *Nat. Rev. Microbiol.* 451: 990-993.
- Jones RN, Sader HS, Erwin ME, Anderson SA (1995). Emerging multiple resistant enterococci among clinical isolates. *Diagn. Microbiol. Infect. Dis.* 21: 85-93.
- Kashyap D, Wang M, Liu L, Boons G, Gupta D, Dziarski R (2011). Peptidoglycan recognition proteins kill bacteria by activating protein-sensing two-component systems. *Nat. Med.* 17: 676-683.
- Kelland K (2011). Scientists find superbugs in Delhi drinking water. London. Online at: www.reuters.com/article/2011/2004/2007/us-bacteria-superbugs-india.
- Kirdar S, Sener AG, Arslan U, Yurtsever SG (2010). Molecular epidemiology of vancomycin-resistant *Enterococcus faecium* strains isolated from hematological malignancy patients in a research hospital in Turkey. *J. Med. Microbiol.* 59: 660-664.
- Klein E, Smith DL, Laxminarayan R (2007). Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999-2005. *Emerg. Infect. Dis.* 13: 1840-1847.
- Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R (2006). Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992-2003. *Clin. Infect. Dis.* 42: 389-491.
- Kohanski MA, Dwyer DJ, Collins JJ (2010). How antibiotics kill bacteria: From targets networks. *Nat. Rev. Microbiol.* 8(6): 423-435.
- Kosack A, Riedel E, Kiehn TE, Small TN, Wexler LH, Dunkel IJ (2009). Vancomycin-resistant enterococcus in pediatric oncology patients: An analysis of potential consequences of colonization and infection. *Pediatr. Blood Cancer*, 52: 300-302.
- Koser CU, Veerapen-Pierce RN, Summers DK, Archer JAC, Bifani P, Wintjens R, Mathys V, Mathema B, Baulard A, Forgacs P, Zimmerman SK, Silverman ML, Wengenack NL, Hall L, Roberts GD (2010). Role of mutations in dihydrofolate reductase *dhfrA* (Rv2763c) and thymidylate synthase *thyA* (Rv2764c) in *Mycobacterium tuberculosis* drug resistance. *Antimicrob. Agents Chemother.* 54: 4522-4525.
- Koskella B, Taylor TB, Bates J, Buckling A (2011). Using experimental evolution to explore natural patterns between bacterial motility and resistance to bacteriophages. *ISME J*: <http://dx.doi.org/10.1038/ismej.2011.1047>.
- Kostopoulou ON, Kourelis TG, Mamos P, Magoulas GE, Kalpaxis DL (2011). Insights into the chloramphenicol inhibition effect on peptidyl transferase activity, using two new analogs of the drug. *Open Enzym. Inhib. J.* 4: 1-10.
- Kuzucu C, Cizmeci Z, Durmaz R, Durmaz B, Ozerol IH (2005). The prevalence of fecal colonization of enterococci, the resistance of the isolates to ampicillin, vancomycin, and high-level aminoglycosides, and the clonal relationship among isolates. *Microb. Drug Resist.* 11: 159-164.
- Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, Agodi A, Frank U, Mertens K, Schumacher M, Wolkewitz M (2011). Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: A cohort study. *Lancet Infect. Dis.* 11: 30-38.
- Lamichhane G, Freundlich JS, Ekins S, Wickramaratne N, Nolan ST, Bishai WR (2011). Essential metabolites of *Mycobacterium tuberculosis* and their mimics. *mBio* 2:doi:10.1128/mBio.00301-00310.

- Lanini S, D'Arezzo S, Puro V, Martini L, Imperi F, Piselli P, Montanaro M, Paoletti S, Visca P, Ippolito G (2009). Molecular epidemiology of a *Pseudomonas aeruginosa* hospital outbreak driven by a contaminated disinfectant-soap dispenser. *PLoS ONE* 6: e17064.
- Leavitt A, Navon-Venezia S, Chmelnitsky I, Schwaber MJ, Carmeli Y (2007). Emergence of KPC-2 and KPC-3 in carbapenem-resistant *Klebsiella pneumoniae* strains in an Israeli hospital. *Antimicrob. Agents Chemother.* 51: 3026–3029.
- Lee Y, Liu H, Lin Y, Sun K, Chun C, Hsueh P (2010). Fluoroquinolone resistance of *Pseudomonas aeruginosa* isolates causing nosocomial infection is correlated with levofloxacin but not ciprofloxacin use. *Int. J. Antimicrob. Agents*, 35: 261–264.
- Lister PD, Wolter DJ, Hanson ND (2009). Antibacterial-resistant *Pseudomonas aeruginosa*: Clinical Impact and complex regulation of chromosomally encoded resistance mechanisms. *Clin. Microbiol. Rev.* 22: 582-610.
- Liu JH, Wei SY, Ma JY, Zeng ZL, Lü, D.H., Yang GX, Chen ZL (2007). Detection and characterisation of CTX-M and CMY-2 beta-lactamases among *Escherichia coli* isolates from farm animals in Guangdong Province of China. *Int. J. Antimicrob. Agents*, 29: 576–581.
- Livermore DM, Canton R, Gniadkowski M, Nordmann P, Rossolini GM, Arlet G, Ayala J, Coque TM, Kern-Zdanowicz I, Luzzaro F, Poirel L, Woodford N (2007). CTX-M: Changing the face of ESBLs in Europe. *J. Antimicrob. Chemother.* 59: 165–174.
- Lledo W, Hernandez M, Lopez E, Molinari OL, Soto RQ, Hernandez E, Santiago N, Flores M, Vazquez GJ, Robledo IE, Garcia-Rivera E, Cortes A, Ramos M, Goering R, Srinivasan A, Gould C, Stine N, Bell M, Anderson K, Kitchel B, Wong B, Rasheed JK, Patel J, Tomashek K, Llata E, Gregory CJ (2009). Guidance for control of infections with carbapenem-resistant or carbapenemase-producing enterobacteriaceae in acute care facilities. *MMWR* 58: 256-260.
- Luzhetskyy A, Pelczar S, Bechthold A (2007). The future of natural products as a source of new antibiotics. *Curr. Opin. Investig. Drugs*, 8: 608-613.
- Maeda Y, Murayama M, Goldsmith CE, Coulter WA, Mason C, Millar BC, Dooley JSG, Lowery CJ, Matsuda M, Rendall JC, Elborn JS, Moore JE (2011). Molecular characterization and phylogenetic analysis of quinolone resistance-determining regions (QRDRs) of *gyrA*, *gyrB*, *parC* and *parE* gene loci in viridans group streptococci isolated from adult patients with cystic fibrosis. *J. Antimicrob. Chemother.* 66: 476-486.
- Mandsberg LF, Ciofu O, Kirkby N, Christiansen LE, Poulsen HE, Hoiby N (2009). Antibiotic resistance in *Pseudomonas aeruginosa* strains with increased mutation frequency due to inactivation of the DNA oxidative repair system. *Antimicrob. Agents Chemother.* 53: 2483-2491.
- Maree CL, Daum RS, Boyle-Vavra S, Matayoshi K, Miller LG (2007). Community-associated methicillin-resistant *Staphylococcus aureus* isolates causing healthcare-associated infections. *Emerg. Infect. Dis.* 13: 236-242.
- McBride SM, Fischetti VA, LeBlanc DJ, Moellering RC, Gilmore MS (2007). Genetic diversity among *Enterococcus faecalis*. *PLoS ONE* 2(7): e582. doi://510.1371/journal.pone.0000582.
- McKee EE, Ferguson M, Bentley AT, Marks TA (2006). Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones. *Antimicrob. Agents Chemother.* 50: 2042-2049.
- Milheiro C, Portelinha A, Krippahl L, de Lencastre H, Oliveira DC (2011). Evidence for a purifying selection acting on the b-lactamase locus in epidemic clones of methicillin-resistant *Staphylococcus aureus*. *BMC Microbiol.* 11: 76-86.
- Miller LG, Diep BA (2008). Clinical practice - Colonization, fomites, and virulence: Rethinking the pathogenesis of community-associated methicillin-resistant *Staphylococcus aureus* infection. *Clin. Infect. Dis.* 46: 752-760.
- Mindlin SZ, Soina VS, Petrova MA, Gorlenko ZM (2008). Isolation of antibiotic resistance bacterial strains from Eastern Siberia Permafrost sediment. *Russ. J. Genet.* 44: 36-44.
- Moore SL, Payne DN (2008). Types of Antimicrobial Agents. Russell, Hugo and Ayliffe's Principles and Practice of Disinfection, Preservation and Sterilization. Blackwell Publishing Ltd. pp. 8-97.
- Moya B, Dötsch A, Juan C, Blázquez J, Zamorano L, Haussler S, Oliver A (2009). β -lactam resistance response triggered by Inactivation of a nonessential penicillin-binding protein. *PLoS Pathog.* 5: e1000353.
- Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, Johnson SK, Vandenesch F, Fridkin S, O'Boyle C, Danila RN, Lynfield R (2003). Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* 290: 2976-2984.
- Nakaminami H, Noguchi N, Sasatsu M (2010). Fluoroquinolone efflux by the plasmid-mediated multidrug efflux pump *qacB* Variant *qacBIII* in *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 54: 4107-4111.
- Newman DJ, GMC (2007). Natural products as sources of new drugs over the last 25 years. *J. Nat. Prod.* 70: 461-477.
- O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, Lee E, Mulholland K, Levine OS, Cherian T (2009). Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: Global estimates. *Lancet*, 374: 893-902.
- Olaniran AO, Naicker K, Pillay B (2011). Toxigenic *Escherichia coli* and *Vibrio cholerae*: Classification, pathogenesis and virulence determinants. *Biotechnol. Mol. Biol. Rev.* 6: 94-100.
- Oliphant CM, Green GM (2002). Quinolones: A comprehensive review. *Am. Fam. Physician*, 65: 455-464.
- Olofsson SK, Cars O (2007). Optimizing drug exposure to minimize selection of antibiotic resistance. *Clin. Infect. Dis.* 45: S129-S136.
- Osburne MS, Rothstein DM, Farquhar R, Murphy CK (2006). *In vitro* time-till Activities of rifalazil, alone and in combination with vancomycin, against logarithmic and stationary cultures of *Staphylococcus aureus*. *J. Antibiot.* 59: 80-85.
- Palacios DS, Dailey I, Siebert DM, Wilcock BC, Burke MD (2010). Synthesis-enabled functional group deletions reveal key underpinnings of amphotericin B ion channel and antifungal activities. *PNAS*, 108: 6733-6738.
- Pantosti A, Venditti M (2009). What is MRSA? *Eur. Respir. J.* 34:1190-1196.
- Perichon B, Courvalin P (2009). VanA-type vancomycin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 53: 4580-4587.
- Périchon B, Courvalin P, Moselio S (2009). Antibiotic Resistance. *Encyclopedia of Microbiology*. Academic Press: Oxford. pp. 193-204.
- Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, Craig AS, Schaffner W, Zansky SM, Gershman K, Stefonek KR, Albanese BA, Zell ER, Schuchat A, Schrag SJ (2008). Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *JAMA*, 299: 2056-2065.
- Polk RE, Johnson CK, McClish D, Wenzel RP, Edmond MB (2004). Predicting hospital rates of fluoroquinolone-resistant *Pseudomonas aeruginosa* from fluoroquinolone use in US hospitals and their surrounding communities. *Clin. Infect. Dis.* 39: 497-503.
- Poole K (2005). Efflux-mediated antimicrobial resistance. *J. Antimicrob. Chemother.* 56: 20-51.
- Poole K (2007). Efflux pumps as antimicrobial resistance mechanisms. *Ann. Med.* 39: 162-176.
- Poole K (2011). *Pseudomonas aeruginosa*: resistance to the max. *Front. Microbiol.* 2:doi:10.3389/fmicb.2011.00065.
- Proctor RA (2008). Role of folate antagonists in the methicillin-resistant *Staphylococcus aureus* infection. *Clin. Infect. Dis.* 46: 584-593.
- Qu T, Chen Y, Yu Y, Lv H, Dong X, Xiao Z, Gu H, Li L (2007). Molecular characterization of vancomycin-resistant enterococci in Hangzhou, China. *J. Antimicrob. Chemother.*:doi:10.1093/jac/dkm1399.
- Queenan AM, Bush K (2007). Carbapenemases: The versatile β -lactamases. *Clin. Microbiol. Rev.* 20: 440–458.
- Ray P, Sharma J, Marak RS, Garg RK (2006). Predictive efficacy of nalidixic acid resistance as a marker of fluoroquinolone resistance in *Salmonella enterica* var *Typhi*. *Indian J. Med. Res.* 124: 105-108.
- Rice LB (2001). Emergence of vancomycin-resistant enterococci. *Emerg. Infect. Dis.* 7: 183-187.
- Robredo B, Singh KV, Baquero F, Murray BE, Torres C (2000). Vancomycin-resistant enterococci isolated from animals and food. *Int. J. Food Microbiol.* 54: 197–204.
- Rubinstein G, Bavdaz B, De Bunder S, Blazquez N (2011). Trends in macrolide resistance for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus pneumoniae* and its association with

- social clustering in Argentina. *Open Antimicrob. Agents J.* 3: 1-5.
- Rupnik M, Wilcox MH, Gerding DN (2009). *Clostridium difficile* infection: New developments in epidemiology and pathogenesis. *Nat. Rev. Microbiol.* 7: 526-536.
- Sakka V, Tsiodras S, Galani L, Antoniadou A, Souli M, Galani I, Pantelaki M, Siafakas N, Zerva L, Giamarellou H (2008). Risk-factors and predictors of mortality in patients colonised with vancomycin-resistant enterococci. *Clin. Microbiol. Infect.* 14: 14-21.
- Sakoulas G, Moellering RC (2008). Increasing antibiotic resistance among methicillin-resistant *Staphylococcus aureus* strains. *Clin. Infect. Dis.* 46: 360-367.
- Sandhyarani N (2011). *Klebsiella pneumoniae*. Online at: www.buzzle.com/articles/klebsiella-pneumoniae.html. (May 25, 2011).
- Scheurwater EM, Burrows LL (2011). Maintaining network security: How macromolecular structures cross the peptidoglycan layer. *FEMS Microbiol. Lett.* 318: 1-9.
- Schroeder GN, Hilbi H (2008). Molecular pathogenesis of *Shigella* spp.: Controlling host cell signaling, invasion, and death by type III secretion. *Clin. Microbiol. Rev.* 21: 134-156.
- Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y (2008). Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrob. Agents Chemother.* 52: 1028-1033.
- Shams-Eldin E, Abdalla S, Shawki AE-DM, Galal-Eldin A (2011). Comparison between outer membrane protein profile of fluoroquinolones sensitive and resistant *P. aeruginosa* isolated from Egyptian patients. *J. Am. Sci.* 7: 100-104.
- Shorr AF (2009). Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit. Care Med.* 37: 1463-1469.
- Sidjabat H, Nimmo GR, Walsh TR, Binotto E, Htin A, Hayashi Y, Li J, Nation RL, George N, Paterson DL (2011). Carbapenem resistance in *Klebsiella pneumoniae* due to the New Delhi metallo- β -lactamase. *Clin. Infect. Dis.* 52: 481-484.
- Sieradzki K, Markiewicz Z (2004). Mechanism of vancomycin resistance in methicillin resistant *Staphylococcus aureus*. *Pol. J. Microbiol.* 53: 207-214.
- Song W, Suh B, Choi JY, Jeong SH, Jeon EH, Lee YK, Hong SG, Lee, Kyungwon (2009). *In vivo* selection of carbapenem-resistant *Klebsiella pneumoniae* by OmpK36 loss during meropenem treatment. *Diag. Microbiol. Infect. Dis.* 65: 447-449.
- Strahilevitz J, Jacoby GA, Hooper DC, Robicsek A (2009). Plasmid-mediated quinolone resistance: A multifaceted threat. *Clin. Microbiol. Rev.* 22: 664-689.
- Tam VH, Chang KT, Abdelraouf K, Brioso CG, Ameka M, McCaskey LA, Weston JS, Caeiro JP, Garey KW (2010). Prevalence, resistance mechanisms, and susceptibility of multidrug-resistant bloodstream isolates of *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* 54: 1160-1164.
- Tenover FC (2006) Mechanisms of antimicrobial resistance in bacteria. *Am. J. Med.* 119: 3-10.
- Todar K (2011). *Todar's Online Textbook of Bacteriology*. www.textbookofbacteriology.net.
- Uttley AH, Collins CH, Naidoo J, George RC (1988). Vancomycin-resistant enterococci. *Lancet*, 1: 57-58.
- Vekshin N (2011). Melting of DNA-actinomycin clusters. *J. Biochem.* 149: 601-607.
- Vila J, Pal T (2010). Update on antibacterial resistance in low income countries: Factors favoring the emergence of resistance. *Open Infect. Dis. J.* 4: 38-54.
- Vilela MA, Souza SL, Palazzo VCI, Ferreira JC, Morais MA, Darini AL, Morais MM (2006). Identification and molecular characterization of Van A-type vancomycin-resistant *Enterococcus faecalis* in northeast of Brazil. *Mem. Inst. Oswaldo Cruz*, 101: 715-719.
- Wagenlehner FME, Weidner W, Naber KG (2008). Antibiotics in urology - New essentials. *Urol. Clin. North Am.* 35: 69-79.
- Wang JL, Chen SY, Wang JT, Wu GHM, Chiang WC, Hsueh PR, Chen YC, Chang SC (2008). Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus*. *Clin. Infect. Dis.* 46: 799-806.
- Waters AE, Contente-Cuomo T, Buchhagen J, Liu CM, Watson L, Pearce K, Foster JT, Bowers J, Driebe EM, Engelthaler DM, Keim PS, Price LB (2011). Multidrug-resistant *Staphylococcus aureus* in US meat and poultry. *Clin. Infect. Dis.*:doi: 10.1093/cid/cir1181.
- WHO (2011). Antimicrobial resistance. www.who.int/drugresistance/en/. (April 25, 2011).
- Willey J, Sherwood L, Woolverton C (2010). *Prescott's Microbiology*. McGraw-Hill.
- Woodford N, Carattoli A, Karisik E, Underwood A, Ellington M, Livermore D (2009). Complete nucleotide sequences of plasmids pEK204, pEK499, and pEK516, encoding CTX-M enzymes in three major *Escherichia coli* lineages from the United Kingdom, all belonging to the international O25:H4-ST131 Clone. *Antimicrob. Agents Chemother.* 53: 4472-4482.
- Woolhouse MEJ (2008). Epidemiology: Emerging diseases go global. *Nat. Rev. Microbiol.* 451: 898-899.
- Wright A, Zignol M, Van Deun A, Falzon D, Gerdes SR, Feldman K, Hoffner S, Drobniewski F, Barrera L, van Soolingen D, Boulabhal F, Paramasivan CN, Kam KM, Mitarai S, Nunn P, Raviglione M (2009). Epidemiology of antituberculosis drug resistance 2002-07: An updated analysis of the global project on anti-tuberculosis drug resistance surveillance. *Lancet*, 373: 1861-1873.
- Yilmaz NO, Agus N, Yurtsever SG, Ozer E, Afacan G, Omer O (2009). Prevalence and risk factors associated with vancomycin-resistant enterococci colonization. *R. Ci. méd. biol., Salvador*, 8: 283-291.
- Yin Y, Tian D, Jiao H, Zhang C, Pan Z, Zhang X, Wang X, Jiao X (2011). Pathogenicity and immunogenicity of a mutant strain of *Listeria monocytogenes* in the chicken infection model. *Clin. Vacc. Immunol.* 18: 500-505.
- Zell BL, Goldmann DA (2007). Healthcare-associated infection and antimicrobial resistance moving beyond description to prevention. *Infect. Control Hosp. Epidemiol.* 28: 261-264.
- Zervos MJ, Hershberger E, Nicolau DP, Ritchie DJ, Blackner LK, Coyle EA, Donnelly AJ, Eckel SF, Eng RHK, Hiltz A (2003). Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 United States teaching hospitals, 1991-2000. *Clin. Infect. Dis.* 37: 1643-1648.
- Zhanell GG, Decorby M, Adam H, Mulvey MR, McCracken M, Lagace-Wiens P, Nichol KA, Wierzbowski A, Baudry PJ, Tailor F, Karlowsky JA, Walkty A, Schweizer F, Johnson J, Hoban DJ (2010). Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: Results of the Canadian ward surveillance study (CANWARD 2008). *Antimicrob. Agents Chemother.* 54: 4684-4693.
- Zirakzadeh A, Patel R (2006). Vancomycin-resistant enterococci: Colonization, infection, detection, and treatment. *Mayo Clin. Proc.* 81: 529-536.