Antimicrobial resistance developed in several pathogens poses an increasing threat to human health across the world. No country can escape from the medical and economic impacts from this serious problem. Although the antibiotic resistance is not a new phenomenon, the current magnitude and speed with which it is developing is a cause for the global concern including in India. There are so many common diseases resulting from the microorganisms such as blood stream infections, urinary tract infections, post-operative wound infections and intra-abdominal infections. In this review the antimicrobial susceptibility or resistance of Enterobacter towards antimicrobial agents and heavy metals, viz. ceftazidime, moxifloxacin, nalidixic acid, sulfamethaxazole, and nickel and lead is discussed briefly along with other antimicrobials and heavy metals. The mechanisms behind the resistance by Enterobacter was analyzed and evaluated by many workers after using currently employed susceptibility testing methods for Enterobacter spp. There are some factors influencing mode of action of fluoroquinolones, quinolones and sulfamethaxazole. History, classification, identification, clinical features and treatment of infections and the epidemiology of antimicrobials (drugs and heavy metals) resistance by the Enterobacter spp. is included in this review. Now a day, antimicrobial resistance is common in hospitals where acquired infections can be perilous. This situation compels scientists to synthesize new antibiotics and treatment modalities. Enterobacter causes nosocomial infections. It is ubiquitous and can survive on skin and dry surfaces and replicate in contaminated fluids. Numerous outbreaks have been described. Various mechanisms have been adapted by microorganisms to resist toxicity of antimicrobials. Antimicrobial drugs may be rendered inactive or ineffective by the major ways such as barrier to antibiotic entry into the bacterial cell, prevention of the antibiotic from reaching the target, often by extrusion, alteration of the target of the drug and inactivation of the antibiotic by modification or destruction. In addition, bacteria may be able to bypass the metabolic pathway affected by a particular drug or may be able to overproduce an enzyme that is inhibited by the drug action, more than one mechanism may operate at any given time.

**Key words:** Enterobacter, resistance, mechanism, ceftazidime, moxifloxacin, nalidixic acid, nickel, lead.

**INTRODUCTION**

Microbes, man and environment have intrinsic correlation that exists since time immemorial. They have evolved umpteen number of mechanisms to survive and keep them fit in nature. Resistance is a complex phenomenon that involves the microorganism, the environment and the patient-separately and interactively. Resistance may be a characteristic of the microbe before exposure to a given drug or may arise as a consequence.
of therapy. Resistance usually involves gradation, rather than being an “all or none” phenomenon. Antimicrobial resistance is defined as a property of bacteria that confers the capacity to inactivate or exclude antimicrobials, or a mechanism that blocks the inhibitory or killing effects of antimicrobials, leading to survival despite exposure to antimicrobials (Bagde, 2014). Simply put, microbial resistance may be defined as the ability of a specific microorganism to withstand a drug that interferes with its growth functions (Meyers, 1987).

The consequence of resistance affects not only patient’s lives but also reaches far beyond the individual patient, affecting health care system and society across the world (Giske et al., 2008). The ongoing pandemic spread of resistance bacteria illustrates that the problem can only be addressed through international cooperation. We may very well be forced with unimaginable setbacks medically, socially, and economically within just few years.

Scope of resistance phenomenon is expanding every day. Microbes initially were resistance to common antimicrobials have now developing resistance to any antimicrobial that is antagonistic to its survival that includes drugs, antibiotics, heavy metals and other antimicrobials such as preservatives and other chemicals (Bagde, 2014). Nowadays, antimicrobial resistance which is spreading rapidly is of great concern, because it is common in hospitals where acquired infections can be perilous. This situation compels scientists to synthesize new antibiotics and treatment modalities. The reason of microbial resistance can be due to increased misuse of antibiotics in foods (livestock, poultry and agriculture). A number of significant factors, such as organism identification, antibiotic sensitivity testing and host factor situations, should be taken into account in order to treat various infections effectively.

Microbial resistance to antimicrobials may be present since immemorial time. It is known that resistance genes and plasmids were present in bacteria even before the advent of antibiotics. It is likely that in their struggle for survival in nature the bacteria may have developed resistance genes.

Although the discovery of antibiotics creates a new era in the treatment of infectious diseases, the bacterial evolutionary response exerts a selective pressure on it. An antibiotic kills the susceptible bacteria and favors the overgrowth of these bacteria that carry a resistant gene. Thus these antimicrobial agents induce the development of resistance by multiplication and spread resistance. Examples of resistance to chemotherapy have been noted in all categories of microorganisms including bacteria, fungi, viruses and parasites. To date, resistance in bacteria is most prevalent (Richman, 1995; Dixon et al., 1996).

The present scenario is such that the available antibiotics have become ineffective in diseases of proven bacterial etiology especially in a hospital setting. To add to this previously harmless species, are now being reported to be posing a serious therapeutic challenge, for example; recently, a study by Prakash et al. (2005) reported high-level aminoglycoside and β-lactam resistance among unusual (non-faecalis and non-faecium enterococci) and atypical (biochemical variant) species of enterococci at a hospital (JIPMER) in South India.

**Phenomenon of microbial resistance**

Antimicrobial drugs may be rendered inactive or ineffective in the following major ways: (1) Barrier to antibiotic entry into the bacterial cell; (2) Prevention of the antibiotic from reaching the target, often by extrusion; (3) Alteration of the target of the drug and (4) Inactivation of the antibiotic by modification or destruction (Berkowitz, 1995; Neu, 1995). In addition, bacteria may be able to bypass the metabolic pathway affected by a particular drug or may be able to overproduce an enzyme that is inhibited by the drug action, such as occurs in resistance to the folate antagonists. More than one mechanism may operate at any given time (Berkowitz, 1995).

**Mechanism of microbial resistance towards antimicrobial agent**

Bacteria may manifest resistance to antibacterial drugs through a variety of mechanisms. Some species of bacteria are innately resistant to more than one class of antimicrobial agents. First of all, the organisms destroy the antibacterial agent before it can have an effect. In this microorganism may undergo gene acquisition encoding B-lactamases enzyme. Second, bacteria may acquire efflux pumps that extrude the antibacterial agent from the cell before it can reach its target site and exert its effect. Third, bacteria may acquire several genes for a metabolic pathway which ultimately produces altered bacterial cell walls lacking the binding site of the antimicrobial agent, or bacteria may acquire mutations that limit access of antimicrobial agents to the intracellular target site via down regulation of porin genes. Thus, normally susceptible populations of bacteria may become resistant to antimicrobial agents through mutation and selection, or by acquiring from other bacteria the genetic information that encodes resistance. The last event may occur through one of several genetic mechanisms, including transformation, conjugation, or transduction.

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genetic exchange mechanisms, many bacteria developed multidrug resistance (Tenover, 2006).

Due to spontaneous mutation, which may be: (1) Alteration of target protein which binds to antibacterial agent. This happens because of modification or elimination of binding site (e.g., change in penicillin-binding protein 2b in pneumococci); (2) Up regulation of the production of enzymes that inactivate the antimicrobial agent (e.g., erythromycin ribosomal methylase in staphylococci); (3) Down regulation or alteration of outer membrane protein channel that the drug requires for cell entry (e.g., OmpF in E. coli), or (4) Upregulation of pumps that expel the drug from the cell (efflux of fluoroquinolones in S. aureus) (McManus, 1997).

In all of these cases, transposons may facilitate the transfer and incorporation of the acquired resistance genes into the host’s genome or into plasmids through pillus in two different organisms. In gram-positive bacteria there is production of sex pheromones by the mating pair, allowing exchange of DNA. During transduction resistance genes are transferred via bacteriophage. In transformation the bacteria releases their DNA complement after cell lysis, can move resistance gene in to susceptible strain. Bacteria also develop resistance through the acquisition of new genetic material from other resistant organisms. This is termed horizontal evolution, and may occur between strains of the same species or between different bacterial species or genera. Mechanisms of genetic exchange include conjugation, transduction, and transformation. Conjugation facilitate the clumping of donor and recipient organisms, allowing the exchange of DNA (McManus, 1997).

Mutation and selection, together with the mechanisms of genetic exchange, enable many bacterial species to adapt quickly to the introduction of antibacterial agents into their environment. Although a single mutation in a key bacterial gene may only slightly reduce the susceptibility of the host bacteria to that antibacterial agent, it may be just enough to allow its initial survival until it acquires additional mutations or additional genetic information resulting in full-fledged resistance to the antibacterial agent (McManus, 1997). However, in rare cases, a single mutation may be sufficient to confer high-level, clinically significant resistance upon an organism (e.g., high-level rifampin resistance in S. aureus or high-level fluoroquinolone resistance in Campylobacter jejuni).

Antibiotic resistance occurs when plasmids coding antibiotic resistance are present in Salmonella typhi. Allied to the problem of resistance is the transfer of resistance plasmid that has been observed to code for multidrug resistance (Daughiri et al., 2005). Drug resistance of pathogen is a serious medical problem, because of very fast arise and spread of mutant strains that are insusceptible to medical treatment. Microorganisms use various mechanisms to acquire drug resistance viz. horizontal gene transfer through plasmid, transposons and bacteriophage, recombination of foreign DNA in bacterial chromosome, and mutation in different chromosomal locus (Klemm et al., 2006).

Brown et al. (2003) have reported that the horizontal gene transfer is the factor in occurrence of antibiotic resistance in clinical isolates and suggested that the high prevalence of resistance to a particular antibiotic does not always reflect antibiotic consumption as suggested by Nwanze et al. (2007). In a report from India it is stated that certain virulence factors such as haemolysin production and presence of fimbriae in E. coli may be associated with urovirulance. Moreover the differences in sensitivity patterns of isolates could be attributed to time differences between two studies or environmental factors such as practices of self-medication, the drug abuse and indiscriminate misuse of antibiotics among the general population which has favored the emergence of resistance of resistant strains (Mandal et al., 2003).

According to Dever and Dermody (1991) reduced antibiotic penetration was also a resistance mechanism for several classes of antibiotics, including the beta-lactam drugs, the aminoglycosides, chloramphenicol and the quinolones. Piddock et al. (1986) reported resistance to nalidixic acid against Enterobacteraceae at 30 μg/ml. The R-factor (Resistance factor) is a plasmid having two components, transfer factor called the resistance transfer factor (RTF) which is responsible for conjugational transfer. The resistance determinants (r) represents for each of the several drugs. These two components can exist as separate plasmids, in such cases though the host cell remain drug resistant the resistance is not transmissible, this infers that resistance transfer factor is required for transferable/infectious drug resistance. Resistance to the sulphonamides may be mutational or plasmid mediated and may involve more than one mechanism, like alteration in metabolic pathway. Some sulfonamide resistant bacteria do not require extracellular Para Amino Benzoic Acid (PABA) and utilize preformed folic acid (Bagde, 2014).

Mechanism of heavy metals action

Guha and Mookerjee (1979) in an attempt to understand the mechanism of action of nickel on macromolecular synthesis showed that NiCl₂ affected it indirectly by inhibiting the activity of dehydrogenases. As a result, due to limitation of energy generating compounds, after a brief lag, synthesis of macromolecules ceased. Martinez et al. (1991) reported inhibition of other enzymes of TCA cycle aconitase and fumerase by nitric oxide in Rhodobacter capsulatus under light anaerobic or dark aerobic condition. The activity of these enzymes was also found to be inhibited in E. coli (Wimpenny and Cole, 1967) and Aerobacter aerogenes (Wimpenny and Warmsley, 1968) when grown anaerobically in presence of nitrate. Bagde and Varma (1983) have also reported similar site of action of chromium and lead.
Mechanism of microbial resistance towards the heavy metals

Metal resistance is inherited by plasmids in many bacteria (Silver and Phung, 1996; Ryan and Colleran, 2002). Mitsuhashi et al. (1963) observed reduced MICs up to 10 fold and complete loss of resistance in some strains of E. coli, after treatment with the curing agent acriflavine. Similar observations have been reported by Ghosh et al. (2001).

In studies on mechanisms of resistance to heavy metals, the chemical form of a metal determines its solubility, mobility, and toxicity towards an organism. Therefore, it also affects the MIC value. Inorganic heavy metals that occur as water-soluble salts exert greater toxicities, than water-insoluble forms of the same metals. Foster (1983) and Silver (1992) reported plasmid mediated reduced accumulation of heavy metals. Resistance of heavy metals due to reduced accumulation has also been reported by Belliveau et al. (1991) and Cooksey (1994). Resistance to heavy metals, pollutants, UV light and other antimicrobial substances such as antibiotics was due to extrachromosomal DNA (Foster, 1983).

When organisms are exposed to metal salts, it is first taken up by the cell and then the metal is localized in different parts of the cell where it exerts its toxic effect on those parts of the cells. Three main fractions of the cells from which the localization of heavy metals could be estimated are: Cell wall, cell membrane, and cytoplasm.

Unlike antibiotic resistance, there are no universally acceptable metal ion concentrations which are used to designate microbial metal tolerance (Calomiris et al., 1984). Bagde and Varma (1983) reported that chromium and lead inhibited the synthesis of protein, DNA and RNA almost equally in E. coli and A. aerogenes. Bagde and Salvi (1994) reported that cobalt and nickel inhibited protein, DNA and RNA synthesis of S. paratyphi B and Shigella flexneri.

The mer, chr, czc, and ncc genes that are responsible for resistance to heavy metals, were shown to be present in these bacteria by using RT-PCR. In the study it is observed that both gram-positive and gram-negative bacteria showed the metal tolerance against Cd\(^{2+}\) and Co\(^{2+}\). In addition, gram-positive isolates (Staphylococcus aureus, Bacillus subtilis, and Bacillus cereus) showed higher expression levels of czcD and nccA genes than merA and chrB genes in comparison to gram-negative bacteria isolates. However, cobalt-zinc-cadmium (czcD) and nickel-cobalt-cadmium (nccA) gene were up-regulated in the all strain of bacteria treated with Co\(^{2+}\) and Cd\(^{2+}\). Therefore, Co\(^{2+}\) and Cd\(^{2+}\) resistance genes are widely distributed in both gram-positive and gram-negative isolates obtained from different samples of Egyptian soils (Laila et al., 2011).

This review summarizes and evaluates the effects of some specific antimicrobials and heavy metals upon the Enterobacter species.

This study have been drawn up so as to be useful for a wide range of healthcare professionals, such as specialist physicians and other healthcare workers (infectious diseases, microbiology, surgery, intensive care), public health officers, infection control professionals, administrative personnel in hospitals, and epidemiologists.

Antimicrobial resistance in the various pathogens has been reported since decades by scientists but not well understood in some instances till the date. Some pathogenic species shows same mechanisms and some species shows varied types of mechanisms in conflict with a single or multiple drug resistance. There are same mechanisms in the same or different species to resist different group of antimicrobials. Somewhere it is observed that there are different mechanisms of resistance existing for different type of antimicrobials among same or different species. The mechanism of resistance to some selected drug and heavy metals is revealed as plasmid mediated resistance.

Some heavy metals are important and essential trace elements, but at high concentrations, most can be toxic to microbes. Microbes have adapted to tolerate the presence of metals or can even use them to grow. Thus, a number of interactions between microbes and metals have important environmental and health implications (Spain and Alm, 2003).

Enterobacter spp. and Serratia spp. (particularly Enterobacter cloacae and Serratia marcescens) are found important as nosocomial pathogens and outbreaks caused by these organisms have been documented. Cross-transmission via transient contamination of Health Care Workers’ hands has also been well documented in epidemic and endemic situations (Yu et al., 1999).

The concurrence of high antibiotic consumption, critically ill patients and a permanent influx of pathogenic species within the healthcare setting nurtures the development of resistance and provides an ideal scenario for the dissemination of resistant microorganisms and horizontal transfer of resistance genes. Therefore the management of Multi Drug Resistant microorganisms (MDR) in healthcare facilities has become a key issue. The degree of antimicrobial resistance in these surroundings depends on intrinsic factors related to the particular idiosyncrasies of each centre as well as on external factors such as the influx of resistant pathogens that originate in the community. Intrinsic differences in resistance rates between hospitals can be attributed to use of individual rooms vs. two or three bedrooms or open units, staffing, antibiotic stewardship, environmental cleaning, adherence to hand hygiene precautions and infection control programs (Tacconelli et al., 2014).

THE GENUS ENTEROBACTER

Enterobacter is gram-negative, facultatively anaerobic,
rod-shaped, non-spore-forming, motile aerobic gram negative bacilli of the family Enterobacteriaceae. They are oxidase-negative, indole-negative, and urease-negative. The genus Enterobacter ferments lactose with gas production during a 48 h incubation at 35 to 37°C in the presence of bile salts and detergents. Several strains of these bacteria are pathogenic and cause opportunistic infections in immunocompromised (usually hospitalized) hosts and in those who are on mechanical ventilation. The urinary and respiratory tracts are the most common sites of infection. The genus Enterobacter is a member of the coliform group of bacteria. It does not belong to the fecal coliforms (or thermodetolerant coliforms) group of bacteria, as does E. coli, because it is incapable of growth at 44.5°C in the presence of bile salts. Two clinically important species from this genus are Enterobacter aerogenes and Enterobacter cloacae (https://en.wikipedia.org/wiki/Enterobacter; Maki et al., 1976).

The history of Enterobacter

They first achieved wide notoriety as pathogens in 1976 following a nationwide outbreak of septicemia in 378 patients at 25 hospitals resulting from contaminated intravenous solutions (Maki et al., 1976). Because they can replicate in glucose-containing parental fluids, they continue to cause sporadic outbreaks of this type. Free-living Enterobacter are capable of nitrogen fixation. Certain species, notably E. cloacae, are involved in symbiotic nitrogen fixation in plants and have been isolated from the root nodules of certain crops, such as wheat and sorghum, and from the rhizospheres of rice (https://www.britannica.com/science/Enterobacter).

Classification and taxonomy

The isolate Enterobacter cloacae PRE9 is gram-negative rod, circular, soft, and cream-colored colony on medium. It is motile, gas producing bacteria which are catalase, citrate, Voges-Proskauer (VP) positive but indole, oxidase, and methyl red test (MR) negative. Stiles and Ng. (1981) isolated Enterobacteriaceae (86%) from different meat samples. The percentages of positive biochemical and identifying characteristics of seven member of Enterobacteriaceae were described. Among all, characteristics of Enterobacter cloacae 89.2% were positive for motility, 95.2% for VP, 92.2% for citrate, 100% were positive for acid and 98.8% for gas production from glucose.

The average guanine-plus-cytosine contents for the defined species and of the new classes are: Enterobacter cloacae (10 strains), 54.5 mol% (standard deviation, 1.32); Enterobacter agglomerans (syn. Erwinia herbicola) (1 strain), 52.4 mol% (standard deviation, 0.41);

Enterobacter aerogenes (1 strain), 53.5 mol% (standard deviation, 0.29). The importance of the guanine-plus cytosine contents for discriminating defined species and new classes is discussed earlier (Izard et al., 1978).

Epidemiology

A landmark study in 1987 by Flynn et al. (1987) highlighted the importance of Enterobacter arising from a patient’s endogenous gut flora causing subsequent infection. In this study of 87 patients undergoing cardiac surgery, all patients underwent surveillance cultures before and after surgery. Of 12 nosocomial infections due to Enterobacter in this group of patients, 9 were due to strains detected colonizing the gut preoperatively.

Enterobacter may also spread from patient to patient due to inadequate attention to infection control measures, especially hand-washing. In a study employing a consensus PCR technique for molecular typing of strains, Davin-Regli et al. (1996) studied 185 clinical isolates of E. aerogenes collected from two Intensive Care Unit’s over a one-year period from a hospital in France. A ubiquitous clone was found to be responsible for two-thirds of epidemiologically related transmissions in these units.

According to data collected between 1992 and 1999 by National Nosocomial Infection Surveillance (NNIS) survey from the Centers for Disease Control (CDC), increased frequency of Enterobacter infections, particularly ICUs was observed (Archibald et al., 1997). Fridkin (2001) reported that Enterobacter was the fifth leading cause of ICU infections in the United States and third most common cause of nosocomial pneumonia overall. Enterobacter species is an opportunistic pathogen to humans and causes nosocomial pneumonia. It carries seven operons with heavy metal resistant gene which make them capable to survive in heavy metal rich environment.

Enterobacter causes nosocomial infections. It is ubiquitous and can survive on skin and dry surfaces and replicate in contaminated fluids. Numerous outbreaks have been described, including infections due to contaminated enteral feedings (Simmons et al., 1989), humidifiers and respiratory therapy equipment (Wang et al., 1991) and hydrotherapy water in a burn unit (Mayhall et al., 1979).

Diagnostics, isolation, identification and species determination

This organism is easy to isolate from clinical specimens and biochemical tests readily separate it from other members of the Enterobacteriaceae family.

In a report of 33,869 gram-negative isolates (16.1% Enterobacter) from 396 ICUs in the United States
A follow-up study from the same investigators analyzed 35,790 isolates from ICUs in the United States sampled between 1994 and 2000 (Neuhauser et al., 2000). In this later collection of organisms, the prevalence of resistance to third generation cephalosporins in Enterobacter was quite stable at 37%. Likewise, resistance to aminoglycosides and carbapenems remained infrequent. The important observation from the more recent data set was a significant increase in the prevalence of resistance to fluoroquinolones in Enterobacter, Klebsiella and Pseudomonas aeruginosa. An analysis of antibiotic usage data was supplied by IMS Healthcare Inc., Westport, CT. This data revealed a highly significant association between the use of fluoroquinolones and resistance to quinolones in gram-negative rods, particularly in the case of Pseudomonas, but also for Klebsiella and Enterobacter. There was significant cross-resistance noted in Enterobacter, Pseudomonas aeruginosa and Klebsiella pneumoniae isolates in this survey. In all three organisms, ciprofloxacin resistant strains were significantly more likely to be resistant to gentamicin, amikacin, ceftazidime and imipenem as compared to susceptible strains. This cross-resistance complicates selection of appropriate empiric therapy of multiresistant strains. A clear gradient of increasing ceftazidime resistance rates was noted. The prevalence of ceftazidime resistance was 12% among community isolates, versus 26% among nosocomial isolates. Within these hospitals, resistance rates were consistently higher among ICU isolates (36% versus 26%) (Archibald et al., 1997).

**Clinical features and treatment of infections**

_E. cloacae_ showed higher MIC values for heavy metals and a larger range of antibiotic resistance than _B. cereus_ (Qing et al., 2007). Enterobacter species causes nosocomial infections, including lungs, urinary tract, intraabdominal cavity and intravascular devices. _E. sakazakii_ causes neonatal sepsis with meningitis (Bar-Oz et al., 2001; Nazarowec and Farber, 1997).

The susceptibility of Enterobacter isolates to Trimethoprim-sulfamethoxazole (TMP-SMX) was examined (Fung-Tomc et al., 1989, Wang et al., 1991). These reports have found susceptibility rates in excess of 90%. A report of Enterobacter bacteremia among pediatric patients emphasized the importance of central venous catheters as a portal of entry (63% of cases) and the excellent activity of TMP-SMX (91% susceptible). This agent is used infrequently in the treatment of Enterobacter infections (Andresen et al., 1994).

**Drug of choice**

The occurrence of nosocomial infections due to _Enterobacter_ is rising and broad resistance to third generation cephalosporins, penicillins and quinolones is a rising problem. A number of agents remain effective for treatment. Aminoglycosides retain good activity but usually require combination with another agent. Quinolones are highly active against most strains, but emerging resistance is a major concern. TMP-SMX is under-utilized as therapy of Enterobacter infections. Among the beta-lactams, the fourth generation cephalosporins and carbapenems are the most attractive options (Archibald et al., 1997).

**CLASSIFICATION OF CEPHALOSPORIN, FLUOROQUINOLONES, QUINOLONES, SULFONAMIDES**

**Cephalosporins**

Cephalosporin is a derivative of 7-aminocephalosporanic acid, for example, cephalixin, ceftazidime, cephoxitin, ceftriaxone.

**Sulfonamides**

Sulfonamides is derived from sulfanilamide, the first successful antibacterial e.g., sulfadiazine, sulfamethoxazole. Trimethoprim is used to "potentiate" the sulfonamides.

**Quinolones**

Quinolones are synthetic, antibacterial agents with broad-spectrum activity. They inhibit the enzyme topoisomerase II, a DNA gyrase that is necessary for the replication of the microorganism, further developed in new generation as Fluoroquinolone.

**Fluoroquinolones**

This form a group of broad-spectrum antibiotics that are derived from nalidixic acid, e.g., ciprofloxacin, and norfloxacin.

**ANTIMICROBIAL RESISTANCE**

It has been shown that a link exists between metal tolerance and antibiotic resistance in bacteria because of the likelihood that resistance genes to both (antibiotics and metals) may be closely located on the same plasmid.
HEAVY METAL RESISTANCE

The experimental findings showed that high level plasmid mediated Cd\(^{2+}\) and Zn\(^{2+}\) resistance in the Enterobacter sp. BN4 strain is due to decreased Cd\(^{2+}\) and/or Zn\(^{2+}\) uptake/accumulation by resistance strain. Based on the fact that subsequent plasmid curing experiments demonstrated the ability to grow in presence of Cd\(^{2+}\) and/or Zn\(^{2+}\) was encoded by the 98 kb plasmid, whereas the ability to grow in presence of Pb\(^{2+}\) was found to be encoded by the chromosome. The Cd\(^{2+}\) and Zn\(^{2+}\) removal capacity of the respective metal resistant strain (pBN4) were about 36 and 45 µg g\(^{-1}\) DW respectively, while the removal capacity of the both metal by sensitive variant showed a significant high Cd\(^{2+}\) and Zn\(^{2+}\) removal capacity of 153 and 228 µg g\(^{-1}\) DW respectively. The order of the metals toxicity to the bacterium was found to be plasmid DNA that was determined by plasmid curing and conjugation experiments. The isolated endophytic Enterobacter was not only tolerant to heavy metals, but also bound considerable amount of heavy metals from the growth medium. The biosorbed order of the metals by parental strain and its cured derivatives strain based on the cell dry weight was found to be in the order of Pb\(^{2+}\)>Zn\(^{2+}\)>Cd\(^{2+}\) (Bahig El-Deeb, 2009).

In high concentrations, heavy metal ions react to form toxic compounds in cells (Nies, 1999). To have a toxic effect, however, heavy metal ions must first enter the cell. Because some heavy metals are necessary for enzymatic functions and bacterial growth, uptake mechanisms exist that allow for the entrance of metal ions into the cell. There are two general uptake systems; one is quick and unspecific, driven by a chemiosmotic gradient across the cell membrane and thus requiring no ATP, and the other is slower and more substrate-specific, driven by energy from ATP hydrolysis. While the first mechanism is more energy efficient, it results in an influx of a wider variety of heavy metals, and when these metals are present in high concentrations, they are more likely to have toxic effects once inside the cell (Nies and Silver, 1995).

Correlation of metal tolerance and antibiotic resistance

Because our current antibiotics are becoming less useful but are used more heavily against antibiotic resistant pathogenic bacteria, infectious diseases are becoming more difficult and more expensive to treat. The increased use of antibiotics in health care, as well as in agriculture and animal husbandry, is in turn contributing to the growing problem of antibiotic resistant bacteria. Products such as disinfectants, sterilants, and heavy metals used in industry and in household products are, along with antibiotics, creating a selective pressure in the environment that leads to the mutations in microorganisms that will allow them better to survive and multiply (Baquero et al., 1998). According to Lawrence's (2000a) discussion of the Selfish Operon Theory, clustering of genes on a plasmid, if both or all genes clustered are useful to the organism, is beneficial to the survival of that organism and its species because those genes are more likely to be transferred together in the event of conjugation. Thus, in an environment with multiple stresses, for example antibiotics and heavy metals, it would be more ecologically favorable, in terms of survival, for a bacterium to acquire resistance to both stresses. In plasmid mediated resistance, those bacteria with clustered resistance genes are more likely to simultaneously pass on those genes to other bacteria, and those bacteria would then have a better chance at survival. During such a situation, one may suggest an association with antibiotic resistance and metal tolerance. For example, Calomiris et al. (1984) studied bacteria isolated from drinking water and found that a high percent of bacteria that were tolerant to metals were also antibiotic resistant.

The selection of heavy metal resistance by microorganisms often promotes for antibiotic resistance in the environment. The resistance of these organisms to both metals and antibiotics could cause hazard into the environment and present very serious health implication because of the ability of these organisms to pass these resistant genes which may be transferred together via plasmids to other microbial cell around and will affect a whole bacterial population thereby complicating treatment (Sulaimon et al., 2015).

MULTIDRUG RESISTANCE IN ENTEROBACTER SPECIES

The saga of Enterobacter as a nosocomial pathogen is closely linked to the logarithmic increase in the use of extended-spectrum cephalosporins in the 1980’s. A series of reports emphasized the proclivity of members of
this genus to acquire broad beta-lactam resistance during therapy with extended-spectrum cephalosporin’s (Chow et al., 1997; Sanders, 1992). Enterobacteriaceae protect them by secreting various enzymes for inactivating antibiotics, modifications in their targeting molecules, and use of antibiotics efflux pump systems. Subsequent studies have shown that prophylaxis with second and third generation cephalosporins has been associated with selection of multiresistant Enterobacter (Flynn et al., 1987).

Quinolones

A cautionary note is raised by the report of Davin-Regli et al. (1997). These authors reported an outbreak of Enterobacter hormachei infections among patients in a French hospital who had been treated with quinolones. Twenty-one resistant isolates were detected over a one-year period. All were clonally related by the random amplification of DNA technique. Quinolone resistance in Enterobacter is usually due to chromosomal genes that may upregulate efflux pumps (Nikaido, 2001) or confer resistance due to altered DNA gyrase (Dekitsch et al., 1999).

In the ISS survey of 5451 Enterobacter isolates from 396 American ICUs collected between 1990 and 1993, ciprofloxacin was effective against 96% of strains. The prevalence of resistance to quinolones in Enterobacter grew significantly between 1994 and 2000, although 90% of strains remained susceptible in 2000. The newer quinolones such as moxifloxacin and gatifloxacin have greater activity against gram-positive pathogens than the older members of this class, but have no greater activity against gram-negative rods in general and Enterobacter in particular. It is reasonable to anticipate that quinolone resistance rates will continue to increase over time as these agents are increasingly employed in the treatment of serious Enterobacter infections.

Beta-lactams and extended spectrum cephalosporins

All of the so-called “third generation” cephalosporins and the monobactams (e.g. aztreonam) have approximately the same risk of emergence of resistance during treatment of Enterobacter infections. The data on preventing this type of resistance by employing concomitant aminoglycoside therapy is mixed. Jacobson et al. (1995) found a lower incidence of emergence of resistance to extended-spectrum cephalosporins among patients treated with concomitant aminoglycoside therapy, while Chow et al. (1991) did not.

A newer group of broad spectrum cephalosporins, the so-called “fourth generation” compounds, (e.g. cefepime and ceftmyme) usually retain their activity against Enterobacter strains resistant to third generation cephalosporins (Segreti and Levin, 1996). The basis for this retained activity is (1) faster penetration through outer membrane porin proteins, (2) superior stability to chromosomal beta-lactamases, and (3) enhanced binding to critical penicillin-binding proteins in Enterobacter as compared to older cephalosporins (Bellido et al., 1991a, b; Fung-Tomc et al., 1989).

Sanders (1992) described successful therapy with cefepime of 17 infections due to Enterobacter strains resistant to third generation cephalosporins. These patients had infections at a variety of sites. All patients responded clinically and bacteriologic eradication was documented in 88%. Cefpirome is structurally similar to cefepime and has roughly comparable activity against Enterobacter strains, including those displaying resistance to third generation cephalosporins (Jones, 2001). There is less data available on clinical efficacy of this agent against multiresistant gram-negative pathogens.

Broad spectrum penicillins

Piperacillin is slightly less active than extended-spectrum cephalosporins against Enterobacter; in the ISS study, 63% were susceptible to ceftazidime vs 60% to piperacillin. In the Chow study, no patient receiving piperacillin experienced treatment failure due to emergence of resistance (Evans et al., 1998). In contrast, the work of Jacobson and colleagues reported a statistically significant association of prior piperacillin therapy with broad beta-lactam resistance.

Carbapenems

Carbapenems exhibit excellent activity against a wide variety of enteric gram negative pathogens, including Enterobacter (Norrby, 1995). Resistance to carbapenems in Enterobacter is rare (1% of NNIS isolates in 1999) (Fridkin, 2001), presumably because Enterobacter isolates require two separate mutations to acquire carbapenem resistance: loss of porin proteins plus hyperproduction of beta-lactamase (Livermore, 1991). Carbapenem resistance among Enterobacter isolates does not appear to be increasing over time.

In the series of Chow et al. (1991) none of seventeen patients receiving imipenem for Enterobacter bacteremia had resistant organisms emerge during therapy. Meropenem has activity comparable to imipenem against Enterobacter and found to be effective in the therapy (Colardyn and Faulkner, 1996; Edwards, 1995). There are a number of new carbapenem and piperacillin agents in development that have excellent activity against Enterobacter. Ertapenem is a new carbapenem
with an extended serum half-life that has superb activity against enteric pathogens including Enterobacter. But this agent has limited activity against nonfermenters like Pseudomonas aeruginosa and Acinetobacter (Livermore et al., 2001).

Aminoglycosides

Aminoglycoside resistance in Enterobacter is usually due to plasmid-mediated aminoglycoside modifying enzymes. 4999 isolates of Enterobacter collected from 396 ICUs in the United States between 1994 and 2000, 98% were susceptible to amikacin and 92% were susceptible to gentamicin and tobramycin. These rates were steady over this time period. In the Chow study only one of 89 patients receiving aminoglycoside therapy failed treatment due to emergence of resistance during therapy (Chow, 1991).

Mechanisms of action of ceftazidime, moxifloxacin, nalidixic acid and sulfamethaxazole

Nucleic acid synthesis requires DNA gyrase enzyme and topoisomerase that removes the positive super twists by nicking and then sealing phosphodiester bonds in DNA backbone. In addition, DNA gyrase can actively introduce negative super twists into close circular DNA at the expense of ATP hydrolysis. These negative super twists promote parental strand separation at the replication fork. For example, all quinolones and fluoroquinolones inhibit microbial DNA synthesis by blocking DNA gyrase (Garrod et al., 1981; Piddock and Zhei, 1991).

Sulfonamides can enter into the reaction in place of Para amino acid benzoic acid (PABA) and compete for the active center of the enzyme. As a result, nonfunctional analogs of folic acid are formed, preventing further growth of bacterial cells. The inhibiting action sulfonamides on bacterial growth can be counteracted by an excess of PABA in the environment (competitive inhibition).

Resistance to some penicillins and cephalosporins may be a function of the loss or alteration of penicillin binding proteins (PBP) in N. gonorrhoeae and in resistant strain of S. pneumonia in South Africa (Domanski et al., 1997).

Resistance mechanisms towards ceftazidime, moxifloxacin, nalidixic acid and sulfamethaxazole

The plasmid mediated ESβLs confer resistance to oxymino-cephalosporins, such as cefotaxime, ceftazidime and ceftriaxone (Vercauteren et al., 1997). Plasmid mediated β-lactamases TEM-1, which has a broad activity range against penicillins and cephalosporins, is carried on a transposon (Tn4). β-

Lactamases are enzymes that act on the β-lactam bond of certain antimicrobials, such as the penicillins and cephalosporins, thus inactivating them (Berkowitz, 1995; Fraimow and Abrutyn, 1995).

Resistance to sulphonamides and trimethoprim is mediated by metabolic bypass, in this case due to synthesis of altered dihydropteroate synthetase and dihydropteroate reductase (Gibreel and Skold, 1999). The major cause of sulfonamide resistance is the plasmid-mediated production of an altered dihydropteroate synthetase, which is 1000 times less sensitive to the drug than mild type enzyme (Satoskar et al., 1999). Tran and Jacoby (2002) reported a multi resistance plasmid that encodes transferable resistance to quinolones. Cooper et al. (1990) reported the cross-resistance among the quinolones. The absence of β lactamase enzyme in resistant Enterobacter was reported previously by Nirbhavane and Bagde (2015).

Nickel and lead resistance in Enterobacter species

E. cloacae showed scanty growth in Pb even at 0.5 mg/L but stop growing at 0.75 mg/L, while Enterococcus cloacae had MIC of 0.5 mg/L of Ni (Sulaimon et al., 2014).

Enterobacter aerogenes has an ability to completely degrade 0.6 mM lead concentration in 60 h while the MIC of lead for the strain was observed to be 3.6 mM. Also it had an optimum pH and temperature of 7.5 and 37°C, exhibited multiple metal tolerances and showed an improved reduction rate of Pb in presence of glucose in the medium (Macklin, 2013). Nirbhavane and Bagde (2016a) observed that the resistance to the heavy metal nickel and lead were found to be 200 and 300 ppm by the resistant Enterobacter, respectively.

In an investigation reported by Banerjee et al. (2015), the isolation and characterization of a potent heavy metal accumulating bacterial strain E. cloacae B1 from polluted soil at Ghaziabad, India was carried out. The minimum inhibitory concentration of the selected bacterial strain was recorded to be 1100 ppm for lead, 900 ppm for cadmium, and 700 ppm for nickel.

Mechanisms of heavy metal resistance

The high value of lead and copper may be due to the fact that lead and copper are used by bacteria cells in small quantities in cellular enzyme as reported by (Ansari and Malik, 2007; Sulaimon et al., 2014) also copper and lead appear to bind to material on the cell surface. Similar results were obtained from the study of Aiking et al. (1985), Roane et al. (2001) and Ansari and Malik (2007). Another implication of heavy metal tolerance in the environment is that it may also select antibiotic resistance
Detected antimicrobial resistance in Enterobacter species

After the screening of pathogens and determination of MIC, selection of a pair of Enterobacter spp. which contain a sensitive and a resistant species towards all the antimicrobials and heavy metals was done. The resistant species of Enterobacter found to be resistant to different classes of antimicrobials, that is, third generation cephalosporin (ceftazidime), sulfa drug (sulfamethoxazole) Quinolone (moxifloxacin), and fluoroquinolone (nalidixic acid). The resistant Enterobacter has shown resistance to all above mentioned antimicrobials and heavy metals, while the sensitive Enterobacter showed susceptibility toward these antimicrobials and heavy metals collectively. This pair was selected amongst the total 121 isolates of 15 different pathogens which were obtained from two different hospitals and a microbiology laboratory (Nirbhavane and Bagde, 2015).

Current trends in resistance research

Antimicrobial resistance has become, a serious public health concern with economic and social implications throughout the world, be it community acquired infections like Streptococcus infections, pneumonia, typhoid fever, etc., or hospital acquired infections due to methicillin resistant Staphylococcus aureus (MRSA), vancomycin resistant enterococci (VRE), vancomycin intermediate Staphylococcus aureus (VISA) or extended spectrum β-lactamase (ESBL) enzyme producing gram-negative bacteria (Dancer, 2001). These infections lead to higher rates of hospitalization, longer hospital stay, and increase in the cost of treatment and thus, increased economic burden on the community.

Nature is abounding with metals in elemental form or in complexed forms. Around 75% of the naturally known elements in the biosphere are heavy metals and out of 90 elements 53 are heavy metals (Weast, 1984) which mostly persist in the environment. Some of them are most hazardous to human health. Microbes develop various mechanisms of resistance to survive in metal polluted sites. Resistance genes may be present on chromosomes or extra chromosomal plastids or transposons. Mechanisms employed by microorganisms to resist metal may be one or more combination of mechanisms, like intracellular sequestration, extracellular sequestration of metals, detoxification or exclusion of metals to resist metal toxicity.

The greatest contributions to medicine in the 20th century were the discovery of potent antimicrobials. Unfortunately, the emergence of antimicrobial resistant bacteria now threatens these advances and is today, one of the greatest concerns with regard to the use of antimicrobials. Increased antimicrobial resistance presents a major threat to public health because; it reduces the effectiveness of antimicrobial treatment, leading to increased morbidity, mortality, and health care expenditure (Smith et al., 2002). This is of particular concern to hospitalized patients, with more and more hospitals worldwide, facing the crisis of the upsurge and dissemination of antimicrobial resistant bacteria; particularly those bacteria which cause nosocomial infections. Today the numbers of antimicrobial resistant bacteria are on the rise and development of new antimicrobials, has not kept pace with.

In studies involving mechanisms of resistance to antimicrobials, preliminary screening is necessary and always an essential part of the study as it assists in identifying and understanding trends in resistance (Jones, 2001).

Certain bacteria such as multidrug resistant gram-negative bacteria are particularly worrisome (Giske et al., 2008). In the US, two thirds deaths due to bacterial infections are caused by gram-negative bacteria (Foster, 2010). Multidrug resistant organisms are defined as microorganisms that are resistant to one or more classes of antimicrobial agents e.g. ESBL, MRSA, VRE etc. These highly resistant organisms deserve special attentions in healthcare facilities as they are associated...
with increased length of stay, costs, and mortality (Siegal et al., 2006). It was observed that when effect of ciprofloxacin on was studied, the growth of sensitive Shigella dysenteriae was completely inhibited at 1μg/ml concentration of ciprofloxacin, while the resistant strain tolerated even 10 μg/ml concentration of ciprofloxacin mechanism of resistance was found to be presence of plasmid (Lankeshwar and Bagde, 2013). When effect of Nalidixic acid and ciprofloxacin was studied, the growth of sensitive *Pseudomonas aeruginosa* was completely inhibited at 1 μg/ml nalidixic acid and 0.9 μg/ml concentration of ciprofloxacin, while the resistant strain tolerated even 60 μg/ml concentration of nalidixic acid and 4 μg/ml concentration of ciprofloxacin. Mechanism of resistance was found to be the presence of permeability barrier (Lankeshwar and Bagde, 2004). When effect of ciprofloxacin and sparfloxacin on *Staphylococcus aureus* was studied, the growth of sensitive *Staphylococcus aureus* was completely inhibited at 0.5 μg/ml of ciprofloxacin and 1 μg/ml concentration of sparfloxacin, while the resistant strain tolerated even 5 μg/ml ciprofloxacin and 50 μg/ml concentration of sparfloxacin and mechanism of resistance was found to be the presence of plasmid (Lankeshwar and Bagde, 2008).

In another study, when the growth of sensitive *Klebsiella pneumoniae* was completely inhibited at 8 μg/ml concentration, the resistant strain tolerated even 256 μg/ml concentration of ceftazidime. Mechanism of resistance was found to be the production of extended Spectrum of Beta-lactamase (Tahur, 2006). The growth of sensitive *Pseudomonas aeruginosa* was completely inhibited at 16μg/ml concentration, while resistant strain tolerated even 128 μg/ml concentration of sulphonamethoxazole. Mechanism of resistance was found to be the presence of plasmid. When effect of nickel on *S. aureus* was studied, the growth of sensitive *S. aureus* was completely inhibited at 30 ppm concentration, while resistant strain tolerated even 180 ppm concentration of nickel. Mechanism of resistance was found to be the presence of plasmid. In strains showing presence of plasmid, curing with ethidium bromide yielded 80 to 90% elimination of resistance (Tahur, 2006).

**Generations of new antibiotics**

When the next generations of antibiotics were developed to overcome the problems of resistance against available antibiotics, bacteria developed mechanisms to resist the newer antimicrobial also. The 3rd and 4th generations of cephalosporins were introduced which were not destroyed by the β-lactamases produced by the gram-negative bacteria (Gotoh et al., 1998).

**Use of ceftazidime with cefepime in hospitals**

Recognizing that exposure to third-generation cephalosporins plays a role in the selection of multidrug-resistant organisms, a number of studies have evaluated the effect of substitution of the fourth-generation cephalosporin cefepime for third-generation cephalosporins on susceptibility patterns. Empey et al. (2002) reviewed antibiotic use and antimicrobial resistance before and after a university hospital formulary change that was aimed at reducing utilization of third-generation cephalosporins. After the formulary change to cefepime, the use of ceftazidime and cefotaxime underwent a combined decrease of 89%. Cefepime use was associated with a significant decrease in infections due to ceftazidime-resistant *K. pneumoniae* and *P. aeruginosa*.

The use of a ceftazidime-glycopeptide combination as initial empirical therapy for neutropenic fever resulted in a 75% reduced rate of susceptibility to ceftazidime among Enterobacteriaceae with AmpC β-lactamase-mediated resistance (Mebis et al., 1998).

**Elimination, prevention and control of microbial resistance**

Prevention is better than elimination, cure and control of any problem. However multifaceted approach is more advisable when the problem is blown out of proportion like resistance problem. Many guidelines, strategies and plans have been developed to deal with resistant microbial infections either generally or for specific organisms (Goldmann et al., 1996; Hospital infection control practices advisory committee, 1996; Department of Health and Human Services and department of labor, 1995).

Bacterial plasmids have genes that confer highly specific resistances to As, Bi, Cd, Cu, Cr, Hg, Zn, and other toxic heavy metals. For each toxic cation and anion, generally a different resistance system exists, and these systems may be linked together on multiple resistance plasmids (Silver et al., 1989).

Tahur (2006) and Lankeshwar and Bagde (2008, 2013) successfully cured plasmid by using various methods such as acrylamide method, acridine orange method and SDS treatment and showed that the resistance species became as sensitive ones to those antimicrobials that showed no activity towards the microorganisms before the treatment in plasmid elimination.

Plasmid was isolated and cured successfully which is a big evidence to reveal the resistance mechanism in these studies. In a study by Akhavan et al. (2015), the plasmid DNA was isolated from *K. pneumonia* with approximate size of 4.9 kb. Curing of plasmid was carried out with SDS. Plasmid curing was achieved by growing the strain treated with SDS. A plasmid isolated from *Klebsiella spp.* was treated with 10% SDS that leads to loss of a plasmid. A Strain of *Enterobacter* (Ent-5) tolerated high concentrations of copper (23 mM), nickel (16 mM),

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chromium (8 mM) and cadmium (14 mM). Cured Ent-5 was not able to grow on Ni and Cu. The sensitivities of the plasmid cured Ent-5 to nickel and copper indicated that copper and nickel resistance is correlated with plasmids (Unaldi Coral et al., 2005).

Nirbhavane and Bagde (2015) showed that Enterobacter carrying resistance plasmid was treated with 2 to 10% concentration of sodium dodecyl sulphate. The treatment was found to be effective to turn the resistant cells in to susceptible ones. The resistance was lost and the resistant species completely changed in to the sensitive species. This was very much in agreement to earlier studies of plasmid elimination using SDS by other workers (Tomoeda et al., 1968; Pan-Hau et al., 1981; Lankeshwar and Bagde, 2008, 2013). Reportedly also acriflavine was used for elimination of resistance to penicillin in S. aureus (Hashimoto et al., 1964).

Elimination of microbial resistance by various means and methods could be an important step in prevention and control of resistant microorganisms. There are many methods available which could be applied for this purpose. Different workers have used different reagents for elimination of resistance factor. Jacob et al. (1965) reported action of SDS in elimination of resistance factor. It may destroy the cell wall first and then cell membrane completely or partially, resistance factor (R) and fertility (F) factor associated more closely with the cell membrane as smaller replicons which then be damaged more easily by SDS.

To find out the location (chromosomal or extra chromosomal) of gene(s) responsible for the resistance to drugs, when plasmid curing experiments were performed using both physical and chemical agents; it was observed that, curing was most effective with ethidium bromide, followed by acridine orange (Hahn and Ciak, 1976; Tahur, 2006).

The reaction of plasmid in development of resistance was studied by Pan-Hau et al. (1981) in Enterobacter aerogens against mercury. Tran and Jacoby (2002) reported a multi resistance plasmid that encodes transferable resistance to quinolones.

Overall, the association of antibiotic use with the development of multidrug resistance underscores the fact that making suboptimal antimicrobial choices has global implications. The use of a particular antimicrobial agent may not only select for overgrowth of bacterial strains with innate resistance, but also may select for the development of diverse genetic vectors that encode and are capable of disseminating resistance mechanisms (O’Brien, 2002). Genetic elements of this kind may spread widely through the world’s bacterial populations.

Challenges of microbial resistance

The number of drug resistant bacteria is on the rise but development of new treatment options have not kept pace. With bacteria replicating as often as once every 20 min, combined with their remarkable ability to change their physical and chemical makeup, resistant strains can evolve with amazing speed. Even greater concern is the fact that bacteria are able to easily transfer genetic information from one strain to another, there by passing on their resistance. This leads to increasing morbidity and mortality and an overall increase in health care costs. The dramatic reduction in development of new antibiotics active against these multi drug resistant pathogens has further complicated the therapeutic dilemma.

To survive under metal-stress conditions, bacteria have developed a variety of resistance mechanisms to counteract heavy metal stress (Spain and Alm, 2003). Though the levels of antibiotic resistance are rising inexorably, yet it has taken a long time to realize the extent of the problem, and there is still much that we need to learn about the mechanisms (Burnet et al., 2000). Despite efforts in the search for new antibiotics as well as the improvement of existing antibiotic performance, bacterial resistance to antimicrobial agents remains a problem in the treatment of infections.

Remedies for resistance crisis

The importance of adhering to the recommendations must be recognized by clinicians to prevent antimicrobial resistance in the healthcare setting (Salgado et al., 2005). Strict policies must be compared against the cost of management of high-level resistance (Vriens et al., 2002). The program optimization of therapy, implementing, teaching and monitoring treatment guidelines can have a major impact on patient care. It is observed that judicious use of antibiotics is essential considering growth of antimicrobial resistance and escalating costs in health care. Specific measures must include the revision of isolation guidelines. In addition, campaigns designed to educate the public and the health care community about the dangers of antimicrobial resistance and what may be done to control it. These campaigns include the “Get Smart” program, which primarily focuses on outpatients (Centers for Disease Control and Prevention, 2005) and the 12-step Campaign to Prevent Antimicrobial Resistance in Healthcare Settings.

The foreseen decline in effectiveness explains the needs for data to inform the public health agenda about the magnitude and evolution of antibiotic resistance as a serious threat to human health and development. Opportunistic pathogens are the cause of the community and hospital acquired infections worldwide.

It is today not possible to present a full picture of the spread of antibiotic resistance, and its health and economic burden due to the lack of global data. Some countries and regions do have surveillance system in place: others have no system at all for collecting the data. Hence the worldwide data on antimicrobial resistance
studies and its burden makes it almost impossible to track and contain emerging outbreaks in particular and challenges in general. It also makes impossible to evaluate the effect of national and regional initiatives to contain antibiotic resistance.

Infectious diseases continue to be a leading cause of mortality the world and more so in developing countries with low access of health services (World Health Organization Report, 2007). ICU is high antibiotic research area; therefore a correlation was simultaneously sought between antibiotic resistance and susceptibility pattern. A positive correlation was observed with carbapenem (imipenem and meripenem) and cefoperazone-sulbactum usage and development of resistance in pathogens. However piperacillin-tazobactum showed a positive correlation with Acinetobacter but a negative correlation with Pseudomonas (Jaggi et al., 2012).

There is the need to pursue detailed studies on antibiotic resistance in various areas which may lead to the better understanding of the magnitude of antibiotic resistance. Number of antibiotics used in the empirical treatments needs to be re-evaluated. Also further research is needed regarding rapid diagnosis of infection, accurate presumptive identification of patients, and development of new antimicrobials for drug resistance. No doubt that physician will eventually need the next generation of novel antibiotics to prevent and treat infections (Curtis, 2005).

The national, state and hospital level programs of surveillance and intervention must be strengthened to prevent the continued emergence of multidrug resistant pathogens and to limit their spread in to other communities or other institutions (Mathai et al., 2002). Continuous local monitoring of resistance patterns is necessary for the appropriate selection of empirical antimicrobial therapy. The frequency of resistance among Shigella isolates has increased substantially between 2000-2002 and 2006-2009 and the spectrum of resistance has widened. The option for antimicrobial therapy in shigellosis in Andman is limited to a small number of drugs (Bhattacharya et al., 2012). Widespread selective pressure and efficient dissemination channels for multidrug resistant organisms are major factor that might have contributed to the rapid emergence and spread of the resistant organisms (Okeke et al., 2005).

The emergence of resistance to several new drugs such as fluoroquinolones, 3rd generation cephalosporins, and macrolides is cause of concern not only at local level but at regional level also. A comprehensive strategy for resistance control involving regulation of drug availability, antimicrobial drug quality assurance, and adequate surveillance and discouraging the culture of antimicrobial abuse needs to evolved (Okeke et al., 2005).

A network of laboratories for real time monitoring of antibiotic resistance among enteric pathogens and timely dissemination of such information is essential immediately.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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