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Drug resistance an international issue

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Abstract

The successful exploit of every therapeutic agent is compromised by the possible development of tolerance or resistance to that compound from the moment it is first employed. Microbial drug resistance has created havoc throughout the world from the last several years. It has become a grand issue that has not been confined to the hospital settings only but has put its devastating effects in community also. Among the microorganisms bacteria has developed tremendous potential for drug resistance during recent years. The development of drug resistance to maximum newly invented antibiotics has challenged the clinicians to treat the various disastrous bacterial infections which have caused great morbidity and mortality throughout the globe. Such types of infections are not only brutal and require longer and more complex treatments, but they are extensively more expensive to diagnose and treat. The molecular mechanisms which are responsible for drug resistance in bacteria are varied and more complicated. The most frequent mechanism is the conjugation by plasmid, which transfers the resistant genes from one bacterium to other thus, makes them resistant. New mechanisms of resistances have also been reported that has given rise to the multidrug resistant (MDR) strains. The haphazard and inappropriate use of antibiotics in outpatient clinics, hospitalized patients and in the community settings is the sole largest factor leading to antibiotic resistance. Various pharmaceutical industries, large academic institutions or the government are not investing the compulsory possessions to manufacture the next generation of newer safe and effective antimicrobial drugs. In several cases, huge pharmaceutical companies have ended their anti-infective research programs on the whole due to economic losses. All these factors are somehow responsible for giving rise to the MDR bacterial strains, thus putting the society at risk for the spread of harmful and serious infections.

INTRODUCTION

With the dawn of antimicrobial agents, some medical leaders thought that infectious diseases would be shortly eliminated and develop into historic interest only. In fact, the hundreds of chemotherapeutic agents developed since World War II, the majority of them are potent and safe, include drugs effective not only against bacteria but also against viruses, fungi and parasites. But, we now understand that as we urbanized antimicrobial agents, microbes developed the talent to avoid our best weapons and to counterattack with innovative endurance strategies. Antibiotic resistance occurs at an alarming rate amongst all classes of mammalian pathogens. Pneumococci resistance to penicillin and enterococci resistance to vancomycin have turn out to be commonplace. Even *Staphylococcus aureus*

resistant to vancomycin has appeared. Such pathogens create real clinical problems in managing infections that were simply treatable just a few years ago (Harrison 2005).

Nosocomial infections cause a significant burden for health and finances worldwide. Bacteria are the most prevalent micro-organisms that cause nosocomial infections. With the onset of deadly strains of carbapenem resistant Enterobacteriaceae and the falling effectiveness of antibiotics in treating widespread infections that has quickened in current years has brought the whole world at the morning of a post antibiotic era (CDC 2013). In highly developed and economical countries, constant and high rates of antibiotics used in the hospitals, community and agriculture have contributed to selection pressure of antibiotics that has given rise to the resistant strains thus forcing a move to classier and broader spectrum antibiotics (Laxminaryan R 2012). In low income and under developed countries antibiotic exploit is rising with elevated rates of hospitalization, growing incomes and high incidence of hospital infections. Amongst gram positive bacteria, common nosocomial agents include S*taphylococci, Enterococci, Streptococci*, *Clostridium difficile* and among gram negative bacteria are *Escherichia coli*, *Klebsiella sp*ecies, *Enterobacter*, *Proteus*, *Serratia*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* species and *Haemophilus* species. *Staphylococcus aureus* is one of the mainly virulent microbial pathogen among gram positive bacteria to cause nosocomial and community acquired infections. An extra anxiety is the appearance and dissemination of nosocomial organisms with improved resistance to antimicrobial agents. Such microbes contain methicillin resistant *S.aureus* (MRSA), *S.epidermidis,* vancomycin resistant *Enterococci* (VRE), multiresistant and extended spectrum β-lactamases (ESBLs) producing gram negative bacteria. Resistant strains of bacteria had been detected before the penicillin was introduced (Abraham EP 1988). The exploit of million tones of antibiotics over the earlier period since antibiotics were introduced has made almost all disease causing bacteria resistant to antibiotics normally used to treat them as we can see in case of β-lactamases class of antibiotics. Almost 1000 resistance related β-lactamases have been recognized that inactivate these antibiotics, which is a boost of ten times since 1990 (Davies J 2010). Quinolone antibiotics are artificial and so do not occur in nature, thus far 30 years after their extensive introduction resistance is endemic in worldwide that has caused a great disaster (Ruiz J, 2012). The stretch of a resistant clone can be speedy and have brutal consequences for susceptible hosts in health care settings. In Enterobacteriaceae carbapenem resistance has become a common factor that has improved harshly over the past decade. In the USA, 4・6% of acute care hospitals has reported at least one health care related infection caused by carbapenem resistant enterobacteria in 2012 (CDC 2013). The appearance of pan-resistant bacterial isolates such as *Acinetobacter* species and carbapenem resistant entero-bacteria in Pakistan, which are responsible for health care associated sepsis in hospitals is rendering these infections untreatable (Saleem et al 2010; Perry et al 2011 and Khan et al 2010). In a study reported between 2004 and 2007 from India, *E.coli* isolated from urine cultures of pregnant women in their first trimesters in the community showed an overall resistance of 75%, 73%, and 59%, to ampicillin, naladixic-acid, and co-trimoxazole (Hollyway et al 2009). Another study has mentioned a rise 40% in 2002 to 61% in 2009 and 2・4% to 52% ESBL producing *E.coli* and *K. pneumonia* isolated from the blood (Datta et al 2012). Resistant strains of gram negative bacteria are with rising resistance to colistin and polymyxin B are being widely reported from countries around the world, including South Korea, Italy, Greece and Saudi Arabia (Ko KS et al 2007; Capone A et al 2013; Antonaidou A et al 2007 and Baadani AM et al 2013). The development of vaccines and drugs that avert and cure bacterial infections was single of the 20th century's most important assistance to human permanence and superiority of life. Antibacterial agents are amongst the most frequently prescribed drugs of any kind at international level. Used correctly, these drugs are life saving; but, their indiscriminate use drives up the cost of health care leading to a plethora of side effects and drug interactions and fosters the appearance of bacterial resistance rendering previously valuable drugs futile (Harrison et al 2005).

MRSA:

Staphylococcus aureus is a dynamic and adaptable bacterium that has an incredible talent to attain antibiotic resistance. Introduction of penicillin had a dramatic impact during the ancient times when mortality from *S.aureus* disease was high but this glorious moment was short lived due to the emergence of penicillinase producing *S.aureus* (Lowy 1998; De Lencastre et al 2007). Methicillin resistant *Staphylococcus aureus* (MRSA) strains had rapidly emerged during 1960 and became a major problem in hospitals immediately after the methicillin was introduced in 1959. At that time those nosocomial MRSA strains were highly multidrug resistant (MDR) but, many being susceptible only to glycopeptides (Boyle-Vavra et al 2007; Afroz et al 2008).

Since last 10 years, many reports of vancomycin intermediate *S.aureus* (VISA) and vancomycin resistant *S.aureus* (VRSA) had been reported in several countries (Smith et al 1999). The genome of methicillin resistant *staphylococci* contains a 21-67kb heterologous mobile genetic element termed staphylococcal cassette chromosome mec (SCCmec), harboring the mecA gene and other resistance determinants. Methicillin resistance is mediated by

production of an altered penicillin binding protein PBP-2a encoded by the mecA gene (Boyle-Vavra et al 2007; Deurenberg et al 2008; Afroz et al 2008 and Kim 2009).

This time, struggle was not due to a hydrolyzing enzyme, but to a more complicated mechanism. Methicillin, like all penicillins exerts its battle by jamming the proteins called penicillin binding protein (PBPs) which are liable for the construction and protection of the bacterial cell wall. *S.aureus* resistant strains acquired a new protein called PBP2a which was not barren by methicillin and could restore the other PBPs, thus, allowing the continued existence of *S.aureus* in the company of methicillin. PBP2a is encoded by the gene mecA, which is the trademark of MRSA. As different to the penicillinase gene mecA, it does not live on a plasmid but on the chromosome fixed in a large movable genetic element called Staphylococcal chromosome cassette mec or SCCmec (Katayama et al 2000). The occurrence of PBP2a means MRSA is not only opposing to methicillin but, moreover to all β-lactam antibiotics together with synthetic penicillins, cephalosporins and carbapenems.

It had been reported that isolates which produce large amounts of penicillinase (penicillinase hyper-producers) may express low level resistance under some test conditions (McDougal et al 1986; Chambers et al 1989). These isolates had been referred to as borderline oxacillin resistant *S.aureus* (BORSA). There are no reports of failure of treatment with penicillinase resistant penicillins in infections with such isolates and animal model experiments indicate that their clinical significance is doubtful (Thauvin-Eliopoulos et al 1990). Methicillin was the first penicillinase resistant penicillin used in 60s and was recognized at that time as the most reliable agent for routine susceptibility testing, though methicillin is now a day's not used in treatment. That's why; resistant strains were termed methicillin resistant *S.aureus* (MRSA). Later, oxacillin resistant *S.aureus* (ORSA) came into existence after the use of oxacillin as an alternative to methicillin in susceptibility tests.

Mec A gene:

When penicillin was revealed, *S.aureus* was gracefully prone to it and *S.aureus* infections were efficiently cured with the ''wonder drug'' but in the path of a few years *S.aureus* became talented of destroying penicillin by making of a particular enzyme called penicillinase encoded by a plasmid that multiply quickly among diverse *S.aureus* strains (Lyon et al 1987). Methicillin modified penicillin specifically designed to stand firm the critical stroke of the staphylococcal penicillinase became accessible for therapeutic use in 1959 but its victory was short lived. Following only 2 years the first case of MRSA was reported (Jevons 1961). The term MRSA came in to existence soon after *S.aureus* acquired the methicillin resistant gene mecA, a 2.1-kb exogenous DNA fragment by parallel transfer. Hartman et al (1981) had reported that an additional methicillin resistant penicillin binding protein (PBP2a) is encoded by mecA gene, which has extremely low attraction for β-lactam antibiotics. PBP2a is a transpeptidase that plays a major role in the cell wall biosynthesis in the presence of β-lactam antibiotics that is supported by transglycosidase domain of the native PBP2 of *S.aureus* (Pinho et al 2001).

The emergence of the mecA gene is still not clear (Couto et al 1996; Wu et al 1996) had reported a mecA homologue with a close sequence amino acid similarity of 88% to the mecA of *Staphylococcus sciuri*. *S.sciuri* isolates were reported to be consistently susceptible to β-lactam antibiotics. However, the role of this particular gene of *S.sciuri* was not confirmed. But, it was described that *S.sciuri* mutants showed a harsh boost in the transcription rate of the mecA homologue due to a point mutation in the promoter and this mutated gene was able to grant increased resistance, when introduced into a methicillin susceptible *S.aureus* (MSSA) strain when selected in the presence of increasing concentrations of methicillin (Wu et al 2001). Thus it is obvious from the above results that the mecA homologue is omnipresent in the antibiotic susceptible animal species. *S. sciuri* may be an evolutionary precursor of the mecA of the MRSA strains.

A mobile genetic element, the staphylococcal cassette chromosome mec (SCCmec) carries the mecA gene which is inserted into the chromosome at a site specific location (Ito et al 1999). Two specific genes nominated as cassette chromosome recombinase A and B (ccrA and ccrB) are carried by SCCmec for transfer. Katayama et al (2000) had reported that SCCmec contains transposons and integrated copies of plasmids that carry a variety of resistant genes against non β-lactam antibiotics in addition to the mecA gene. Ito et al (2001) had described the structure of three mec elements which are also termed as staphylococcal chromosomal cassette (SCC mec). The size of the SCCmec type-I was 34kb that was isolated from United Kingdom (strain NCTC10442) in fact, it was the first MRSA strain reported in 1961. SCCmec type-II was identified in an MRSA (strain N315) with a size of 52kb from Japan in 1982 while as, the SCCmec type-III was recognized in an MRSA (strain 82/2082) with a size of 66kb in 1985 from New-Zealand (Ito et al 1999; Ito et al 2001). Another study reported SCCmec type-IV with a smaller size of 20-24kb, from the pediatric clone and two community acquired MRSA strains (Oliveira et al 2001; Ma et al 2002).

Recently, a different SCCmec type nominated as 'New type' was identified among the community acquired MRSA (CA-MRSA) but, it is still under investigation (Okuma et al 2002). Till date, seven SCCmec types and

several variants had been described but, SCCmec type I, II, III, IV and V being the most common (Milheirico et al 2007). So far emergence of SSCmec is unknown and no bacterial isolates of any other genera had been reported to carry this element. The occurrence of IS1272 insertion sequence widespread in *Staphylococcus haemolyticus* in the SCCmec types I and IV led to the proposal that SCCmec type I was transferred from this species to *S.aureus* in the past (Archer et al 1996). The discovery of different MRSA lineages as well as the identification of different SCCmec types within an MRSA genotype evidenced that MRSA has arisen by numerous independent introductions of mec into successful MSSA lineages (Fitzgerald et al 2001; Oliveira et al 2002 and Enright et al 2002).

Vancomycin resistance in *Staphylococcus aureus*:

It had been recorded that MRSA infections are difficult to treat as compared to MSSA infections if, they are located at anatomical sites because, at those sites antibiotic penetration is very less (Duckworth 2003).

Vancomycin was the first glycopeptide antibiotic that was introduced into clinical practice in 1958 after it was isolated in the mid 1950s (Woodley et al 1961). Vancomycin had been the drug of choice for treatment of staphylococcal nosocomial infections especially MRSA throughout the world for the last 20 years. Vancomycin is the second most common antibiotic used in hospitals throughout the world, about 16 tons of the vancomycin is being used every year. Only 8 clinical vancomycin resistant *S.aureus* (VRSA) isolates had been isolated to date, all in the USA and mostly from the state of Michigan (Sievert et al 2008). However, recent reports proved some sort of concern regarding vancomycin (Tenover et al 2007). The first clinical vancomycin intermediate resistant *S.aureus* (VISA) with a minimum inhibitory concentration (MIC) of 8mg l^{-1} was documented in 1996 while, as the first hetero vancomycin intermediate resistant *S.aureus* (hVISA) with an MIC range of <4 mg l^{-1} but, possess stable sub populations (ca. $1/10^6$) that can grow in the presence of >4 mg l^{-1} of vancomycin was computed by (Hiramatsu et al 1997).

Since then, vancomycin intermediate resistant *S.aureus* (VISA) strains had been reported in many parts of the different countries around the world where such reports were not recorded earlier (Walsh et al 2001). It was determined that the prevalence of hetero vancomycin intermediate resistant *S.aureus* is 0-5% of MRSA in different parts of the world but, in certain countries like France, Germany, Spain and possibly Japan the prevalence is more common (Walsh et al 2002). It had been assessed from various countries like Japan (Hiramatsu et al 1997), New York (Sieradzki et al 1999), Spain (Ariza et al 1999), France (Heym et al 2002), Poland (Krzyszton-Russjan et al 2002), Germany (Bierbaum et al 1999), Brazil (Oliveira et al 2001) and Greece (Kantzanou et al 1999) that vancomycin intermediate resistant *S.aureus* and hetero vancomycin intermediate resistant *S.aureus* had emerged from MRSA clones prevalent in those countries i.e., the New York / Japan MRSA (Roberts et al 1998; Aires de Sousa et al 2000), the Iberian (Dominguez et al 1994; Sanches et al 1995) and the Brazilian clones (Teixeira et al 1995).

Although, the mechanism of vancomycin resistance is different e.g., VRSA has acquired vanA gene cluster mediated resistance in contrast glycopeptides intermediate *S.aureus* / hetero glycopeptide intermediate *S.aureus* (GISA/hGISA) have achieved mutation directed resistance (Woodford et al 1995; Weigel et al 2003 and Tenover et al 2004). Although the genetic mechanism had not been fully understood but, the thickening of the cell wall through accumulation of increased amounts of peptidoglycan with reduced levels of cross linking, either by increased synthesis or by reduction of the turn over seems to be common factor to all VISA and hVISA strains. This causes an increase of free D-Ala-D-Ala side chains to which vancomycin can bind which result in trapping of more and more vancomycin molecules in the peptidoglycan layers before they could reach to the cytoplasmic membrane where the synthesis of peptidoglycan takes place (Hanaki et al 1998; Cui et al 2000 and Avison et al 2002). The most active antibiotics for the nosocomial infections caused by MRSA are limited to vancomycin, linezolid and daptomycin.

ESBLs:

One of the significant mechanisms of resistance is the manufacture of beta-lactamases, in gram negative bacteria, which hinder protein transpeptidases participating in bacterial cell wall synthesis (Bradford 2001; Paterson and Bonomo 2005). Presently, several such enzymes are well known and more continue to be described. ESBLs and AmpC beta lactamases are of particular clinical and epidemiological significance, which are talented of inactivating the effects of broad-spectrum cephalosporins and penicillins. Due to the production of these enzymes in clinically significant *Enterobacteriaceae* resulting in high patient morbidity and mortality (Paterson and Bonomo 2005). ESBLs are those enzymes that arbitrate resistance to extended spectrum cephalosporins (ESCs), such as cefotaxime (CTX), ceftriaxone, and ceftazidime (CAZ), and the monobactam aztreonam (ATM) (Livermore 2001). In *Klebsiella pneumoniae* and *Escherichia coli* such enzymes are most frequently set up and have been freshly detected in *Pseudomonas aeruginosa* at low incidence (Ben-Marez et al 1999; Lee et al 2005; Poirel et al 2004). As the introduction of β-lactams nearly 60 years ago, β-lactams have constantly been the most broadly used antibiotics worldwide (Livermore DM 1996). Resistance to β-lactams antibiotics is dogged by the manufacture of periplasmically located β-Lactamases and by diffusion of antibiotics through the outer membrane through porins.

The mainly familiar β-Lactamases are the plasmid borne class A (Bush KG et al 1995; Medeiros AA 1997). TEM and SHV β-Lactamases. TEM-1 was first reported in 1965 confers a high intensity of resistance to penicillin's, cephalosporin's and azetreonam (Datta N 1965). Opening in the early 1980s extended beta lactamases (ESBL) derived from TEM-1 and SHV-1, began to emerge in reply to the wide broaden use of cephalosporin's that had occurred in the preceding decade. The rapid appearance of resistant TEM- β-Lactamases subsequent the introduction of new β-Lactams antibiotics has been such a steady pattern that it has conditioned thoughts about the development of antibiotic resistance and has powerfully affected public health policy. The amp-c or class (e) β-Lactamases have comparatively lately moved into plasmids and become extensively swelled (Javrin B 1981). The first plasmid borne amp-c gene for CMY-1, was reported in 1988 followed rapidly those for MIR-1and CMY-2.In the previous 50 years more than 50 different amp-c genes have been reported together with over 20 plasmid borne amp-c genes in clinical isolates globally (Bavern Feind et al 1989; Papanicolaov G et al 1990). A topical survey of 20 U.S hospitals reported that plasmid borne amp-c genes were more common than TEM-type ESBL-genes, though they were less frequent that SHV-type ESBL genes. Accurate typing methods will help to set up modes of transmission in hospitals and community out breaks and execution of preventive measures like immediate patient isolation screening of patient contacts, staff and carriers. This will help in rationalizing antibiotic usage from treating such types of infections thus limiting the proliferation of ESBL producing strains.

Accurate detection methods like double disk synergy test, three dimensional test, inhibitor potentiated disc diffusion test, disk approximation test, MIC reduction test, E-test and identification by genotypic method will help to establish the modes of transmission in hospitals and to execute preventive measures, it will also aid in establishing rational use of antibiotics. *Pseudomonas aeruginosa* is responsible for 10-15% of nosocomial infections worldwide (Derek F et al 2000). The infections are frequently difficult to treat because of both the natural resistance of the species and its remarkable ability to acquire further resistance mechanisms to multiply groups of antimicrobial agents. *Pseudomonas aeruginosa* represents a phenomenon of antibiotic resistance, demonstrating practically all known enzymic and mutational mechanisms of bacterial resistance. These mechanisms are often present simultaneously, conferring combined resistance to many strains (Tassios P et al 1997). Multidrug-resistant strains of *Pseudomonas aeruginosa* resistant to ceftazidime, imipenem, gentamicin and ciprofloxacin are often isolated among patients suffering from nosocomial infections particularly those receiving intensive care treatments (Lee K et al 2001). The increasing rate of *P. aeuroginosa* strain is a wide spectrum of clinical settings determines them as emerging pathogens, especially in intensive care units (ICUs) and justifies the necessity for antimicrobial resistance surveillance. Enzymes conferring resistance to extended spectrum β-lactam antibiotics came to be known as extended spectrum β-lactamases (ESBLs). These are plasmid mediated enzymes capable of hydrolyzing and inactivating a wide variety of β-lactams including third generation cephalosporins, penicillins and aztreonam (Paterson DL 2005). The first ESBL producing isolates were discovered in Western Europe in mid 1980's and subsequently in US in the late 1980's; the resistant organisms are now a worldwide problem. ESBL's are frequently plasmid encoded and frequently carry genes that encode resistance to other drugs as well. This phenomenon has serious clinical implications as the treatment options are limited. Carbapenems are often a last resort in treating infections due to multidrug resistant gram-negative bacilli due to their stability to extended-spectrum and Amp C β-lactamases (Nathisuwan S et al 2001; Lee K et al 2003).

Reports of carbapenemase producing isolates have been mounting over the previous few years. Carbapenemases occupied in acquired resistance are of Ambler molecular classes A, B and D. Class A, clavulanic inhibited carbapenemases are exceptional, being also chromosomally encoded (Nmc-A, Sme-1 to Sme-3, IMI-1) in *Enterobacter cloacae* and *Serratia marcescens* or plasmid encoded as kpc-1 in *Klebsiella pneumoniae* and GES-2 in *P. aeruginosa*. Class D carbapenemases are ever more reported in *Acinetobacter baumanii.* Class B or metallo-beta-lactamases are the mainly important of all the carbapenemases; powerfully hydrolyze all β lactams apart from aztreonam (Nordmann P 2003).

MBLs can be divided into those that are normally chromosomally mediated and those that are encoded by transferable genes as is the case with all other β lactamases. MBL was first reported as a zinc dependent enzyme in *Bacillus cereus* in mid 1960's. A few decades' later imipenem hydrolyzing metalloenzymes were found in *Aeromonas hydrophilia* and *Bacteroides fragilis.* All these enzymes were produced by chromosomal genes and at first were recovered only from single clinical isolates.

MBL's were initially regarded as resistance determinants of low clinical importance compared with serine-β-lactamases, as they were detected in only a few species of minor pathogenic potential (e.g. *Bacillus cereus, Stenotrophomonas maltophilia* some *Aeromonas* species, *Bacteroides fragilis* and some *Flavobacteria)*. The view however changed abruptly with the appearance of acquired MBLs, encoded by genes carried on mobile DNA elements among major gram-negative pathogens including members of the family Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* species (Lee K et al 2003; Jacoby GA 2005).

Until very recently the carbapenem class of antibiotics remained the ultimate choice for the clinician in treating *Acinetobacter* infections and in fact remains so in many geographical areas of the world. However the development of Carbapenem resistance has limited this proposition. This assumes a greater importance in light of the fact that not many newer classes of antimicrobials antibiotics are being developed which could circumvent the resistance mechanisms of *Acinetobacter*. Thus it is imperative to recognize and identify factors associated with *Acinetobacter* resistance and preemptively treat such patients with appropriate antimicrobials.

Rational antibiotic use in hospitals:

The set of actions and policies to develop the normal use of antibiotics is moreover recognized as antibiotic stewardship. Crucial elements of an antibiotic policy include an established and limiting list of antibiotics in exercise, usual treatment guidelines, review and feedback of prescriptions, supervision of bacterial resistance and antibiotic use and education to everyone (Paterson DL 2006). Antibiotic stewardship has naturally residential in the hospital context in resource affluent countries, but stewardship activities should be prolonged to primary care on a national level. Its mutual goals are better outcomes for patients, suppression of antibiotic resistance, and amplified charge efficiency of care. Antibiotic stewardship must be done by every health-care facilities and should be branch of official recognition programmes. Successful stewardship programmes can reduce antibiotic exploit by 20–40%, prevalence of health-care related infections (*C. difficile*, MRSA and others), lengths of stay and dominance of bacterial resistance (Lawes T et al 2012; Vernaz N et al 2009).

Balanced antibiotic use in the community:

A programme on coherent antibiotic use in the community must cover a broad variety of settings, such as ambulatory care facilities, pharmacies, drug vendor outlets, households, and agriculture. Overdo and illogical use of antibiotics either obsessed by the supply or requires sides have been known in all these settings (Apisarnthanarak A 2009). Lying on the supply side, physicians are regularly role models for other health professionals and patients who hear how to utilize antibiotics from their prescriptions (Laxminarayan R 2012). Distant from medical training, physicians are subjective by their peers and alleged demands of patients. Therefore, physicians may find it complicated to obey with treatment guidelines (Radyowijati A. 2003). These barriers to fulfillment should be detached or minimized and options for substitute measures for guideline conformity should be concurrently provided (Thorgeirsson T 2013). Examples of options for non antibiotic treatment in viral or self-limiting infections is the medicine of herbal origin, as opposite to antibiotics, (Sumpradit N 2012) and use of a late prescription practice with open instructions for patients regarding when to utilize antibiotics (McDonnell Norms Group 2008).

Education and shifting community norms:

As absurd use of antibiotics repetitively happens amongst community and health professionals, it becomes the rule. To shatter this pattern, antibiotic stewardship programmes must focus not only on correct use, but moreover on ensuring sustainability of behavioral alteration and reorientation of societal norms (WHO 2002). Various bottlenecks linger in the endorsement and sustainability of high-quality prescription practices, mainly with regards to social norms. Solutions require to hub on versatile and multilevel interventions that describe restricted barriers and beliefs, which can differ widely among cultures, countries and regions. Education of every health-care worker, laboratory staff, veterinarians and the community on appropriate antibiotic exercise and antibiotic resistance is crucial and educational strategies have recently been reviewed (Pulcini C 2013).

Infection management:

Prevention of infection is better than treatment. From a resistance point of view, prevention reduces antibiotic exploit and the spread of resistant bacteria; but, prevention is not the chief approach to control resistance since antibiotic use also needs to be prohibited. However, at the community level, perfection of sanitation, poverty drop, access to clean water and vaccination will have a vast effect on both infectious disease occurrence and move of and colonization by resistant genes and multidrug-resistant organisms. At the hospital level, avoidance of health-care-associated infections that are frequently multidrug resistant is necessary, but not easy. In addition hand hygiene, the significance of which cannot be over-emphasized, bench marking of frequencies of health-care-associated infections is helpful to reduce the number of these infections. Surveillance makes one extra cautious; the majority of the infection control policies in place have been developed about MRSA, Vancomycin resistant enterococci, *C. difficile*, catheter associated bloodstream infections, catheter allied urinary tract infections and ventilator pneumonia. Infection control interventions have to be reassessed and enhanced in a period with multi drug resistant gram negative bacilli and mobile antibiotic resistance genes. Furthermore, cultural barriers for execution of fundamental hygiene measures are possibly an extensive crisis that needs a great deal of study.

Defending the future:

In observation of the current signal of antibiotic resistance will every set of interventions be effectual as much as necessary. Recommended interventions are not voluntary; they are fundamental requirements to make sure normal

use of antibiotics and most favorable outcomes for patients. Progressive countrywide and global management is required besides with adequate technical facility at all diverse policy levels. Complete national and worldwide plans, similar to those in the Europe are desired (Allerberger F et al 2009) and must have related visibility and outcome to those for new significant health problems such as Tuberculosis, HIV and Malaria. Moreover, these state plans need to get into explanation their interfaces with health care organization, quality assurance, financing and specialized education. The scientific society ought to explain the causes, scale and fast rate of development of resistance. Antibiotic resistance should be a worldwide political agenda, not just the agendas of infectious disease meetings. Stress is located on reinvigoration of the drug discovery industry, but here is a logic that all low lynching fruit have already been pulled out and that new developments, even if victorious, cannot satisfy demand and determination should be merely a temporary fix. A lot of public consider that with billions of years of advancement, bacteria will be forever superior genetic engineers than people. Antibiotics are the natural products of bacteria and thus resistance mechanisms are not new. So, antibiotics are a valuable public product and their proposed and unplanned ecological discharge needs to be monitored and prohibited.

Conclusion:

However the problem of antibiotic resistance among the bacteria cannot be solved by the production of new and stronger antibiotics. If the previous history is the predictor of future history in any way, microorganisms will more firmly adopt themselves to the environment by developing resistance to newly invented antibiotics. Today, almost all important bacterial infections in the India and throughout the world are becoming resistant to antibiotics. Development of resistance among bacteria is generally due to the overuse, misuse and indiscriminate usage of antibiotics by all health care professional and self medication. It is estimated that 70-80% of prescriptions for antimicrobials are probably advised unnecessarily by the health professionals. Clinicians should be familiar with local antibiotic sensitivity profiles and should comply with the local antibiotic guidelines. A hospital antibiotic policy should be formulated based on local antimicrobial resistance data. Prescribers should be educated about the use of antibiotics and also the infection control strategies.

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