ANTIMICROBIAL RESISTANCE: A MAJOR PUBLIC HEALTH CONCERN IN INDIA

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ABSTRACT

Antimicrobials are essential for life threatening cases but inappropriate use of these agents is primary reason for antimicrobial resistance (AMR) which is a major concern. After the first identification of Multidrug resistance (MDR) positive pathogens, the countries including India, Pakistan, and USA pointed out tourism as one of the promoting factor. Amongst MDR pathogens, gram-negative bacteria are more resistant than gram positive one. AMR is directly associated with increase in mortality rate, length of stay and cost of therapy. Colistin, the global antibiotic of last resort, also expressed resistance with a rate of 4-5% in Delhi which is an alarming signal to the society. Due to absence of specific standard treatment guidelines and physician's own practice which deviate from guidelines lead to irrational use of antibiotics. Central Drugs Standard Control Organization (CDSCO) revealed that about 70.8% prescriptions were without specific indication. Around 50% national antimicrobial consumptions are to promoting growth of food animals, which produce resistance to *salmonella* like species to human. Unhygienic environment and improper treatment of hospital sewage act as a nutritive medium for superbugs to flourish. Intensive Care Unit (ICU) settings are most prone area for resistance because of excessive use of antibiotics. In India, in order to reduce the rate of AMR, there is need of upgrading the surveillance system to international standard. Since Over the Counter (OTC) drugs play a major role in creating AMR, Drug Controller General of India (DCGI) putting the efforts to control sale of antibiotics from retail pharmacies. Schedule H1 has been introduced to prevent the sale of medications as OTC drug and a system of color coding was also introduced for broad spectrum antibiotics to restrict its sale only to tertiary care hospitals. All global policies are working on containment of resistance, rational and restricted use of antibiotics. European commission is now focusing their attention to new antimicrobial development. Education for promoting compliance to prescriptions and discouraging self-prescriptions are equally important to fight against AMR.

KEY WORDS: Antimicrobial resistance, antibiotics, Infections, Nosocomial infections, ICU, India, Resistant bacteria

INTRODUCTION

Antimicrobial resistance is a sheer marker of danger across the world, including India. Antibiotics are essential in life-threatening cases but overuse of antibiotics can adversely affect the society (Ganguly NK et al., 2011). Widespread use and availability of antimicrobials over the counter for human as well as animal consumption are the two most

responsible factors for antimicrobial resistance (Leung et al., 2011).

Alexender Fleming, in 1928, discovered the first antibiotic – Penicillin. He already had warned on the time period of 1945 that there is complete possibility of developing resistance to these magic bullets. Since late 1980s, his prediction has taken shape. Expert group of UK government stated that least estimate of mortality due to AMR is 7,00,000. If it is not controlled, the rate will turn to 10 million in 2050 which is more than cancer deaths today (Gupta, 2015). It was found that mortality rate due to AMR was 5,00,000 in USA and Europe (Gupta, 2015) in 2013 and at the same time 58,000 children died in India (Harris, 2014). In 2013, around 44% of under-five deaths occurred during this period, up from 37% in 1990 (2015c). Annually pneumonia causes 4,10,000 deaths in children in India (Mathew, 2009). Factors like limited access and use of antibiotics without any specific indications (Cold, Uncomplicated cases of diarrhea Etc.) are accountable for this swelling menace (Levine and Cherian, 2007; Ganguly et al., 2011).

Dr. Timothy R. Walsh of Cardiff University, UK, highlighted that India's dreadful sanitation, uncontrolled use of antibiotics and overcrowding coupled with lack of monitoring the problem has created a tsunami of antibiotic resistance that is reaching just about every country in the world (Harris, 2014). India's then Health Minister asserted in the Parliament that number of multidrug resistant (MDR) TB cases in India expanded five times from 2011 to 2013 (Gupta, 2015).

The resistant organisms are free to move across countries through travel and trade so that antimicrobial resistance has become a global challenge requiring concerted efforts at national and international levels to preserve the available antimicrobial agents (Plianbangchang, 2011). It can bead dressed through treatment policies such as combination therapy, rational prescription, patients' compliance, a strong regulatory mechanism coupled with educational activities and an efficient surveillance system that monitors the emergence & spread of resistance as well as the optimal utilization of antimicrobial agents (2011c).

This review covers the outbreak of AMR, possible risk factors, its determining factors, consequences, and preventive measures.

OUTBREAK

The discovery of antibiotics and its spectacular success in combating infections and decline in mortality rate had been realized in early part of 20th century. Over the past six decades, these magic bullets have played a critical role in reducing the global burden of communicable diseases. This success was eclipsed by the counter blast of microbes resulting in persistent and relentless rise of antimicrobial resistance and had rendered the management of many infectious diseases difficult (Bhatia and Narain, 2010; Arias and Murray, 2009). In 2007, first case of New Delhi metallo-beta-lactamase 1 (NDM-1) was identified in a Swedish patient in hospital at New Delhi who was suffering from UTI associated with MDR *K.pneumoniae* (Yong et al., 2009). Subsequent reports on incidence of MDR positive bacterial infections in UK, India, Pakistan were found (Wear, 2010) and it was also identified that tourism was one of the major promoting factors for these infections (Nordmann et al., 2011).

Kumarasamy and his team identified 44 isolates with NDM-1 in Chennai, 26 in Haryana, 37 in the UK, and 73 in other sites in India and Pakistan. NDM-1 was mostly found among *E.coli* (36) and *K.pneumoniae* (111) which was highly resistant to all

antibiotics except to tigecycline and colistin (Wear, 2010). In 2010, there was an outbreak of food poisoning due to NDM-1 *E.coli* in India. Spellberg found that these MDR pathogens are not limited only to hospital setting but also seen in community (Spellberg, 2011).

In 2011, a study revealed that supply water in Delhi also contained NDM-1- MDR pathogens (Walsh et al., 2011). At the same point, the WHO's regional director for Europe observed that "We are at a critical point in time where antibiotic resistance is reaching unprecedented levels"(2011a). In 2011, WHO reported that there are 6,30,000 MDR cases out of 12 million TB cases (Jindal et al., 2015).

Findings of a study conducted by Guidry et al. outlined 330 cases of ICU acquired infections; 237 cases were with gram-negative isolates and 93 cases with gram positive isolates. While receiving antimicrobial therapy, 65% MDR cases for gram negative and 50.6% MDR cases for gram positive pathogens were found (Guidry et al., 2015). A study conducted by Singhal R et.al. found 51 % MDR gram negative isolates and 16% MDR gram positive isolates at an ICU setting (Singhal R et al., 2012).

Sligl et al. reported 74 cases with gram-negative bacterial hospital acquired infections with rate of 0.97/1000 patient days. According to culture reports, *E.coli* (20%) and *P.aeruginosa* (18%) were most prevalent isolates (Sligl et al., 2015). Findings of a study conducted at ICUs of a private tertiary care hospital said that maximum cultures were found positive with 18% *E.coli* and 33% *A.baumannii* (Singhal R et al., 2012).

Taking cognizance of the reports from the scientific community, the Indian health authorities responded and tried to keep India on the safe side of results. Director General of health services stated that the environmental presence of NDM-1 gene carrying bacteria is not a significant finding since there is no clinical or epidemiological linkage of this finding in the study area. Another official of the Ministry of Health and Family Welfare added that the study was nonscientific and that the journal repeatedly targets the Indian capital when it is known that 'superbugs' are found globally. A separate study carried out by the government over the last two years, based on the stool samples of 1,944 pregnant women at a multispeciality hospital in Delhi, found that all microbes in the samples were sensitive to carbapenems (Tandon, 2011).

According to a report published on data in leading English daily, AMR had global effect and it had quietly been sweeping India and amongst victims, newborns were most affected because once miraculous cures no longer work. Report showed that more than 58,000 newborns had died due to MDR infections last year and estimated that nearly 8,00,000 died annually. Now Indian pediatricians also believe that this uncontrolled rise of resistant infections could neutralize efforts to improve India's dreadful infant death rate.

The Chief of pediatrics at the AIIMS stressed that reducing newborn deaths in India is one of the most important public health priorities in the world and this will require treating an increasing number of neonates who have sepsis and pneumonia. If resistant infections keep growing, that progress could slow, stop or even reverse itself that would be a disaster for not only India but for the entire world (Harris, 2014).

DOMAINS

Antimicrobial resistance is an important obstacle for national authorities to confront infectious diseases. Substantial work has

been published from India that indicates the strength and extent of challenge of antimicrobial resistance in general. This heading is emphasizing on possible various prone areas of resistance like population type (geriatric, pediatric, immunosuppressive), location (hospital, community, agriculture), and species wise.

Since antibiotics are highly prescribed in ICUs, so MDR pathogens are more prevalent in this setting. Amongst MDR superbugs, Gram negative bacteria have been found to be more resistant than gram positive and *A.baumannii* was at the highest rank among gram negatives (92%). In case of Gram positive pathogens, 50% *S.aureus* were resistant to Methicillin (Ravi et al., 2013). This uncurbed web of MDR pathogens have also been jeopardizing special treatments including Cancer Chemotherapy, Organ Transplantation etc. (Kumar et al., 2013). The microbes present in natural environment act as resource for transferring infections from one patient to other in hospital. Patients with infectious disease which are already on heavy antibiotics, geriatric & immune-compromised population and patients with invasive procedures are at higher risk for morbidity and mortality associated with hospital acquired infections (HAIs) (2002). Community acquired infections (CAIs) are also facilitating this resistance problem. Results of a study found 11.2% prevalence of nosocomial infections and 10.7% of CAIs (Ott et al., 2013) and one another study showed comparable results in context of prevalence of CAIs and HAIs that was 12.5% and 22% respectively (Navarro-Zarza et al., 2010). The two most common community-acquired and nosocomial infections affected areas were respiratory and genitourinary tracts (Ott et al., 2013). The most common pathogens were *E.coli* (19%), coagulase-negative staphylococci (18%), *Candida* spp.(15%), *Enterococcus* spp. (13%), and *P.aeruginosa* (10%) (Navarro-Zarza et al., 2010). Methicillin resistant *S. aureus* (MRSA) is a major hurdle in treatment of HAIs in almost all countries (Tyagi et al., 2008).

Resistance was also observed even against Colistin, the global antibiotic of last resort, in Delhi hospitals at the rate of 4-5%.Teixobactin and similar interventions cannot help India until unless steps are not taken for combating AMR (Gupta, 2015). The number of hospital born babies has doubled up to 82% in ten years because women were paid on having babies in hospital under a Govt. program while bed capacity of hospital was same which allowed infections to spread rapidly. Unhygienic atmosphere of hospitals nourish superbugs. In a United Nations Children's Fund (UNICEF), survey of 94 district hospitals and health centers in Rajasthan, it was found that 70 percent had possibly contaminated water and 78 percent had no soap available at hand-washing sinks, while 67 percent of toilets were unsanitary (Harris, 2014). India's Agriculture ministry found residue of antibiotics in dairy and meat products due to indiscriminate use of antibiotics in poultry and animal husbandries which intend to cultivate AMR. Even a study conducted by Delhi based science non-governmental organization (NGO) centre for Science & Environments in 2014 showed 40% chicken samples with antibiotic residues (Gupta, 2015). Infants, especially premature babies were found to be more vulnerable due to incomplete development of immune system and Extended-spectrum beta-lactamases (ESBL) producing pathogens were more prevalent in newborns (Chandel D and Johnson J, 2011). Indias' top neonatologists estimated that there is large number of MDR infection cases at the first day of life of newborns which are blossoming in communities and even in pregnant ladies

(Harris, 2014). Not only newborn but everyone is at risk which has been justified by death of Uppalapu Shrinivas, one of India's most famous musician, at the age of 45 because of an infection that doctor could not cure. Seniors in society are at higher risk because they are more prone to get infections, weakened immune system, and more probability for close contact.

It was found that 1,80,000 cases of MDR-TB reside in South East Asian (SEA) regions (India, Bangladesh, Indonesia, Myanmar and Thailand). The Director of the National Institute for Research in Tuberculosis, uttered that these patients are catching resistant bugs at home, not hospitals, making the epidemic very difficult to control (Harris, 2014). Resistant Malaria had also become a major issue. WHO regimen, Bihar, outlined the failure of convent dosage of pentavalent antimonials for kala-azar up to 60%. Pentamidine is also acquiring resistance (25%) even in higher doses. Miltefosine, newer potent anti-leishmanial drug is only the option left for today (Bhatia and Narain, 2010).

According to WHO's Assistant Director General for Health Security, "Without urgent, coordinated action by many stakeholders, the world is headed towards a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill" (2014).

DETERMINANTS

Under this category possible reasons for AMR are highlighted. AMR is extending from local areas to international level. There are multiple factors which have the potential of promoting MDR infections. Due to continuous change in genetic traits of superbugs, they are evaded from grab of antibiotics. These escaped bacteria continuing the chain by transferring these traits to vulnerable bacteria.

Present scenario of healthcare delivery system is also associated with MDR infections. Public health sector contribute to only 0.9% of gross domestic product (GDP) in India out of total GDP spent on health and remaining contributor include private sector. Therefore, limited number of people can have access to these facilities (Kumar et al., 2013). The WHO defines appropriate use of antibiotics as "the cost-effective use of antibiotics, which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antibiotic resistance" (2001). Irrational use of antibiotics is increasing due to limited or absence of standard treatment guidelines and physicians' own practice which differ from guidelines. CDSCO in 2012 reported that 70.8% of antibiotic prescriptions were without specific indications and in 2007 CDSCO reported that 1800 out of 2000 brands of fixed dose antibiotic combinations had wrong or unnecessary compositions (Gupta, 2015).

Utilization of these wonder drugs is tremendously increasing. A comparison of pilot surveys carried out at private retail pharmacies in 2004-2006 and 2008 showed increase in use of cephalosporins while decline in macrolides consumption (Ganguly et al., 2011). There was increment of 36% in global sales of antibiotics from 2000 to 2010 among Brazil, China, India, and Russia. In India, private doctors have driven much of that growth and much of these doctors' income comes from drug sales. This creates the evidence of inappropriate prescription pattern of antibiotics (Harris, 2014).

Cost is also one of the constraints for limited procurement of drugs by patients. Poor compliance to regimen and self-prescription are also contributing the inappropriate use.

Prescription of antibiotics for viral infections is high because of lack of inexpensive and easily accessible diagnostic measures to differentiate viral infections from bacterial (Cornaglia et al., 2004).

Now-days more than 50 per cent of the national consumption of antimicrobials is for promoting the growth of food animals. Travel and trade are majorly contributing in evading the man-made boundaries through humans or food chain includes resistant *Salmonella* species (MacPherson et al., 2009; Ellerbroek et al., 2010; Aarestrup et al., 2007). Therefore, USA govt. banned the use of feed contaminated with drugs in chicken farms. A New Delhi science group recently found antibiotic residues in 40 percent of chicken samples tested (Harris, 2014).

Unhygienic environment in India makes it first ranker for bacterial infections amongst all countries which results in higher prescription of antibiotics. Keeping this issue in mind, Indian government took a step on Oct. 2014 for cleaning the country and to build the toilets. But the task is monumental. (Harris, 2014)
Improper treatment of hospital sewage provides a way to superbugs for exposure. MDR pathogens causing newborn infections in India were found in untreated human waste. Such bacteria rarely infect newborns in developed nations, said Dr. Paul. India and other developing nations are by no means alone in threatening the future of antibiotics.(Harris, 2014)
Recent analysis done by European Centre for Disease prevention & Control and European Medicine Agency, intimated dry antibiotic pipeline (2009). It could be because of reluctant behavior of industry towards investment in new antibiotic development. Such reluctance could be because of consumption of more generic antibiotics as first line and new ones as last option, treatment for short duration in comparison to drugs for chronic conditions, lower profit due to failure of therapy because of resistance and tedious process of clinical trials (Bhatia and Narain, 2010; Morel and Mossialos, 2010).

MANIFESTATIONS

AMR results illness for a longer period of time which in turn protracted treatment with expensive and toxic drugs is required (Kumar et al., 2013). Sometimes patients were found to be infected with resistant microorganism after a successful intervention in that case impact of intervention consider to be nullified. In public healthcare sector, patients are vectors for pathogens thus they are the great threat for community and health care workers (Bhatia and Narain, 2010).

Antimicrobial resistance affect patient outcomes by various manners such as, resistant gene alter bugs virulent properties, delay in administration of appropriate medications. Lautenbach et al. demonstrated that treatment for infections produced by ESBL pathogens was not started even after 3 days of culture reports.(Cosgrove and Carmeli, 2003)
AMR is a major factor for failure of treatments to complicated infections. It was found that resistance to fluoroquinolones and cephalosporins by E.Coli was increased by spread of CTX-M beta-lactamase producing fluoroquinolones-resistant strains and the emergence of community onset methicillin resistant *Staphylococcus aureus* (MRSA). It also affect human illness, length of stay in hospital, cost of treatment and also produce poly-pharmacy related adverse effects (Rice, 2009).

Organisms, type of antimicrobial therapy and mechanism of resistance are major factors used to assess the correlation between antimicrobial resistance and microbiological

outcomes. Resistant strains are talented to survive, adapt and even can flourish antimicrobial abode which make them more competent than other strains (Bjorkman and Andersson, 2000). Hospital, third party payer, patients and society are other determinants for monitor the impact of antimicrobial resistance (Cosgrove and Carmeli, 2003).

Chandy et.al studied cost difference between resistant and susceptible groups. And the study revealed that average cost for resistant groups was 41,993 INR/700USD as compared to that of susceptible group 21,492INR/358USD (Chandy et al., 2014). Whereas, both gram positive and gram negative bacteria are equally contributor in increased direct medical cost (Paladino et al., 2002).

AMR increases the mortality and length of stay in hospital in affected patients. Now it is increasing its grab to those patients also who never had an infection with resistant organism. So, use of broader spectrum antibiotics for common bacterial infections as empirical therapy is supported (Cosgrove and Carmeli, 2003).

Without having specific solutions for AMR, there is big compromise in performance of newer surgical procedures, transplantations, prolonged chemotherapy and treatment of critical ill and immuno-compromised patients (2015a).
Ramanan Laxminarayan, vice president for research and policy at the Public Health Foundation of India, stated that in the absence of better sanitation and hygiene, we are forced to rely heavily on antibiotics to reduce infections. The result is that we are losing these drugs and newborns are already facing the consequences of untreatable sepsis," or blood infections (Harris, 2014).

SOLUTIONS

The problem of resistance is complex and involves biological, behavioral, technical, economic, regulatory, and educational dimensions which require a comprehensive response (2010-2015). After significant control on communicable diseases in India, there is still burden in poor and marginalized sections of society. It is due to lack of current disease control programs that are not taking care of diversity of disease profiles in different parts of country. This should involve generation of epidemiological data for different regions within bigger cities.

Regulations on use and misuse of antibiotics in the country, national surveillance system for AMR, mechanism of evaluating prescription audits, regulatory provisions for monitoring use of antibiotics in Humans, veterinary & industrial sectors, identification of specific interventions for rational use of antibiotics and diagnostic methods pertaining to AMR monitoring are critical to evaluate AMR rate (Leung et al., 2011).

Since OTC drugs having major role in creating AMR, DCGI putting the efforts to monitor the sale of antibiotics in retail pharmacies and prescriptions were made compulsory for certain drugs to sell (2011a; Ghafur et al., 2013). Separate schedule H1 has been introduced under the act of Drug & Cosmetics to regulate the sale of antibiotics as OTC drugs. A system of colour coding is implemented to restrict the access of broad spectrum antibiotics only to tertiary care hospitals.

Along with growth of laboratory and monitoring & evaluation of antiretroviral treatment, focus on detection of resistance is required. Now national authorities are emphasizing mainly on evaluation and introduction of newer vaccines, which

manifests decline in disease burden, antibiotic utilization, and AMR. To decrease the rate of AMR, India strengthens the surveillance system to international standards (2011b). There should be individual antimicrobial policy and hospital infection control guidelines in individual hospitals for infectious diseases like enteric fever, diarrhea, respiratory infection etc (Leung et al., 2011).

Revised National Tuberculosis Programme (RNTCP) was progressed for complete national coverage in 2006 for increasing awareness about prevention and treatment of tuberculosis (2011b).

All global policies are working on containment of resistance, rational and restricted use of antibiotics. New hope arises with some new significant measures. European commission is focusing on development of new antibiotics to combat AMR. For encouraging the process of antibiotic development, many incentives are provided to the industry which is the topic of global discussion (Anthony D et al., 2010).
A meeting was conducted by Health Minster States of the WHO South-East Asia Region at Jaipur, India on Sep.6, 2011 to discuss actions which should be taken for prevention and containment of AMR to improve public health (2011d). For highlighting haphazard use of antibiotics, WHO announced the World Health Day on April 7 2011 and warned about rising threat (2011e).

In 2014, WHO kept the theme of Micro-bacterial resistance and forced a global action to secure antibiotics for future. According to AMR surveillance report of WHO 2014, there was not complete information about MDR pathogens and also found that the limitations in surveillance quality, data collection, data sharing and absence of common standard on these issues (2015a).

At the 68th World Health Assembly in May 2015, the WHO endorsed a global action plan to certify persistent success of treatment & preventive measures of infections and access to effective & safe medicines for all who need them. WHO will work with countries to support the development and implementation of their national plans, and will report progress to the Health Assembly in 2017 (2015b).

Thus there should be combined action of academia, health care setting, industry, and Govt. to combat the problem of AMR. Emphasize on better diagnostic facilities, education and a standard treatment guideline is required. It also requires ownership and active participation of all stakeholders (2010-2015) and systematic approach to establish national alliance for prevention and control of AMR, surveillance system that captures the emergence of resistance, as well as the trends of its spread, monitoring the utilization of antimicrobial agents in different settings, promotion of rational use of antimicrobial agents at all levels of health care and veterinary settings, strengthening infection control measures to reduce the disease burden and supporting basic and operational research. Education for promoting compliance to prescriptions and discouraging self-prescriptions are equally important steps in mankind's' fight against AMR. International agencies are also putting efforts for resolving the issue of AMR but co-ordination is required to harmonize the global efforts. AMR issue was under the shadow for too long time so time to act is now (Bhatia and Narain, 2010; 2010-2015).

CONCLUSION

Everyone should perceive that the emergence of AMR is an inevitable consequence of overuse of these life saving agents.

Availability of tools is few and pipeline of new products is also dry. NDM-1 superbugs demand for vigilance at community, local and national levels for assessing AMR. The possible solution lies in implementation of focused antibiotic use and restriction on the sale of over the counter & prescription of antibiotics for cold, flu, and sore throats. Missions like Swachh Bharat Abhiyaan must proactively involve state governments, local communities, and municipalities to promote hygiene and sanitation standards. Use of antibiotics needs to be restricted to use in poultry farms and animal husbandry.

To make available the toilet and sanitation facilities to a larger population is a big challenge which can be possible by sustained increase in public health care spending (central govt. healthcare budget was shockingly cut by 30 percent for 2014-15 recently). It is not possible for India to discover great number of new antibiotics in short time but effective and rational use of antibiotics can be assured to save millions.

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