Int J Pharm Bio Sci 2013 Apr; 4(2): (P) 338 - 343

Review Article **Pharmacology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

ANTIMICROBIAL RESISTANCE: UNDERSTANDING SOLUTIONS AND FUTURE DEVELOPMENTS.

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ABSTRACT

Antimicrobial resistance is a major public health concern nowadays. It is considered to be one of the three most important health problems by the World Health Organisation (WHO).To cope with this, large worldwide surveillance systems are set up to identify early trends of resistance. At the same time, active protection of antibiotics by adopting Antimicrobial Stewardship Programs is advocated among prescribers. For the future, discovery and development of novel and more efficient antibiotics is emphasized for containment of resistance. The burden of antibiotic resistance will continue to increase, unless aggressive control measures are implemented globally, as resistant microorganisms do not recognize geographic boundaries. Need of the hour is international coordinated actions where individual strategies are combined into one integrated venture to fight this impending crisis.

KEYWORDS: Antimicrobial resistance, Antimicrobial Stewardship, Multidrug resistance.

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INTRODUCTION

Antibiotics have been the cornerstone of infectious disease therapy for more than half a century.The dramatic reduction in the mortality due to their widespread use in 1960s led to the belief that door to infection diseases will be closed permanently. In this euphoria,little thought was given to the adverse consequences of their indiscriminate use. However, their indiscriminate use is no longer viewed as benign. Treatment with these drugs is acknowledged to be a two edged sword resulting in steady increase in the number of microorganisms that are resistant to antimicrobial agents due to selection process[1]. Antimicrobial resistance is now a global issue[2].The World Health Organization (WHO) has identified antimicrobial resistance as one of the three most important problems for human health[3]. Further it is shrinking the range of antimicrobial drugs that are available to combat fatal infections[2].

MAGNITUDE OF PROBLEM

Methicillin-resistant Staphylococcus aureus(MRSA), vancomycin-resistant Enterococcus(VRE), Mycobacterium tuberculosis, Streptococcus pneumonia are considered a substantial threat to public health in the United States[4]. European Antimicrobial Resistance Surveillance System (EARSS), the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMEA) in 2007 reported many resistant strains of Methicillin-resistant Staphylococcus aureus(MRSA), Vancomycin-resistant Enterococcus faecium(VRE), Penicillin-resistant Streptococcus pneumonia, 3rd generation cephalosporin-resistant Escherichia coli , 3rd generation cephalosporin-resistant Klebsiella pneumonia, Carbapenem-resistant Klebsiella pneumonia and Carbapenem-resistant Pseudomonas aeruginosa from Europe, Norway, Iceland and U.S.A[5]. Emergence of new mechanisms of resistance like extended spectrum β-lactamases, carbapenemases and spread of new resistance genes, the New Delhi metallo-beta-lactamase 1(NDM-1) haveall added to the problem. These are resistant to most available antibiotics and can disseminate worldwide very rapidly, because of medical tourism[6].In India NDM-1 was first reported in 2009. NDM-1 is an enzyme produced by the gene bla_{NDM-1} which is named after New Delhi because the Swedish patient in whom it was detected had undergone surgery in a New Delhi hospital. This gene confers resistance to most antibiotics including carbapenems [7].

Some authors have summarized the phenomena of antibiotic resistance with word 'ESKAPE' which includes Enterococcus faecium, Staphylococcus aureus, Klebsiellapneumoniae, Acinetobacterbaumannii, Pseudomonas aeruginosa and Enterobacter spp. indicating their escape from the effect of available antibiotics [8]. Truly,the return to preantibiotic era is becoming a reality as no new antibiotic class active against multi-resistant Gram-negative bacteria is anticipated in near future[6].

FACTORS LEADING TO DEVELOPMENT OF ANTIBIOTIC RESISTANCE

The major cause is the massive overuse of antibiotics worldwide. Overprescribing and overuse are seen in all settings, be it in humans, animals or agriculture[6]. Many surveillance systems have documented a positive correlation between antibiotic consumption and resistance development. Countries with high consumption have higher rates of antibiotic resistance than countries with lower rates of antibiotic consumption[9].Overprescribing in the outpatient settings like for viral respiratory tract infections is influenced by patients demand and expectations[10].In USA, a survey concluded that nearly half(48%) of the respondents expected an antibiotic when they visit a doctor[11]. Direct-to-consumer advertising of antibiotics by pharmaceutical manufacturers and direct sales via the internet are also increasing and difficult to control[12]. These advertisements are skillfully constructed to promote the ease or effectiveness of the product thereby persuading the patients to demand newer and costly antibiotics. For physicians, time pressure and desire to maximize the patient satisfaction is universal.

Economic factors that include lack of microbiological facilities or patients' unwillingness to pay for diagnostic tests often contribute to overprescribing especially in developing countries[7]. Further longer life expectancy with increased use of antibiotics in the elderly and survival of patients with severe illness like in critically ill, immune-suppressed and patients with congenital diseases e.g cystic fibrosis who are at increased risk of infections are additional risk factors for the development of antibiotic resistance[13].Antibiotic resistance is affecting the developing nations much harder, as antibiotics are much easier to obtain without prescription in these countries. They can be purchased in pharmacies, general stores and even market stalls[14]. Lack of use of proven and effective preventive infection control measures such as hand washing and proper isolation of patients with resistant infections, have all added to the dissemination of resistant organisms [13].Apart from human usage the extensive use of antibiotics in agriculture has increased the reservoir of resistance genes. They are also used as growth promoters, prophylactics and therapeutic agents in veterinary medicine[15,16]. The world organization for animal health in 2003 reported increased frequency of treatment failures and severity of infections due to resistant organisms resulting from non-human usage of antimicrobials[7].

CURRENT MEASURES TO COMBAT ANTIMICROBIAL RESISTANCE

In reaction to this impending threat of antibiotic resistance many national and international workforces have been developed. Large worldwide surveillance studies are carried out during the last decade to monitor resistance[17]. Any ideal surveillance system should collect data from all countries in a defined geographical region, include clinically important bacteria which represents the current public health problem and should also be able to identify early trends of resistance. The European Antimicrobial Resistance Surveillance System (EARSS) is the best known example of a successful initiative taken in this direction. Recently, it is renamed as EARS-Net. In USA, The Surveillance Network(TSN) is a corporate surveillance system which covers greater than 500 reporting partner healthcare institutions in the country. It is one of the largest sources of antimicrobial susceptibility data worldwide[18]. Similarly, there is a global project on Anti-Tuberculosis Drug Resistance Surveillance and SENTRY Antimicrobial Drug Resistance Surveillance[19].US Centers for Disease control and Prevention(CDC) and (World Health Organisation) WHO are actively addressing the primary issues associated with overuse and misuse of antibiotics[20]. On April 17, 2011 WHO chose antimicrobial resistance as its theme for World Health Day. WHO strongly recommends that Governments around the world should implement (AntimicrobialStewardshipPrograms) ASPs for containment of antibiotic resistance[21]. Antibiotic stewardship is a model of patient care that aims to optimize clinical outcomes while minimizing the unintended consequences of antibiotic use like toxicity, emergence of resistance and selection of pathogenic organisms[22]. In other words, good antimicrobial stewardship involves selection of the most appropriate antimicrobial drug at its optimal dosage and duration resulting in the best clinical outcome while minimizing side effects and impact on subsequent resistance[23].In United Kingdom(UK), the department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) has recently produced guidance for antimicrobial stewardship, in hospitals. The initiative is 'Start Smart and then Focus' which provides an evidence based approach to antimicrobial stewardship. It includes the importance of obtaining cultures for microbiological investigation and not starting antibiotics in the absence of clinical evidence of infection[24].Nowadays, 'care bundle' approach is being advocated to improve prescribing of antibiotics. It can serve as pillar for any ASP. It involves the use of smallest number of agents as initial therapy, re-evaluation of initial treatment, when culture results are available and the use of optimal dosing and route of administration for shortest time to obtain a successful outcome[22,25].A major component of AS is education and feedback to prescribers regarding antimicrobial use. Optimal antibiotic prescribing requires that the prescribers have

adequate knowledge of medicine, infectious diseases, microbiology andpharmacokinetic/pharmacodynamics properties of different formulations of antibiotic[17, 4].Success can be achieved in combating resistance only if ASPs are implemented along with infection control programs and environmental interventions[17]. This includes recommendations to increase hygienic measures like use of universal precautions, improved hand hygiene and specific contact precautions when necessary. To promote hand hygiene worldwide WHO has initiated a programme "Clean care is safer care" [6].

FUTURE APPROACHES TO IMPROVE THE CURRENT SITUATION

There are some potential alternatives to antibiotic treatment such as passive immunization or phage therapy. Decline in Haemophilus influenza infections after introduction of the type B conjugate vaccine and decrease in number of fatal secondary bacterial infections after use of viral influanzae vaccine are examples in support of this [15]. Similarly, phage lytic enzymes have been used to destroy cell wall of pathogenic bacteria such as Streptococcus pyogenes, Streptococcus pneumoniae and Bacillus anthracis[26].Also, key to reduce the rate of emergence of resistance is by developing new antibiotics which induce resistance at a lower rate than the existing antibiotics like the development of antibiotics which target complex bacterial systems such as membrane. As synthesis of membrane requires so many enzymes bacteria cannot easily produce mutants with altered membrane[27]. Secondly, increase the rate of production of new classes of antibiotics. The search for new classes requires exploration of ecological niches like soil, marine environment, plants and animals[28]. Even genomic approach, in which essential enzyme pathways in bacteria are targeted by inhibitors, may provide the new class[27].Many large pharmaceutical companies do not invest in antimicrobials as antibiotic courses are short and resistance is likely [29]. The pharmaceutical industry needs to be encouraged to discover new antibiotics. This would require intervention of governments worldwide with increased grants, subsidies, tax incentives, high prices, fast track designation similar to orphan drugs, prolongation of patent duration and changing requirements for approval of new drugs like approval on efficacy towards specific organisms rather than specific infections[5,30]. This would also encourage the development of antimicrobials with narrow spectrum(reduce resistance) than broad spectrum. Truly, 2020s can see premium-priced, novel, small spectrum antibiotics against one pathogen only or to the extreme against one serotype of pathogen only[31]. Along with pharmaceuticals, Universities, Charities and regulatory bodies also need to change in order to encourage antibiotic discovery.

WHAT IS FURTHER NEEDED

International coordinated actions are required to curb this escalating antibiotic resistance problem. Combining individual strategies into integrated venture is the need of the hour. This complex problem requires concerted efforts of microbiologists, ecologists, health care specialists, educationalists, policy makers, legislative bodies, agricultural and pharmaceutical industry workers, and the public to deal with. In this direction a coordinated programme based on six main lines of action was defined during a two-day meeting held in France in June 2011[6]. It included-

- Measures to limit cross transmission of resistant bacteria worldwide by adoption of infection control practices.
- A worldwide antibiotic steward-ship strategy.
- The improved use of diagnostic techniques.
- An acceleration in the discovery and development of new antibiotics
- An acceleration of vaccine development programmes,
- A strong educational programme for both health-care practitioners, consumers, and children.

So far, the majority of all these efforts to reduce antibiotic resistance has occurred in the field of healthcare whereas there is a massive use of antibiotics for both therapeutic

purposes and growth promotion in agriculture and food industries and in veterinary medicine. There is lack of proper regulations in these areas like current regulations do address discharge of chemicals used to produce antibiotics by pharmaceutical factories but no guidelines are there for antibiotics themselves that end up in factory effluent. Unused antibiotics are flushed down the toilet in majority of the households[32].These areas are a matter of concern and should be addressed immediately.

CONCLUSION

We must continue to address the challenge of antibiotic resistance by development of novel strategies in the search for new antimicrobial designing, more effective preventive measures and better understanding of the ecology of antibiotics and their resistance. This clearly needs government incentives and political appreciation globally.

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