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Irrational use of antibiotics as major cause of drug resistance in developing and developed countries

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The rational use of drugs requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and community. On other hand irrational use of refers to use of medicine without prescription of registered medical practitioner. First antibiotic was discovered by Alexander Fleming the potent effect of this antibiotic earlier against many microorganism is due the fact at that time there was a lack of drug resistance among many of the microorganism. This antibiotics work best for sometimes but after sometimes the irrational use of this antibiotics came in to being. Irrational use of antibiotics leads to the emergence of drug resistance and medicinal therapy failure. WHO announces that antibiotics is the most prescribed drugs all over the world and approximately 50% of antibiotics is prescribed or use without need of the patients. Therefore it is needed to use it appropriately. First step in minimizing the irrational use of antibiotics is to properly observe the quantity of dose, proper diagnoses of the disease so that particular antibiotics may be prescribed, measure the overall use of medicines. The second principle is to choose a drug that has the fewest adverse events for that patient. Third, clinicians should choose a drug that has efficacy in treating or preventing the disease but leaves other bacteria in the body intact. This review is an effort to highlight the risk associated with irrational use of antibiotics and step to minimize the irrational use of antibiotics.

Keywords: rational use, irrational use, antibiotics, WHO, drug resistance.

INTRODUCTION

The remedy of infectious diseases gains an immense interest when the first accidental antibiotic was discovered by Alexander Fleming in 1928 this antibiotic save millions of lives during the word war 2. the potent effect of this antibiotic earlier against many microorganism is due the fact at that time there was a lack of drug resistance among many of the microorganism and the drug was to expensive so that many people cannot buy it. Thus the use of these antibiotics was in a limited range because many of the people have no access to costly antibiotics. (Kendall, 1994).but then a time came when the

antibiotics cost fall down abruptly and many of the people got access to it. Many pharmaceuticals industry gets benefited with the declining cost of antibiotics and they introduce many new antibiotics in the global market. Approximately in every week new antibiotic was introduced into the market. Many of the doctors cannot get up-to-date with the prescription of the antibiotics. But this irrational use of the antibiotics give much more time for the microorganisms to develop strategy against these newly discovered drugs and become resistant. WHO defines the rational use of antibiotics: The rational use of drugs requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and community (WHO, 1985). WHO announces that antibiotics is the most prescribed drugs all over the world and approximately 50% of antibiotics is prescribed or use without need of the patients. (Swindell et al. 1983). Upper respiratory infections are self-limiting infections and mainly caused by viruses and as antibiotics is ineffective against viral infection still 50-100% of antibiotics are prescribed in upper respiratory infections. A survey was carried out by World health organization between 1992 to 1996 on the irrational use of antibiotics the report of the survey suggest that about in 30% of the upper respiratory infections wrong antibiotics were prescribed in about 13 developing countries .(Swindell et al. 1983). In Pakistan antibiotics are the most prescribed drug accounting for about 76% (Memon, 2000). Most antibiotics is prescribed in rural areas by untrained physicians and accounting for about 78 %.(Memon, 2000). In many emergent countries the quantity of sales of these drugs far exceeds the rate of the disease they are supposed to treat (WHO, 1995).

As all over the world antibiotics are mostly recommended by the doctors, hence the rational use of antibiotics is perquisite. Doctors should keep careful while prescribing antbiotics and there are several aspects which should be observed by the doctors while prescribing antibiotics: (a) first of all it should be keep in mind that either the antibiotic is necessary or not? (b) Second observation is on the suitable antibiotics doctors should see which antibiotic is suitable for that particular infection (c) analysis of proper dose (d) analysis of effectiveness of that particular antibiotic. (WHO, 2002). In the U.S, and many other developed countries the funding for antibiotics research has been lowered and many of the micro-organisms become resistant to conventional antibiotics. That is the reason that mortality from nosocomial and other infection has been increased. (Srinivas, 2004). Another reason for antibiotic resistant is that upto 50% of antibiotics are prescribed by the non-trained physician. (WHO, 1985).about 25% of the population has no access to essential and prescribed medicine to cope with a disease. And the main reason behind this is mainly the budgets released by the developing and underdeveloped countries are very much lower in the field of medicine. Thus all these leads to irrational use of antibiotics.(WHO, 2002)..

Rational use of drugs, especially rational prescribing should meet certain criteria as follows (Hardon and Grand, 1993; Sekhar et al. 1981; Calva and Bojalil, 1996):

1-Appropriate indication: The decision to prescribing drug(s) is entirely based on medical rationale and that drug therapy is an effective and safe treatment.

2-Appropriate drug: The selection of drugs is based on efficacy, safety, suitability and cost considerations.

3-Appropriate patient: No contra-indications exist and the likelihood of adverse reactions is minimal. And the drug is acceptable to the patient.

4-Appropriate information: Patients should be provided with relevant, accurate, important and clear information regarding his or her condition and the medication(s) that are prescribed.

Common types of irrational use of medicine are (WHO, 2006):

1-The use of too many medicines per patient (polypharmacy);

2- Inappropriate use of antibiotics, often in inadequate dosage, for non-bacterial infections;

3- Over-use of injections when oral formulations would be more appropriate;

4- Failure to prescribe in accordance with clinical guidelines;

Inappropriate self-medication, often of prescription-only medicines;

History of antibiotics

Gr. anti, "against"; bios, "life"-- An antibiotic is a chemical substance produced by one organism that is destructive to another. The word antibiotic came from the word antibiosis a term coined in 1889 by Louis Pasteur's pupil Paul Vuillemin which means a process by which life could be

used to destroy life.in many countries old was used as conventional source for antibiotics production having no knowledge of mechanism through which molds suppresses or kills bacteria . Germ theory was used in 1800s while seeking for antibiotics. Then many scientists contributed for antibiotics production at large scale. Joseph Lister contributed that urine contaminated with fungus can stop the growth of bacteria. Pyocyanase the first antibiotics used in hospital was discovered by German doctors, Rudolf Emmerich and Oscar Low. Alexander fleming discovered penicillin form Penicillium notatum. German chemist Gerhard Domagk (1895–1964) discovered Prontosil, the first sulfa drug. Howard Florey (1898–1968) and Ernst Chain (1906–1979) synthesize Penicillin G Procaine. Antibiotic streptomyocin use against Tuberculosis was discovered by American microbiologist Selman Waksman (1888–1973).Lloyd Conover discovers Tetracycline and Nystatin. Amoxicillin was patented by SmithKline Beecham patented.

Antibiotic Uses and Challenges

Antibiotics Uses and challenges are very much important subject in the field of medicine. It helps to provide information on source of antibiotics, effectiveness, mechanism of action, microbial resistance toward antibiotic, discovery of new antibiotics, adverse effects of antibiotic's on humans, route of administration (Walsh, 2003). Antibiotics and immune system functions (Pankey and Sabath , 2004).

Basic Principles of Prescribing Antibiotics

Prescribing effective antibiotic's for patients can help to improve their health. Antibiotics may cause many adverse reactions and is considered to the main cause of liver injury and anaphlatic shocks (Neugut et al.2001). Nausea, vomiting, diarrhea are less common complications associated with antibiotics. Taking antibiotics without prescription can cause drug resistance. The basic principal for the use of antibiotics is first properly diagnosing the cause of infection the treat it with appropriate antibiotics. Antibiotics should be prescribed against those infections for which the mechanism of actions is very much clear. Antibiotics should be avoided in infections in which the mechanism of action and effective role of antibiotic is not much clear because it would lead to antibiotics resistance. The second principle is to choose a drug that has the fewest adverse events for that patient. This maximizes the benefit and minimizes the risk. Third, clinicians should choose a drug that has efficacy in treating or preventing the disease but leaves other bacteria in the body intact. (Colgan and Powers, 2001).

Mechanisms of Bacteriostatic or Bactericidal Action

Antibiotics have diverse mechanism through which they stop the growth of bacteria or kills bacteria the earlier mechanism was called as bacteriostatic while the later was known as bactericidal. Bacteria have peptidoglycan linkages in their cell wall this peptidoglycan creates cross linking in the bacterial cell wall. Bacterial growth can be slows down by inhibiting the enzymes which helps in peptidoglycan such antibiotics which stops the growth of microorganism's through this mechanism are known as cell wall synthesis inhibitors. Proteins are the essential components for bacterial growth some antibiotics stops protein synthesis and are called as protein synthesis inhibitors. PSI blocks either the 30S or 50S subunits of bacterial ribosomes. Antibiotics which stop the topoisomerase enzyme thus inhibiting DNA synthesis are called as DNA synthesis inhibitors (Walsh, 2003).

Steps to minimize the Inappropriate Medicine Use

First step in minimizing the irrational use of antibiotics is to properly observe the quantity of dose, proper diagnoses of the disease so that particular antibiotics may be prescribed, measure the overall use of medicines. Without measuring the use of antibiotics we cannot know how to invest money to combat with irrational use of antibiotics. Worldwide approximately 50% of medicines are used with lack of knowledge, without prescription which at last leads to reduction of effectiveness of medicine and patients believe on the health system is also declined (WHO, 2006). (WHO, 2004).

Irrational Use of Antibiotics in Developed Countries

In USA and Europe about 12% in older people and 40% in nursing homes antibiotics are used without prescriptions (Gallagher et al. 2007). Only 4-21% of the patients in United Kingdom is benefited from medicines because of the wrong prescription and care management system (Garfield et al. 2009). Large variation in the usage of antibiotics across 25 countries was observed and recorded by the European Surveillance of Antibiotic Consumption (Ferech et al. 2005;

Ferech et al. 2006).the data recorded from Greece for analyzing the daily dosage of antibiotics in nearly 1000 patients shows that daily doses varied up to 30 (DDDs). Cephalosporin was the most used antibiotic in Greece. And in Netherlands the number of defined daily doses was approximately 10 (Van Roosmalen et al. 2007). In pediatric practice larger variation in antibiotic use has similarly been described (Rossignoli et al. 2007). Surgical prophylaxis was found in 40% of patients in hospital practice (Rossignoli et al. 2009). Similar reports were present on the outpatient's antibiotics usage in southern European countries and in the USA (Goossens et al. 2007) (Grigoryan et al. 2006).

Irrational Use of Antibiotics in Developing Countries

Database of quantitative information on medicine use is created by WHO based on the study of different articles published from 1990 to 2006 and this is purely a complete survey on the irrational antibiotics usage in developing countries (Neugut et al. 2001). In this survey study was conducted in about 97 countries. The result was very disappointing as the about 40% of medication is prescribed wrongly since last 20 years. The prescription analysis shows that prescription of medicines was much and more accurate in public sector as compared with private sector. The data further suggest that the consultation time for the patients was much and more less as a result the patients did not get proper guidelines about the use of medicine. The data suggest that 80% of the medicines is prescribed by the non-trained physician and 20% off labelled medicine are dispensed of by the medical sector. With such short consultation time and dispensing of the off labeled medicine come in in the irrational use of medicines. (Radyowijati and Haak, 2003).

Patient Adherence

A study of 569 patients was published from 1948 to 1998 in which approximate adherence was studied in patients with AIDS, arthritis, GIT disorders and cancer the result shows that adherence in these patients was 24.8% and was very much lower in patients with other disorders . (DiMatteo, 2004).when therapy was done for 6 months in patients with chronic infections there adherence drops steeply (Osterberg and Blaschke, 2005). A survey was also carried out on the usage and prescriptions of antibiotics in 11 countries shows that 22.3% of the patients having different types of acute infections did not complete their course of antibiotics. (Pechère et al. 2007). (Colgan et al. 2004).

Determinants of Inappropriate Use

Identifying the cause of irrational use of antibiotics is very much beneficial to reduce inappropriate use of antibiotic. There are many determinants for the irrational use of antibiotics. Lack of authentic research on antibiotics, lack of knowledge, lack of implementation of law regarding the use of antibiotics. For combating with irrational use of antibiotics we should first study the determinants of irrational use of antibiotics and the outcomes of these consequences (Rowe et al. 2005). Thus, most research has addressed lack of knowledge (Radyowijati and Haak, 2003), (Neugut et al. 2001) ,(Homedes and Ugald, 2001) (Sketris et al. 2009). It is essential to understand all the factors influencing the use of medicines by providers and consumers in order to develop effective strategies and interventions to improve use (Radyowijati and Haak, 2003).

National Policies to Improve Appropriate Use of Medicine

Implementations of strong national policies would be helpful regarding the use of medicine. And many policies has been recommended by world health organization (WHO, 2002). WHO has a proper database on the medicine prescriptions (WHO, 2006). The survey conducted by WHO regarding the implementation of policies shows that half of the countries follows the (WHO, 2010) many countries have untrained doctors and having less knowledge of clinical guideline. (WHO, 2001).only 40% of countries have basic training of medical staff (WHO, 2010).all the policies recommended are poorly implemented and many of the countries have less investment on health which leads to inappropriate use of medicine. (Grol and Grimshaw, 2003). Many of the task forces have been assigned and many international laws has been put forward for appropriate use of medicine (WHO, 2007). Australia is one few country who strictly follow international recommendation on medicine. Sweden has also started a program to reduce the risk of antibiotic resistance Swedish Strategic Program against Antibiotic Resistance (STRAMA) (Molstad, 2008). Europe has also proper planning to reduce the irrational use of medicine. (Ferech, 2006).their government also has a greater contribution to improve public health (Huttner et

al. 2009). Campaign against irrational antibiotic usage is very much successful in France (Ratanawijitrasin et al. 2001). In South Korea, a national policy introduced in 2000 prohibited dispensing by general practitioners and was associated with a reduction in antibiotic use from 80.3 to 72.8% for viral illness episodes and from 91.6 to 89.7% for bacterial illness episodes (Park et al. 2005).

Future Challenges

Researchers have provided a proper policy to overcome irrational use of medicine in future. We should follow all recommendation to overcome antibiotic resistance in future. We should have successful management system on the use of medicine.

Lack of Institutionalization of Promoting Appropriate Use of Medicines

The main reason behind the irrational use of antibiotics is the lack of proper knowledge on institutional level regarding the appropriate use of medicines. In many countries there are no proper structure designed to combat with inappropriate use of medicines. Pakistan is one that country having no regulation authority on the rational use of antibiotics. There is no infrastructure in developing countries; however developed countries have adapted strong national policies to overcome the irrational use of antibiotics.

Lack of Investment

Implementation of strong national policies on the elimination of irrational antibiotics usage would need a huge investment on research and institutional basis which seems impossible in under developed country. Manufacturing and effective medicine having low side effects is not possible in case having low economic budgets on medicine. Another problem is if we are successful in making such medicine then poor people will have no access to such expensive medicines. Therefore there is a need of an infrastructure to make such medicine and provide it to the subjects at low economic cost.

Fragmentation of Health Systems

A third reason for the lack of action is that increased fragmentation of health systems, particularly in developing countries and largely driven by agencies that donate money or medicines (donors), is actually making it more difficult to restructure health systems and take a more coordinated approach. Often, MOH staff spend more time addressing donor needs than actually running their own health system. For example, some countries have as many as 50 different drug-supply systems to satisfy all the donors (Babaley, 2009).This is the case despite calls for health system strengthening and for better donor coordination and efforts to streamline aid by pooling donor funds and having a single reporting system within recipient countries.

Imbalance in Drug Information

A fourth reason for the lack of action is the major imbalance in information concerning the appropriate use of medicines. While governments are not investing in promoting more prudent use of medicines, the pharmaceutical industry is promoting increased use of their products. Globally, most prescribers receive most of their prescribing information from the pharmaceutical industry and in many countries this is the only information they receive. Unfortunately, the information from the industry may be biased, emphasizing the positive aspects and omitting the negative aspects of use (WHO, 2004). The huge imbalance in expenditure between industry and government, with regard to providing prescribers with adequate information, needs to be urgently addressed.

Research & Informational Needs

A fifth reason for the lack of action is that while much is now known about how to improve medicine use, particularly in public primary care at a local level, relatively little is known about how to promote appropriate use of medicines at a national level and in the private sector or in communities. Particular areas that require further research include: Prescribing and dispensing in the private and informal sectors, where financial incentives encourage overuse of medicines and the use of more expensive medicines; Establishing and monitoring quality-assurance mechanisms, such as supervisory systems and drug (medicine) and therapeutic committees; Monitoring implementation of national policy and regulation; Improving adherence in patients with chronic diseases, which is especially important with the global increase in the number of patients needing chronic medication. While robust indicators exist for monitoring medicine use in primary care, they have not been developed for the previously highlighted points for which further research is needed. Only with robust indicators will it be possible to set up the management information systems that are needed to monitor

use and stimulate action to improve use.

Lack of Pharmaceutical Public Health Experts

Promoting appropriate use of medicines requires a multidisciplinary public health approach involving pharmacists, prescribers, healthcare managers and consumers. Bringing together all the participants will require multidisciplinary expertise that includes a thorough understanding of both public health and pharmaceutical issues. However, public health has fragmented into various subspecialties, for example, communicable and non-communicable diseases, disease prevention, health promotion, HIV/AIDS, TB and malaria. Moreover, there are few public health subspecialists in pharmaceuticals. Few schools of public health teach modules on the pharmaceutical sector – covering topics such as pharmaco epidemiology, the essential medicines concept, and drug selection, development of clinical guidelines, managing continuing medical education, drug supply and regulation, among others.

Where to Start?

The causes of inappropriate use of medicines are multiple – inadequately trained prescribers, inadequate drug supply, poor regulation, absence of monitoring and supervision, pre- and in-service curricula that do not include prescribing skills, and uncontrolled drug promotion. Small-scale interventions or even national-scale training alone will not control these factors. System change is needed. Since health systems are so varied and complex, no single package of interventions will fit all countries – instead, different packages will be needed for different countries. In countries with multiple problems and limited resources, where does one start? The WHO recommends undertaking a national situational analysis of the pharmaceutical sector health system to identify and prioritize problems and to develop a package of solutions that are context specific (Holloway, 2007; WHO, 2010).

CONCLUSION

Promoting appropriate use of medicines requires a multidisciplinary public health approach involving pharmacists, prescribers, healthcare managers and consumers. Implementation of strong national policies on the elimination of irrational antibiotics usage would need a huge investment on research and institutional basis which seems impossible in under developed country. Instead of all these hurdles we have to strongly emphasize on the rational use of medicine because if this irrational use continues a time will came when our “Drug of last resort” will not be effective against a disease and microorganism will get resistance to all the available antimicrobial drug.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization ,S. Z. K, methodology S.F.MR.; software, S.S; validation, Z.A., Z.H; formal analysis, M.N.U and HS; writing—original draft preparation, SAS and S.F; writing—review and editing, R.U and S.H.A.; supervision, S.A.S., S.S.

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