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Review Article

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A Review on Antibacterial Resistance

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Abstract Antimicrobial resistance is a natural biological phenomenon of response of microbes to the selective pressure of an antimicrobial drug. Resistance may be inherent, which explains the phenomenon of opportunistic infection or acquired. The emergence of multidrug resistant strains of Gram-negative bacteria (Pseudomonas, Klebsiella, Enterobacter, Acinetobacter, Salmonella species) and Gram-positve organisms (Staphylococcus, Enterococcus, Streptococcus species) is the more worrisome in the present therapeutic scenario. Multidrug - resistant tuberculosis is another serious public health problem. It is highly recommended that practicing physicians should become aware of the magnitude of existing problem of antibacterial resistance and help in fighting this deadly threat by rational prescribing.

Keywords Rationaldrug use, Multidrug resistance, Newer antibiotics

Introduction

Drug Resistance can be described as a state of insensitivity or of decreased sensitivity to drugs that ordinarily cause growth inhibition or cell death. This phenomenon has been recognized since the latter part of the 19th century in the micro-organisms and more recently in mammalian cells in vitro and in cancer cells in vivo. The discovery of antimicrobial agents by Paul Ehrlich was one of the most remarkable discoveries, that changed the face of medical practice. However, the increased global flow of antimicrobials brought with it the threat of antimicrobial resistance. Concern about the resistance increased in the late 1990′s since then, many governmental and agency reports have been published regarding the agricultural use of antibacterials, advising less use of antibacterials, appropriate choice of antibacterials and regimens, prevention of cross-infection and development of new antibacterials. As antimicrobials are frequently misused and overused in many developing countries, thus resistance to antimicrobials, has led to an increase in morbidity, mortality and cost of health care. To maintain the useful life of antimicrobial drugs in developing countries there is need to improve access to diagnostic laboratories, improved surveillance of the emergence of resistance, better regulation of the use of antibiotics, and better education of the public, doctors, and veterinarians in the appropriate use of the drugs.

Mechanisms of Drug Resistance

Resistance may be inherent, which explains the phenomenon of opportunistic infection or acquired. Anaerobic bacteria, Enterococcus species are inherently resistant to aminoglycosides, Pseudomonas species to tetracycline and penicillins except ureidopenicillins, Gram-negative bacteria to glycopeptides and Gram-positive bacteria to aztreonams. Acquired resistance can be developed by mutation or gene transfer. Gene transfer can occur through transformation, transduction and conjugation. Mutation may occur in the gene encoding target protein, transport protein, protein for drug activation or promoter or regulatory gene affecting expression of the target transport protein or an inactivating enzyme. Production of beta-lactamases by the bacteria is the most important mechanism associated with beta-lactam antibiotic resistance. There are over 200 types of beta-lactamases. Moreover, for many antibiotics including beta-lactam group, the primary means of transport across the outer memberane of enteric bacteria are a remarkable group of plasma proteins called as porins. Three major porins have been identified in E. coli, namely- (a) large porin channel outer membrane protein F(Omp F), (b) small channel porinOmp C and (c) Pho E (present in mutants and of no significance in antibiotic movement). Factors like the charge on the molecule and hydrophobicity of the compound also play an important role in the transport of drug molecules. The negatively charged molecules like methicillin hang up in the negatively charged porin channel of Gram negative bacteria; whereas beta-lactam antibiotics having long side chain (piperacillin, ceftazidime) can also cross the membrane poorly, except imipenem with compact structure. The energy dependent efflux mechanism is a prime defense for bacteria against tetracycline, quinolones and macrolides. P-glycoprotein transports a wide range of drugs like rifampin, sparfloxacin etc.

Antibacterial Resistance in India

Antibacterial resistance is a natural biological phenomenon of response of bacteria to the selective pressure of an antibiotic. In recent years, emergence of macrolide-resistant S. pyogenes was reported in some areas of the world. Currently, the majority (80-90%) of Staphylococcus aureus strains in the community are beta-lactamase producers and thus are resistant to penicillin and ampicillin. However, these strains are susceptible to beta-lactamase resistant beta-lactam antibiotics such as nafcillin, methicillin or oxacillin. Recently more than 90% Staphylococcus aureus isolates from South Maharashtra have been found resistant to ampicillin, tobramycin, penicillin, erythromycin, kanamycin and gentamicin; whereas, only 39.1% strains are resistant to methicillin. However, methicillin resistant Staphylococcus aureus (MRSA) strains are found sensitive to vancomycin. In a retrospective study of bacterial isolates from cases of neonatal septicemia over a period of 5 years (July 1998 - June 2003) from Chandigarh, India, netilmicin and ciprofloxacin were the most effective drugs for S. aureus and Pseudomonas aeruginosa respectively. Recently ciprofloxacin resistant S. aureus has also been reported from India, which necessitates the use of an alternate therapy for S aureus infection. Acute respiratory tract infections cause 3.5 million deaths in children each year. The most important pathogens associated with pneumonia are Haemophilusinfluenzae and Streptococcus pneumoniae. Many penicillin resistant pneumococci are also resistant to chloramphenicol, and cephalosporins such as cefuroxime and ceftriaxone, thus limiting treatment options. Multidrug - resistant tuberculosis (MDRTb) is another serious public health problem. The median prevalence of MDRTb in new cases 1% and 9.3% in previously treated cases. Even in presence of in-vitro sensitivity to an antimicrobial agent failure of therapy or relapse of infection (due to change in the host′s immune system) with an organism can occur resulting in a state of clinical resistance [4]. Resistance to most of the commonly used antimicrobial agents indicates a need to replace these drugs with other agents and maintenance of surveillance to detect changing patterns of resistance, as well as, an urgent need for proper guidelines, dissemination of information to practitioners and supervision of antimicrobial usage in low income countries like India.

Possible Solutions

Rational use of Antimicrobials

Ideal antimicrobial use involves use of correct drug by the best route in right dose at optimum intervals for the appropriate period and after an accurate diagnosis. The high prevalence of resistant bacteria seems to be related to

irrational antimicrobial usage: 1) easy availability without prescription at drug stores, 2) injudicious use in hospitals, and 3) uncontrolled use in agriculture, animal husbandry, and fisheries. Many traditional practitioners are using allopathic drugs irrationally. Moreover, it has been reported that dispensing medical practitioners (who earn by sale of medicines) prescribe more drugs than non-dispensing practitioners, thus further adding to irrational drug use. In many developing countries the use of antimicrobial drugs for treating people and animals is unregulated; antibiotics can be purchased in pharmacies, general stores, and even market stalls. In a study from five districts of Tamilnadu state, India,: 285 general practitioners and specialists believed that antibiotics are overprescribed, especially broad-spectrum antibiotic and purulent discharge (65%), antibiotic-resistance concerns (48%), fever (40%), and patient satisfaction (29%) were proposed as the strong reasons to prescribe an antibiotic. Factors like patient and time pressures, diagnostic and treatment uncertainties, poor patient compliance due to high cost and fear of antibiotic resistance are the key forces behind irrational prescription of antimicrobial combinations. Moreover, antimicrobials have been increasingly used to treat diseases in animals and plants. Antibiotics like glycopeptides and streptogramins are increasingly used as growth enhancers in subtherapeutic dose in animals further adding to the threat of antibacterial resistance. The widespread use of antimicrobials in farming is also leading to emergence of resistant bacteria (Salmonella, Campylobacter) in animals, which in turn gets transmitted to humans from food of animal origin or through direct contact with farm animals. It is urgently required to ban the sale of antibiotics without prescription, to use antibiotics more judiciously in hospitals by intensive teaching of the principles of the use of antibiotics, and to establish better control measures for nosocomial infections. Regulation of antimicrobials for other than human use is also required. These issues require the collective action of governments, the pharmaceutical industry, health care providers and consumers.

Regulation of OTC (over the counter) drugs

In developing countries like India, easy availability of a wide range of drugs coupled with inadequate health services result in increased proportions of drugs used as self medication compared to prescribed drugs thus resulting into impending health problems like irrational use of antimicrobials resulting into antimicrobial resistance, increased load of mortality and morbidity and economic loss. The need for promoting appropriate use of drugs in health care system is not only because of the financial reasons with which policy makers and manager are usually most concerned, but also for health and medical care of patients and the community. There is need for authorities to make the existing laws regarding OTC drugs strong to ensure their rational sale and use of antimicrobials.

Preserve existing agents

In the prevailing situation of antimicrobial resistance, it is advisable to preserve the existing antimicrobials for future use and the new molecules should only be used if the old ones are ineffective. The emergence of reduced susceptibility to ciprofloxacin among Salmonella enterica serotype Typhi and serotype Paratyphi A leading to clinical failure of treatment poses a great therapeutic challenge. However, Salmonella species, sensitive to chloramphenicol are increasingly emerging. It has been reported that a formulary switch to amikacin from gentamicin resulted into decline in resistance to the latter. Whereas, a shift from ceftazidime and imipenem from older cephalosporins resulted in the emergence of imipenem resistant Acinetobacter and Pseudomonas aeruginosa. Recently data from Sir Ganga Ram Hospital, New Delhi also reported a correlation between Escherichia coli resistance to third-generation cephalosporins and increased cephalosporin use, as well as resistance to co-amoxyclav and its use.

Future approaches under development

Antimicrobial resistance has snowballed to a serious public health concern with economic, social and political implications. The problem of changing resistance patterns will remain an ongoing threat for both developed and developing countries. Resistance to some agents can be overcome by modifying the dosage regimens (e.g., using high-dose therapy) or inhibiting the resistance mechanism (e.g., beta-lactamase inhibitors), whereas other mechanisms of resistance can only be overcome by using an agent from a different class. Understanding of the

mechanisms of action of various agents can help clinicians to identify the agents that will increase the likelihood of achieving optimal outcomes. However, large number of commercial preparations, unethical drug promotions by pharmaceutical houses and irrational prescribing habits of clinicians are the important reasons for irrational prescription of drugs in clinical practice. Physician-industry interactions appears to affect prescribing and professional behavior which may result into negative outcomes like inability to identify wrong claims about medication, positive attitude toward pharmaceutical representatives, increasing prescription rate, prescribing fewer generic but more expensive, newer medications at no demonstrated advantage, antibiotic prescribing for viral conditions, prescribing of irrational antimicrobial combinations, antimicrobial prescribing for inadequate period etc. Thus, it is highly recommended that practicing physicians should become aware of the magnitude of existing problem of antimicrobial resistance and help in fighting this deadly threat by rational prescribing.

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