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Review Article

Antibiotic resistance : Epidemiology, molecular mechanism and preventive strategies

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Abstract: Antibiotic resistance is an alarming health crisis. With the large-scale use of antibiotics a large number of microorganisms (both Gram-negative and Gram-positive organisms) have acquired resistance or multi resistance to different antimicrobial drugs. This antibiotic resistance is common in hospitals and community. This review article focuses on the molecular mechanism and preventive strategies of antibiotic resistance.

Keywords: Antibacterial, Resistance, Epidemiology, Prevention

Antibiotic resistance:

Antimicrobial resistance is a global pandemic. The worldwide use of antimicrobial compounds to treat infection lead to the evolution of microbes resistant to these compounds. Beginning in the 1930s, antibiotics have had a near-miraculous impact on human and animal mortality and morbidity caused by bacterial infections. They have also been exploited for other uses, such as improved yields of meat from animals. The price of these dramatic benefits is that the prevalence of resistant microbes has dramatically increased to the point where, in some cases, antibiotics are no longer effective. The general trend to more widespread antibiotic resistance is relentless and, if it continues unabated, deaths from what were previously treatable infections will occur with increasing frequency. As the World Health Organization (WHO) (2004) stated unambiguously, 'Today we are witnessing the emergence of drug resistance along with a decline in the discovery of new antibacterials. As a result, we are facing the possibility of a future without effective antibiotics. This would fundamentally change the way modern medicine is practiced.'

Evolution of Antibiotics:

In the late 1920's, the Scottish microbiologist Alexander Fleming returned from a trip to find that one of his petri dishes containing the bacterium, Staphylococcus aureus, was contaminated with the mold, Penicillium notatum. Like a good scientist, he made an observation: there were no bacterial staphylococcal colonies growing directly around the mold. There was a zone that was free of bacterial growth directly surrounding the mold. Upon closer inspection, he noticed that the mold was secreting a liquid (now called penicillin) that he later learned was the cause of death to the bacteria growing in close proximity to the mold. What Fleming had discovered (actually, re-discovered) was an antibiotic: A chemical that inhibits the growth of or kills microorganisms (e.g. bacteria). Antibiotics have evolved in fungi and bacteria as defenses against other microbes. In response to competition, many fungal and bacterial species have evolved chemical weapons to inhibit other species. Antibiotics are the chemical weapons of fungi and bacteria. Scientist quickly realized that antibiotics could help humanity in wedging war against bacteria, within a few decades; both naturally occurring and synthetic antibiotics were produced in mass quantities and given to people who were sick with infectious diseases and they worked. Antibiotics were the miracle cure to all kinds of infectious diseases that had been plaguing humans for hundreds of years. Antibiotics worked so well, in fact, that in 1969, the U.S. Surgeon General declared: "It is time to close the book on infectious disease." The war against bacteria was over, and we had won! Had we really won?

Evolution of Antibiotic resistance:

Whenever antibiotics wage war on microorganisms, a few of the enemy are able to survive the drug. Being living organisms, these surviving microbes want to protect themselves. Microbes are always mutating; some random mutation eventually will develop resistance against the drug. The danger was already recognized by Alexander Fleming, back in 1945, he had warned that misuse of penicillin could lead to the selection and propagation of mutant forms of bacteria resistant to the drug. The first penicillin-resistant bacteria appeared few years later. Their mutant gene encoded for a penicillin-destroying enzyme, penicillinase. Penicillin treatment kills non-resistant, but leaves behind resistant bacteria. Today, especially in hospitals, there are strains of staphylococcal bacteria that are resistant to nearly all known antibiotics. Although most of the multiple-drug resistant staphylococcal strains are only found in hospitals, recently, four children in North Dakota and Minnesota were killed by staphylococcal infections that they had acquired outside of a hospital. Staphylococcus is not the only problem bacterium. More than two-dozen types of bacteria are now resistant to one or more types of antibiotics that had previously been effective against them. People are dying from infections that were easily treated just a few years ago. It has been estimated that infections caused by resistant bacteria kill as many as 77,000 people every year in the United States alone. Resistance to antibiotics costs money as well as lives.

Uneven fight:

Quoting from the British Medical Journal "To 395-million-year-old strains of bacteria, a half-century of antibiotics is like

bagatelle! (1), Yes, for a bacterium that has existed for million of years without any opposition, a 50-year-old antibiotic may sound a little bit difficult to digest. This could be summarized as war between microbial evolution vs. microevolution. Microbes not only have rapid generation time but also posses' efficient means for vertical as well horizontal genetic transfer which in turn swiftly disseminates resistance among different bacteria. Bacteria have continued to react to human attempts of controlling them by evading the mechanism of action of antibiotics. Growth of new antibiotics has slowed down – resistant microorganisms are increasing at rapid tempo; microbes have clearly outpaced man's ingenuity for antibiotic development.

Epidemiology:

More than 50 years of the large-scale use of antibiotics have resulted in a number of microorganisms which have acquired resistance or multi resistance to different antimicrobial drugs. Both Gram-negative and Gram-positive organisms have demonstrated excellent capability to undermine the effectiveness of one or more antimicrobial agents (2). Although problems related to antibiotic resistance differ from unit to unit, hospital to hospital and country to country however notably resistant microorganisms do not recognize boundaries between countries; hence, the epidemiology of resistance may be multinational, with some transferable determinants are prevalent worldwide. Medical literature on the transfer of resistance from city to city and country to country is widely available. Emergence of multidrug resistance among certain strains of gram-negative bacteria such as Shigella, Klebsiella, Enterobacter, Acinetobacter, Salmonella species and Gram-positive organisms such as Staphylococcus, Enterococcus and Streptococcus species is extremely troublesome. In recent years there has been a progressive increase in frequency of methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus species and extended spectrum ß-lactamase producing Klebsiella pneumoniae and Escherichia coli (2-3).

Antibiotic resistance in Hospitals (ABR):

Resistant nosocomial infections are common in hospital settings. Antibiotic usage has been shown to have a critical role in the selection of antibiotic-resistant bacteria as the dominant colonizing flora as well as the nosocomial pathogens of hospitalized patients. Resistance acquisition has two mechanisms: firstly antimicrobial-resistant flora may be endemic within the institution and may be transferred to the patient within the hospital setting. Second, a small population of antimicrobial-resistant bacteria that are a part of patient's endogenous flora at the time of hospitalization may emerge under the selective pressure of antibiotics and become the dominant flora. ICU related infections are common and often associated with resistant microorganisms.

In ICUs in the USA, the proportion of MRSA isolates among S. aureus isolates increased remarkably from 1992 to 2003. A study in the ICUs in USA showed that resistant Staphylococcus aureus isolates accounted for 52% of the ICU infections, followed by Enterococcus sapprophyties. (28%), Pseudomonas aeruginosa (23%) and Klebsiella pneumoniae (10%).

The overall susceptibility to ciprofloxacin among aerobic Gram-negative bacilli declined from 89% in 1990-1993 to 86% in 1994 and 76% in 2000. The most notable reductions in ciprofloxacin susceptibility were seen with P aeruginosa. The decline in activity of ciprofloxacin correlates directly with increase in use of quinolones. Evolving problem of antimicrobial resistance in Pseudomonas aeruginosa, Acinetobacter baumannii and K. pneumoniae is so grave that it has led to the emergence of clinical isolates susceptible to only one class of antimicrobial agent; these isolates are termed as pandrug-resistant isolates. Pandrug-resistant strains are associated with significant treatment failures and consequent mortality (2-3).

Antibiotic resistance in community:

Antibiotic resistance in the community is an emerging global problem. The normal individual flora, which is important for the maintenance of individual health, can play a critically important role in infectious diseases. Carriage of resistant bacteria such as MRSA, Entended- Spectrom- Beta-Lactamase (ESBC) Enterobacteriaceae and pneumococci may result in infections. In fact, carriage of such pathogens and infections related to them is not rare in the community. In a study performed in Saudi Arabia, fecal carriage of ESBL+ organisms was detected in 26.1% of 272 in-patients, 15.4% of 162 out-patients, and 13.1% of 426 healthy individuals. The ESBL rate of community-acquired urinary tract infections related E. coli strains are 7.9% in Turkey and 34.4% in India (4). Streptococcus pneumoniae which used to be exquisitely sensitive to penicilline has acquired resistance against it; cross-resistance with other frequently used antibiotics is common among these community acquired penicillin resistant organisms. Streptococcus pneumoniae have important community reservoirs. Yildirim et al reported 8.3% intermediately resistant S. pneumoniae carriage in 484 children (4).

MRSA has emerged as a cause of skin infections and, less commonly, invasive infections among otherwise healthy adults and children in the community. A surveillance study was conducted simultaneously at three centers across India. A total of 13,610 test samples from various sites were obtained. Antimicrobial susceptibility testing of the isolated strains of staphylococcus aureus and staphylococcus epidermidis to various antimicrobial discs were carried out according to standardized disk diffusion method

recommended by National Committee for Clinical Laboratory Standards. Of the total 739 cultures of S. aureus, 235 (32%) were found to be multiply resistant with the individual figures for resistance being 27% (Mumbai), 42.5% (Delhi) and 47% (Bangalore). MRSA carriage was reported to be 2.6% in 500 healthy adults and 1.9% in 500 healthcare workers (5).

ABR: Molecular mechanism:

Microbes are endowed with molecular mechanisms for resistance development, determinants of antibiotic resistance are much older than our antibiotic therapy; nevertheless, unrestrained antibiotic prescribing has fuelled resistance to a very high and level. Bacteria acquire resistance by either genetic mutation or Horizontal gene transfer from other organisms (6).

Genetic Mutation: Under pressure from antibiotic therapy bacteria undergo spontaneous single or multiple changes in bacterial DNA, some of these changes code for resistance; resistant survivors may undergo separate mutations over hundreds of generations that favors maintenance of resistance.

Horizontal gene transfer (HGT): This could be by addition of plasmid or transposons.

a) Plasmids: A circular, double-stranded unit of DNA that replicates within a cell independently of the chromosomal DNA. Plasmids carry resistant genes which could be easily transferred to other bacteria.

b) Transposons are short, specialized sequences of DNA that can insert into plasmids or bacterial chromosomes. Transposon's house genes for resistance determinants, some of these also contain genes for their chromosomal integration and expression.

ABR: Physiological Mechanism:

Bacteria engineer varied physiological mechanisms to protect themselves from antibiotic onslaught. Majority of these mechanisms effectively decrease antibiotic efficacy.

Some of these mechanisms are as below (6):

1.Diminishing intracellular drug concentration:

I.Decreasing outer membrane permeability (B-lactams)

II.Decreasing cytoplasmic membrane transport (Quinolones, aminoglycosides)

III.Activating antibiotic efflux pumps (Multiple drugs, Quinolones, Macrolides, Tetracyclines)

By above mechanisms bacteria decrease the intracellular drug to such a low level that the concentration of the drug becomes therapeutically ineffective.

2.Drug inactivation (Reversible or irreversible) some resistant bacteria inactivate the antibiotic by destroying or modifying the drug itself so that it is no longer toxic.

I.Modifying enzymes (ß-lactams destroying ß-lactamases)

II.Inactivating enzymes (Chloramphenicol)

3. Altering the Antibiotic target:

Several resistant species have an altered form of the target site of the drug (the place on the cell where the drug binds), so the antibiotics fail to "find" its target.

I.Target modification (Quinolones, ß-lactams, Macrolides, linezolid)

II.Target bypass (Glycopeptides, trimethoprim)

ABR development: clinico epidemiological settings:

Antibiotic therapy unintentionally selects resistance, McGovan and Tenovar (7) describe following six basic mechanisms by which resistance is introduced, selected, maintained and spread in health care settings.

1) Acquisition of resistance by a few previously susceptible strains through genetic mutation in reservoirs of high organism concentration such as an abscess.

2) Acquisition of resistance by a susceptible strain through transfer of genetic material, for example in the gut or on the skin.

3) Emergence of inducible resistance that is already present in a few strains in the bacterial population. Usually from direct selection by antibiotic prescribing.

4) Selection of a small resistance subpopulation of organism, again by antibiotic prescribing.

5) Introduction of a few resistant organisms into a population where resistance previously was not present, usually by transfer from another healthcare system but also from community.

6) Dissemination of inherently resistant organism locally within the specific setting due to poor infection control procedure. In the want of effective antibiotic policies once selected resistance rapidly grows; there are four interacting variables: Patient, organism, drug and environment which need proper understanding for developing effective resistance control strategies (8).

Patient:

Large inoculum of organisms as in abscess cavity potentiates the increase in preexistent resistant mutants. Presence of foreign body which may lower antibiotic concentration at the site of infection is likely to select resistance; immune compromised patient with slower eradication of infection may also favor resistance development.

Organism:

Certain organisms are more capable of producing resistance, staphylococcus, enterococcus, pseudomonas, and many other gram negative bacilli have high potential for

AB with high resistance potential	AB with high low resistance potential
Ampicillin	Amoxicillin
Carbenicillin	Pipercillin
Tetracycline	Doxycycline, Minocycline
Ciprofloxacin	Ofloxacin, Glevofloxacin
Gentamicin	Amikacin
Ceftazidime	Ceftriaxone, cefepime
Imipenem	Meropenem

acquiring antibiotic resistance, conversely antibiotic resistance has not been a problem in among the atypical pulmonary pathogens (e.g., legionella, mycoplasma pneumoniae, Chlamydia pneumoniae). Rickettsia and spirochetal organisms also have not shown significant resistance development.

On removal of selective pressure, reversion to sensitivity may occur, although it may take longer than the initial process of resistance development, however, in certain organisms' genetic compensation for the cost of resistance may well occur, i.e. the resistant survivors can undergo separate mutations over next several generations that would favor maintenance of the resistant gene. MRSA and VRE have shown this kind of genetic compensations. Generally compensation is more likely outcome than reversion however; adaptive resistance is more likely to revert unless it is mutational. Situation is complex where resistance evolves to multiple drugs collectively. The worst scenario is the presence of an integron, a type of transposon, which can accommodate resistant determinants for many drugs in concert. In integron coded resistance it is likely that use of any antibiotic which is represented on that integron will select evolution of resistance to all the antibiotic agents to whom the resistance determinants are coded on that particular integron. Transposons can also code for active efflux of many different classes of antibiotics (the 'sump-pump' resistance mechanism). The fluoroquinolones possess capability to activate this resistance mechanism.

Drug:
Antibacterial Resistance Development (ABRD) potential:

Not all antibacterial drugs exert analogous resistance selection pressure. Some antibacterial drugs possess exceptional resistance development potential, while others lack this character (9). Ceftriaxone is an excellent example of a low ABR development potential antibiotic; despite high volumes uses over a long period, it has generally remained free of significant resistance problem. Conversely resistance against ciprofloxacin and imipenem among pseudomonas was reported even during clinical trials and early after introduction in clinical use (9). Knowledge of this particular characteristic of antibacterial agents should be one of the most vital determinants of antibiotic choice. Antibiotics with high resistance development potential should have restricted clinical uses, while antibiotics with low resistance development potential could have free clinical uses.

Collateral damage:

Human body is studded with lots of bacteria, according to an estimate around 5000 to 10000 different species of bacteria live in the human body. Called as commensals these bacteria constitute a significant defense mechanism of our body. When a broad spectrum antibiotic is deployed in a patient, it not only kills offending bacteria but vastly damages commensal flora. Many of these commensal under go mutational changes and acquire antibacterial resistance. Increasing ESBL producing E. coli is a classic example of this kind of collateral damage. Practice of using oral third generation cephalosporins for community acquired respiratory infections and fevers is playing a huge havoc world over. Cephalosporins have a hand, not only for selecting extended spectrum-lactamase (ESBL)-producing Enterobacteriaceae and stably depressed mutants of inducible Enterobacteriaceae, but also enterococci, methicillin-resistant S. aureus (MRSA), Clostridium difficile and yeasts. Many studies have shown a reduction in the incidence, if not complete eradication of problem organisms by decreasing cephalosporin uses (8).

Inappropriate antibiotic therapy:

Inappropriate antibiotic therapy can be defined as one or more of the following (9):
· Unnecessary antibiotic prescription for viral diseases
· The wrong choice, dose or duration of therapy
· Ineffective initial empiric treatment of serious bacterial infection.
· Poor tissue penetration of chosen antibacterial.

Unnecessary antibiotic prescription for viral diseases:

Hospitals are the places where lots of antibiotics are supposed to be used, nonetheless; community originated ailments like community originated respiratory infections, fevers, and diarrheas consume a much higher proportion of antibiotics. It is difficult to asses' indications and rational for out patient antibiotic prescriptions, but in 1992 a study using physician surveys revealed that, in the United States, five diagnoses accounted for 76% of all antibiotic prescriptions in community practice: otitis media, upper respiratory infections, bronchitis, pharyngitis, and sinusitis (10). Many of these conditions are considered to be of viral etiology and do not benefit from antibiotic therapy, and therefore a substantial proportion of outpatient antibiotic prescriptions can be considered inappropriate or unnecessary. In USA according to a study based extrapolation it is estimated that 6.5 million prescriptions were written for children diagnosed with a URI or the common cold (11). Despite knowing too well that antibiotics are unnecessary in upper respiratory infections, physicians tend to prescribe them more out of a habit. Except a false sense of security there aren't good reasons for this habitual compulsion. Unfortunately

prevalence of this bad habit is equal among junior practioners, among senior practioners, in private practioners and as well in academicians. These scientifically base less prescriptions have a stupendous effect in terms of antibacterial resistance. It is very well known that after a short course of antibiotic like ampicillin, resistant bacteria may persist in faces for as long as three months, these resistant bugs are potentially infectious to other members of the family and community long after the cessation of therapy (9). Physician prescribing practices in turn influence their patients' attitudes about the need for antibiotics. In an emergency interview study almost one-fifth of patients had used antibiotics without consulting physician from left over drugs of previous illnesses citing that there physician regularly prescribes antibiotic for common cold. This creates a tremendously dangerous situation in countries where there are no controls over procuring medicines from chemist. Patients may start antibiotics by themselves in the case of fever or common cold or to overcome malaise, fatigue or pain. Antibiotic leftovers, especially by the point of disappearance of the symptoms, are also common. In a multicenter study performed in ten countries, overall prevalence of possession of leftovers was reported to be 51.9% in 3649 subjects who obtained antibiotics by filing for a new prescription or received them from a medical professional (12). The prevalence ranged between 13.5% (The Netherlands) and 90% (China). Further use of leftover antibiotics in subsequent infection was also very high (70% in 2252 subjects, ranging between 44.4% in The Netherlands and 90.2% in Russia) (12). Aggressive marketing practices by drug companies greatly fuel these wrong practices.

The wrong choice, dose or duration of therapy:

In the developing world decision about antibiotic therapy are taken empirically, even in hospitalized patients microbiology support is very meager. Many a time's treating physician is in a dilemma about pathogenic microbe, this dilemma invariably induces insecurity; to overcome this predicament physician tends to prescribe a broad spectrum antibiotic. Broad spectrum antibiotic inflicts detrimental collateral damage which in turn breeds antibacterial resistance (8).Traditional teaching maintains that infections initially should be treated with low doses of mild antibiotics and only a failed treatment should be the contemplation for up scaling the drug doses or consideration of stronger antibiotic. Unfortunately these concepts disregard the vital fact that a failed treatment means more chances for mutation and increased odds for antibacterial resistance development. It is the recovering partially damaged bacteria which tend to mutate; antibacterial therapy should brutally kill maximum number of bacteria in a shortest period of time, it must never leave any chances for bacteria for mutation (13).
Duration of therapy is generally decided empirically. For economic considerations physicians and or patient may try to shorten the course of antibiotic therapy. This may increase the chances for bacterial mutation and a consequent antibacterial resistance development. Patient's desire and capability for taking medicines should receive appropriate considerations; a few underlying assumptions about human nature, as highlighted by Sanson-Fisher et al (11), may ensure that a prescription translates to more than a slip of paper.
·No patients take pills more than 3 times daily.
·No patients take a medication for more than 5 days in a row.
·Frequent dosing increases the chances for missed doses.
·No patients take medication that makes them feel worse.

Delayed Appropriate Therapy:

Even at the best of the centers, pending culture sensitivity reports initial antibiotic therapy is selected empirically. A proper selection of antibiotic regimen is vitally important for patient's survival and recovery. A wrong initial choice of antibiotics invariably culminates into poor outcome.
Starting inappropriate therapy affects not only mortality but also duration of hospitalization; as inappropriate therapy is prolonged, the likelihood of resistant bacteria arising will increase, which sometimes may result in the occurrence of outbreaks. Mortality rates are higher among patients with ventilator-associated pneumonia who receive inappropriate empirical treatment (13).

Poor tissue penetration:

Microbes are likely to develop resistance if exposed to low antibiotic concentrations; this is particularly true for antibiotic which has a high antibacterial resistance development potential. Antibiotic failure and resistance development is more common in body sites where achieving adequate antibiotic concentration is usually difficult. Abscess cavities, pyelonephritic kidneys, and CSF are some of the places where sub optimal antibiotic concentrations could be anticipated. Low antibiotic resistance potential and good tissue penetration should receive due considerations in making antibiotic choice in such conditions (9).

Environment:

Hospital or community is the environmental places where bacteria cultivate resistance.
Hospitals facilitate bacterial resistance development by providing number of opportune circumstances; some of them are listed as below (8):
·Greater severity of illness of hospitalized patients.
·More severely immunocompromised patients.
·Newer devices and procedures in use.
·Increased introduction of resistant organisms from the community.
·Ineffective infection control and isolation practices and compliance.
·Increased empirical poly microbial antimicrobial therapy.

·High antimicrobial usage for geographical area per unit time.
However as earlier been stated community offers much greater chance for bacterial resistance development by providing unnecessary antibiotic uses for viral respiratory infections.

Livestock feed:

Antibiotics and steroids are commonly added to animal feed, steroids are used to increase the size of animal, while antibiotics are added to chicken and cattle feed to prevent infections. While evidences are lacking that such addition of antibiotics to livestock feed prevents infection; there are enough data that these practices disgustingly increase antibacterial resistance (14). According to Burke A. Cunha who heads the division of infectious diseases at Winthrop-University Hospital in Mineola, N.Y. animal agriculture is playing a disproportionately large role in induction of antibacterial resistance; the volume of antibiotics used in animal feeds equals or exceeds that used to treat infections in humans; worst is, many of the antibiotics that have been used to supplement animal feeds are the very ones most likely to induce resistance e.g. ciprofloxacin, tetracycline. Resistant bacteria developed in livestock can taint the meat or foods exposed to the animals and thereby gain into human gut (13).

Strategies to prevent antibacterial resistance:

Antibiotic resistance is a direct consequence of antibiotic use. There is continuous escalation of both, equally in the hospital and in the community despite many calls for moderation in antibiotic use. Eradication of resistance is impossible and development of resistance to any particular antibiotic is inevitable yet with proper strategies antibacterial resistance could be decreased and pace of resistance evolution may be stalled. Strategies need to address to: Contain and/or decrease the already existent resistance, prevent further emergence and spread of resistance (13).

Control of resistance in the community:
Ending in-appropriate antibiotic uses:
Watchful waiting:

Most of the community acquired fevers, diarrheas, and respiratory infections are viral in origin and aren't much benefited with antibiotic therapy, conversely needless antibiotic therapy provoke unnecessary anti bacterial resistance development. Good symptomatic therapy with a watchful waiting is sufficient intervention in majority of such patients (15). Timely laboratory help, telephonic counseling, and repeat clinical evaluation are integral to such watchful waiting.

Use antibiotic with least antibacterial resistance development potential:

Antibiotic usage is an important contributor to antimicrobial resistance. The ideal is to have all patients treated with the most effective, least toxic and least costly antibiotic for the optimal time. In a particular indication, when the treatment options have similar clinical efficacy; using the antibiotic with the least resistance-inducing capacity is of critical importance (9). Unfortunately this particular aspect of antibiotic therapy hasn't been properly addressed and emphasized till far. Medical professionals should have adequate information regarding antibacterial resistance development potential of antibiotics which they use in their clinical practice.

Avoid broad spectrum antibiotic:

Routine use of broad-spectrum antibiotics for minor infections significantly adds to infection and colonization of the general population with increasingly hardy and difficult-to-treat microbes. According to the Centers for Disease Control and Prevention (CDC) sources, indiscriminate use of broad-spectrum antibiotics more than doubles an individual's chance of acquiring future infection with resistant organisms.

Use antibiotics by Guidelines/ protocols based on local organisms and drug sensitivity pattern:

Antibiotic administration guidelines/protocols developed locally or by national societies potentially avoid unnecessary antibiotic administration and increase therapeutic effectiveness. Unfortunately, even well-developed guidelines/protocols may not translate into widely accepted treatment algorithms. Some deviation from guidelines/protocols is expected because medical decision-making should be guided by an individual patient's characteristics and the judgment and experience of the caregivers. Locally developed guidelines therefore often have the best chance of being accepted by local health care providers and hence of being better implemented (16).

Controlling resistance in the hospitals:

As has earlier been discussed hospitals particularly ICUs provide enough opportunities for development of antibacterial resistance. Various antibiotic policies: antibiotic cycling, antibiotic rotation, antibiotic combination, restricting broad spectrum antibiotics, restricting hospital formulary etc. have been tried to decrease antibiotic resistance development. None of these barring restricting use of antibiotic with high resistance potential development has given consistently desired results (17). The selection of antibiotic in a hospital formulary must take in to account different factors but resistance potential should be the most important feature in such selection. Antibiotic with known resistance problem should be removed from hospital

formularies. A properly restricted hospital formulary is the best antibiotic resistance measure (17). By substituting a vacuum cleaner antibiotic (e.g., an antibiotic with an equilant spectrum but no or little resistance potential) a hospital environment can be restored to a relatively resistance free atmosphere. Replacing ceftazidime, imipenem and gentamycin by drugs like cefepime, meropenem and amikacin respectively could result into significant decrease in resistance among resistant pseudomonas, enterobacter, VRE, and MRSA (9).

Controlling transmission of antibiotic resistance:

Transmission of antibiotic resistance need following strategies (18):

a) Techniques for the early recognition of resistant microorganisms via methods such as more rapid diagnostic techniques, surveillance systems and screening of patients and staff:

b) Reduction of infectivity through the use of antimicrobials and disinfectants.

c) Reduction of the chance of spread by isolation of the colonized or infected cases and through improvements in hand hygiene (Alcohol based hand rubs, Universal gloving).

d) Improvements in the spacing of beds in hospitals.

e) Screening & Isolation

Decreasing antibiotic supplementation in animal feeds:

It is estimated that more than half of all antibiotics produced worldwide are used in animals: there is need to continue developing the evidence base to assess the risks to human health associated with the presence in food and feed of antibacterial-resistant micro-organisms, co-ordination with veterinary bodies and convincing them to stop this kind antibiotic uses is of paramount importance (16).

Newer antibiotic research:

The main expense to the drug industry related to resistance is the money spent on R&D on new antibiotics and, unfortunately, there is an absolute decline in the development of new antibiotics by pharmaceutical companies. Aventis, Eli Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Proctor & Gamble, Roche and Wyeth have greatly curtailed, wholly eliminated or spun off their antibacterial research.

"The pipeline for new antibacterial is drying up" says Infectious Diseases Society of America (IDSA) (19), since 1998, only 10 new antibiotics have been approved, and only two of those were truly novel - defined as having a new mechanism of action with no cross-resistance with other antibiotics and resistance to antibacterial continues to increase; maybe it's time to look at older antibiotics again.

Critical Issues:

Microorganisms will keep on developing and disseminating resistance as an opposite reaction to anti microbials in accordance with the laws of evolution and natural selection.

Multidrug-resistant bacterial infections comprise a great problem both in community-acquired and healthcare-associated infections. Antibiotic resistance is usually associated with significant morbidity, longer hospitalization, excess costs and mortality.

Inappropriate antibiotic usage is an important contributor to antimicrobial resistance; unfortunately awareness among medical professionals is lacking about this vital issue; there is an urgent need to heighten consciousness of doctors about this problem. In most of the situations antibiotic choice is made empirically. During residency antibiotherapy, choices regarding several clinical conditions are generally learnt from the seniors. The seniors, in turn, had learnt from their seniors. Hence, acceptance of new knowledge into traditional practice needs acceptance first by senior members of this teaching pyramid. Unfortunately such an acceptance occurs very rarely (20). Proper antibiotic policies vastly improve antibiotic consumption, and this improvement results in less antimicrobial resistance. Knowledge about antibiotic resistance development potential and choosing antibiotic with least resistance development problem can solve and prevent lots of problematic issues.

Antibiotic policies, and implementation of infection control measures (such as hand washing), screening and isolation are the strategies aimed at prevention of emergence and spread of antibiotic resistance. Drug industry is shying away from investing in antibiotics research and development. We are dependent on the pharmaceutical industry to provide us with new antimicrobial agents; there is an urgent need for dialogue between stakeholders on how investment in antibiotic development can best be achieved (21).

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