

ANTIBACTERIAL RESISTANCE: AN OVERVIEW AND IMPLICATIONS

MUGHIS UDDIN AHMED

Chemicals used to kill or stop growth of bacteria are known as antibiotics. Sulpha group was first to be used against microorganisms but with discovery of penicillin by Alexander Fleming in 1928 revolutionized antibiotic era. Florey and Chain synthesized penicillin and all three scientists received Nobel Prize for their work. This antibiotic was considered as miraculous medicine or magic bullet against bacteria. Since then antibiotics discovered at regular interval with different mechanisms and site of actions. In the last 66 years, major improvements in the early recognition and the treatment of infectious diseases have resulted in an extraordinary reduction in the morbidity and mortality associated with these illnesses. This has been due, in part, to our better understanding of the ?ne molecular biological mechanisms of these diseases and to our improved understanding of their pathophysiology and their epidemiology but, most notably, to the rapid development of safe and effective new antimicrobial treatments that have been able to attack the specific agent causing the infection, thus helping the infected host to eliminate the infection being treated. Seen initially as truly miraculous drugs, access to the ?rst available systemic antibiotics (sulfonamides and penicillin) was not immediately available for the general public. In fact, these drugs were scarce and very expensive and were initially reserved for use by the military during World War II. As more antibiotics were discovered, manufacturing processes were simplified, and newer formulations developed, access to antibiotics eased considerably and their use became widespread. Antibiotics had truly become the

“panacea” of medicine and were being used to treat even the most common and trivial types of infections, many of these non-bacterial in nature. Today about 150 types of antibiotics are in use.

Antibiotic resistance occurs when an antibiotic has lost its ability to effectively control or kill bacterial growth; in other words the bacteria are “resistant” and continue to multiply in the presence of therapeutic levels of an antibiotic. When antibiotics are used to kill the bacterial microorganisms, a few microorganisms are able to still survive, because microbes are always mutating, eventually leading to a mutation protecting itself against the antibiotic. The emergence and spread of antibiotic resistance constitutes a major risk for human health. Resistance to antimicrobials limits the success of these drugs in the therapy and prevention of infectious diseases. Yet we should be aware of the fact that many accomplishments of current medicine have only been possible because of the availability of a protective antibiotic umbrella. However, continuous positive selection of resistant bacterial clones, whether pathogenic, commensal or even environmental microbes, will modify the population structure of bacterial communities, leading to accelerated evolutionary trends with unpredictable consequences for human health. Resistance to antibiotics started with sulpha in 1940, penicillin in 1946, tetracycline 1953, streptomycin in 1959, chloramphenicol in 1959, methicillin in 1960, cephalosporin in late 1960s, ampicillin in 1973, erythromycin in 1988, vancomycin in 1988, monobactams, quinolones and now even newer antibiotics eg. linezolid, tigecycline. In 1917 four hundred (400) microbial strains were isolated from natural sources and sealed into vials. Recently 11 out of 400 strains

(Ex. Professor of Pathology KMDC & ASH, Karachi)
Consultant & Head of Microbiology & Serology
King Abdulaziz Hospital (NGHA)KSA

had resistance. Troublesome bacteria are "ESKAPE" or "ESCAPE" Enterococcus faecium, Staphylococcus aureus, Clostridium difficile, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae. Different resistant organisms have been assigned name like BORSA (Boderline Resistant Staphylococcus Aureus), MODSA (Moderately Drug Resistant Staphylococcus Aureus), MRSA (Methicillin Resistant Staphylococcus Aureus), ORSA (Oxacillin Resistant Staphylococcus Aureus), VISA (Vancomycin Intermediate Staphylococcus Aureus), VRSA (Vancomycin Resistant Staphylococcus Aureus), VRE (Vancomycin Resistant Enterococcus), ESBL (Extended Spectrum Beta Lactamase), GRSA (Glycopeptide Resistant Staphylococcus Aureus) and GRE (Glycopeptide Resistant Enterococcus). We are also confronted by Multi-Drug Resistant Organisms (MDRO) or MARO (Multi-Antibiotic Resistant Organisms) like MDR Pseudomonas aeruginosa, MDR Acinetobacter baumannii, MDR Escherichia coli, MDR tuberculosis and XDR (Extensive Drug Resistant) tuberculosis.

Reasons which lead to antibiotics resistance are:

1. Misuse, disuse and abuse of available antibiotics.
2. Low dose of antibiotic for age and weight
3. Used for less duration of time.
4. Self medication
5. Over-the-counter sale of antibiotics
6. Non medical people treating patients with antibiotics
7. Pharmacy staff treating patients with antibiotics at pharmacy counter
8. Improper use of antibiotics
9. Not care on the antibiotics sensitivity pattern.
10. Over marketing and advertisement of pharmaceutical companies
11. Misuse of antibiotics by physicians
12. Use of the sub-standard antibiotic just because of the cost.
13. Pharmaceutical companies provide incentives or bribes for their product
14. Use of antibiotics for colonization
15. Use of antibiotics for viral infections
16. It is noted that antibiotics were wrongly used or misused in 20% of ear problem, common cold 100%, non bacterial bronchitis 80%, non bacterial sore throat 50%, and non bacterial sinusitis 50%.
17. Inappropriate use of antimicrobial medicine in 20-50%.
18. Improper selection of antibiotic.
19. Use of many hospital devices in the inpatients.
20. No local antibiotic policies and guidelines.
21. Poor regulation and enforcement of antimicrobial products.
22. Weak pharmaceutical management.
23. No infection prevention and control policies and guidelines or poor implementation.
24. No antibiotic Stewardship program.
25. Injudicious use of antibiotics in human and non human settings.
26. Lack of surveillance of antibiotic resistance.
27. Non development of newer antibiotics.
28. No research to look after for other remedy for treating infections like gene therapy etc.
29. Increased opportunities for clonal dissemination of antibiotic-resistant bacteria both within and outside the hospital settings (or even global dissemination).
30. Emergence of some strain totally resistant to all available antimicrobials.
31. No internal and external antibiotics audit
32. Improper hygienic procedures.
33. No vaccination program for bacteria for which vaccine is available
34. Antibiotics are used for animals (24.5 million pounds).
35. Antibiotics are used for birds.
36. Antibiotics used for fishes.
37. Antibiotics used for agriculture items.
38. Transfer of resistant patients from one hospital to other hospital.

39. Nosocomial infections from hospital strain.
40. Hospital staff surveillance for carrying resistant bacteria.
41. No successful research to find substitute of antibiotics.
42. Very high research and development cost (US \$ 800 million to \$ 1.7 billion) and it requires 10 or more years to find one antibiotic. Due to this reason many companies like Avantis, Abbott, Bristol-Myers Squibb, Eli Lilly, Proctor & Gamble, Roche and Wyeth have withdrawn from the antibiotic research and development market.

ANTIMICROBIAL RESISTANCE

- Natural resistance: absence of target eg. no cell wall like mycoplasma species, L-forms of bacteria, spheroplasts, protoplasts , inadequate concentration of antibiotic at target site Penicillin (*Klebsiella pneumoniae*) and Carbapenem (*Stenotrophomonas maltophilia*)
- Acquired resistance:
 - Chromosomal
 - Normally one antibiotic
 - Cannot spread faster by more replication
 - Cannot spread between different species
 - Single step: streptomycin
 - Multiple step: penicillin
 - Structural changes
- Resistance in the same antibiotic depends on whether it is chromosomal or plasmid mediated
- Chromosomal-mediated most likely results in structural change (Target site alteration) eg. Streptomycin (alter ribosomal binding) and chloramphenicol (alter OMP)
- Plasmid-mediated is most likely by enzymatic deactivation eg. streptomycin (phosphotransferase) and chloramphenicol (acetyltransferase) Resistant gene transmission:
 - conjugation
 - transduction via bacteriophage

- transformation: direct transfer of free DNA from medium or environment
- transposon: chromosomal to plasmid or bacteriophage
- Target alteration is seen Penicillin Binding Proteins eg. penicillin vs gram positive cocci, DNA gyrase (quinolone) and ribosome (streptomycin, macrolide)
- Enzymatic inactivation is by beta lactamase (penicillin) gram negative bacilli AG modifying enzyme AG acetyltransferase, adenylation (chloramphenicol)
- Decreased access to target by a decrease in permeability (OMP for b-lactam and quinolone) and active efflux (tetracycline, erythromycin)
- Miscellaneous by using alternative metabolic pathway
- Enzymatic inactivation
- Target alteration
- Decrease access to target

BETALACTAMASE ENZYME

- Plasmid mediated : blocked by clavulanate
 - TEM, OXA, CARB, SHV
 - ESBL: destroy 3rd and 4th generation cephalosporin, sensitivity to ceftazidime (only in vitro) and carbapenem
 - ESBL: first reported in 1983 from mutant, plasmid-mediated b-lactamase, which was derived from older, broad-spectrum b-lactamase (TEM-1, TEM-2, SHV-1) responsible for hydrolysis of all cephalosporins, penicillin and aztreonam excluding ceftazidime. Most commonly produced by *K pneumoniae* and *E coli*. ESBL enzymes are plasmid mediated and Genes are located on plasmids and also carry genes conferring resistance to several non-β-Lactam antibiotics. Most ESBL isolates are resistant to many classes of antibiotics. Two indicators of

ESBLs are an 8-fold MIC reduction in the presence of clavulanic acid using the broth dilution method and the potentiation of the inhibition zone by clavulanic acid (> 5-mm increase in diameter of inhibition zone) when using the disk diffusion method e.g. an isolate with an MIC of 16 µg/ml against CAZ but an MIC of 2 µg/ml when CAZ plus clavulanate is tested, indicates Plasmid-mediated AmpC β -lactamase arisen through the transfer of chromosomal genes for the inducible AmpC β -lactamase onto plasmids with one exception, plasmid-mediated AmpC differ from chromosomal AmpC in being uninducible. It will unable to be blocked by clavulanic acid from Fermenting (GNR) Gram Negative Bacilli (*Klebsiella pneumoniae*, *Escherichia coli*).

- The AmpC β -Lactamases are encoded by genes located on chromosomes, often inducible, which is commonly found in *Enterobacter* sp, *Citrobacter freundii*, *Morganella morganii*, *Serratia marcescens*, and *Pseudomonas aeruginosa*, since genes encoding these enzymes are located on chromosomes; they are not easily transferable to other bacterial species. AmpC β -Lactamases are only weakly inhibited by β -Lactamase inhibitors and usually confer resistance to cephamycins. In contrast, ESBLs are generally well inhibited by β -Lactamase inhibitors and usually retain sensitivity to the cephamycins. The ESBLs are encoded by genes located on plasmids, resulting in easy transfer to other bacterial species.
- Chromosomal mediated enzymes are penicillinase, cephalosporinase, 4th generation or Carbapenem carbapenemases eg. *Stenotrophomonas maltophilia* and few *Bacillus fragilis*.

CARBAPENEMASES

Stenotrophomonas maltophilia and few *Bacillus fragilis* first acquired metallo- β -lactamase IMP-1 beginning to emerge in *Pseudomonas aeruginosa*, *Enterobacteriaceae* isolated in Japan, Singapore and IMP-1 producing *Acinetobacter* identified in Italy and Hong Kong and second: VIM type: from *Pseudomonas aeruginosa* in Eurasia countries can be combined with other mechanism eg. decrease in permeability.

RESISTANCE TO AMINOGLYCOSIDE

Resistance to aminoglycoside is by enzymatic inactivation acetylation, phosphorelation, adenylation or by target alteration at ribosomal subunit.

RESISTANCE TO QUINOLONES

Resistance to quinolones in the past considered to be only by mutation but now known to be by DNA gyrase, decrease OMP penetration, cross with chemically unrelated ATB e.g. tetracycline, chloramphenicol and now via plasmid is also recorded.

In the development of resistance it is to be noted that it can be by preformed genetic complexes, mutation or uptake of R plasmid, selection process, and survival in specific ecosystem and spread in environment is most important.

Impact of Antimicrobial/Antibacterial Resistance:

1. Patient's unresponsiveness to antibiotics against different bacteria in different infections.
2. Patient's hospital stay is increased.
3. Bed occupancy days increased.
4. Long waiting list of the patients to be admitted to hospitals
5. Cost per patient increased.
6. Economic losses to much (In the USA only in outpatients it is from US \$ 400 million to 18.6

billion & much more on inpatients and in Canada US \$ 14-26 million with additional 26 million on investigation of these cases).

7. Increase in the morbidities and mortalities
8. Spread of resistant organisms through different mechanisms around the globe.
9. Nosocomial infections with resistant strains.
10. Hospital staff may carry these organisms to infect admitted patients

CONCLUSIONS

Antibiotics have revolutionized medicine and saved millions of lives. In the final analysis, however, the problem of antibiotic resistance will not be solved with the creation of many more, or stronger, bactericidal antimicrobials. If past history is in any way a good predictor of future history, microorganisms will consistently continue to adapt to their environment by developing resistance to newer antimicrobials and serious infections caused by these bacteria will continue to pose a major threat to the practicing clinician. It will take a collaborative effort among industry, academia and government for us to strike a "balance" in the war against pathogenic microbes. An effort which will include the implementation of several strategies simultaneously such as a better and broader use of existing public health and preventive measures to avoid infections in the first place, better infection control practices, better availability of diagnostic tools that allow us to more clearly and rapidly distinguish those patients, especially those in the outpatient community, who truly require an antibiotic prescription. All of this needs to be done at a reasonable cost.

It will also take a far more rational use of antibiotics emphasizing the need to use narrow-spectrum agents while saving the broad-spectrum ones for special circumstances. Finally, it will also take the creation and broader use of vaccines capable of preventing infections with some of these multi-resistant bacteria.

In summary, antibiotic resistance is a big concern for everyone. Investment in newer anti-infective platforms is essential and urgent as it is a seamless collaboration among industry, academia and government that results in a revolution in our understanding of bacterial resistance and new approaches to control it. However, the era where acute or chronic bacterial infections used to be treated with "antibiotics-only" appears to have come to an abrupt end.

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