

## CONTINUED MEDICAL EDUCATION

## The Menace of Antimicrobial Resistance

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The discovery of Penicillin in 1926 was followed by discovery and use of several groups of antimicrobials, which gave a major boost to modern medicine by significantly decreasing mortality and morbidity. Thus, antimicrobials were regarded as a major breakthrough as they not only cured infectious diseases but also played a key role in success of advanced medical practices viz organ transplant, immunosuppressive therapy, cancer chemotherapy, complicated surgeries specially in contaminated areas, implants etc. However, these 'miracle drugs' are slowly losing their efficacy due to emergence and spread of antimicrobial resistance (AMR). (1,2,3)

Emergence of AMR is a natural evolutionary phenomenon shown by microorganisms against widespread use of antimicrobials. Beta lactams were the first affected group ([Table-1](#)) and since then bacteria have gained resistance to other groups of -antibiotics too. None of the classes including even the recently discovered antibiotics have been able to escape this dynamic phenomenon. (3,4,5,6)

Unlike the 'golden era' of modern medicine (1930's to 1960's) there has been stagnancy in the discovery of newer antibiotics in the 21st century due to many persistent and costly failures to bring out novel antibiotics. (6)

New strains of bacteria have emerged which are resistant to not just one antibiotic but have gained resistant to several classes of antibiotics (multi drug resistant) making them 'untreatable' and are termed as 'superbugs'. In the past, most superbugs were restricted to healthcare settings, where already sick patients in a weakened condition were more susceptible to contracting infections. More recently, these infections have started to appear in the wider general population outside of hospitals. Community-acquired AMR is of particular concern, as these infections can become common and can be easily transmitted. (2,3,5) Some clinical isolates of pathogenic bacterial species — ESKAPE group of pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter) Mycobacterium tuberculosis, Neisseria gonorrhoeae and species of Salmonella, and Shigella are now resistant to most antibiotics. (7,8)

World Antibiotic Awareness Week (WAAW) in November aims to increase global awareness of antibiotic resistance and to encourage best practices among general public, health workers and policy makers to avoid further emergence and spread of antibiotic resistance. (9)

## Causes of Antibiotic Resistance

While receiving the Nobel prize for Medicine in 1945 for discovery of penicillin, Sir Alexander Fleming and Howard Walter Florey raised the first alarm regarding antibiotic overuse by warning that:

“public will demand [the drug and] ... then will begin an era ... of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted” (10)

Inappropriate prescription, besides having questionable benefits and exposing a person to unnecessary side effects also leads to development of drug resistance. As published by ICMR, antimicrobial prescribing facts follow 30% rule: (11)

- nearly 30% of hospitalized inpatients at any given receive antibiotics
- over 30% of antibiotics prescribed inappropriately
- up to 30% of all surgical prophylaxis is inappropriate
- about 30% of hospital pharmacy costs can be saved by ASP

It is commonly seen that patients often do not stick to the entire course of antibiotics and leave taking medicine after a few doses as symptoms subside. As a course of antibiotic targets removal of entire population of pathogenic bacteria, the remaining bacteria, in case of default, develops resistance against the acting drugs as an evolutionary process. Antibiotics are not solely used in the treatment of human beings but are widely used in animals, fish farming and agriculture. Antimicrobials are indiscriminately used as growth supplements in livestock not just to treat infections but also as a preventive measure and growth supplement. Thus, the gut microbiota of the livestock becomes highly resistant and acts as a reservoir of these resistant bugs. These are then shed into the environment via stool, urine and meat products. (12,13)

Poor infection control in health care settings further leads to the spread of drug resistance by vertical as well as horizontal transfer in bacteria. (13, 14, 15)

Poor hygiene and sanitation amongst the general population especially in third world countries further leads to exposure of resistant bacteria with non-resistant ones and leads to horizontal transfer of resistance

## Mechanism of Resistance

By Darwinian selection process microorganisms develop resistance to substances ‘toxic’ to them after repeated prolonged exposure by different molecular mechanisms. Bacteria may be innately resistant or may acquire resistance to various antimicrobial agents. Acquired resistance arises either by mutations in cell genes or through various methods of gene transfer from one bacteria to another eg. conjugation / transformation/ transposition / transduction. Once a bacterium gains these resistance genes it can use different resistance mechanisms like antibiotic inactivation ( $\beta$ -lactams and glycopeptide), target alteration (macrolides, tetracyclines, fluoroquinolones and rifampin), altered permeability (aminoglycosides, chloramphenicol), and "bypass" metabolic pathway (trimethoprim-sulfamethoxazole).(4) Antibiotic resistance can occur at individual human level or population level with both human and animal population.

## SUPERBUGS (MDR)

‘Superbug’ is a term coined by lay media but well accepted by medical community to describe MDR bacteria prevalent in community and hospital. Superbug are bacteria that cannot be killed using multiple antibiotics. As per the Infectious Diseases Society of America (IDSA) “there is no real definition” to describe the phenomenon in its entirety. Technically term like "multidrug-resistant bacteria" is more correct as a given superbug isn't necessarily resistant to all antibiotics. It actually refers to bacteria that can't be treated using two or more antibiotic group and any species of bacteria can turn into a superbug. (15) It is increasingly considered an urgent, worldwide concern, urging for swift action. As per CDC release, about 2 million people are infected and 23000 die out of superbug related problems. There are often media reports of

outbreaks by these agents, especially in developed world. (16)

In 2013, CDC published a comprehensive report in the U.S., titled Antibiotic Resistance Threats in the United States, 2013 (AR Threats Report). It ranked 18 threats (bacteria and fungi) into three categories based on level of concern to human health. (17)

CDC definitions	Bacteria
<b>Urgent –These bacteria are immediate public health threats that require urgent and aggressive action</b>	<i>Clostridium difficile</i> Carbapenem resistant Enterobacteriaceae Drug resistant <i>Neisseria gonorrhoeae</i>
<b>Serious-These bacteria are a serious concern and require prompt and sustained action to ensure the problem does not grow</b>	Multi drug resistant <i>Acinetobacter</i> Drug resistant <i>Campylobacter</i> Fluconazole resistant <i>Candida</i> ESBL Enterobacteriaceae Drug resistant non typhoidal <i>Salmonella</i> Drug resistant <i>Salmonella</i> Typhi Vancomycin resistant <i>Enterococcus</i> Drug resistant <i>Shigella</i> Methicillin resistant <i>S.aureus</i> Drug resistant <i>Streptococcus pneumoniae</i> Drug resistant tuberculosis
<b>Concerning –These bacteria are concerning and careful monitoring and prevention action are needed</b>	Vancomycin resistant <i>S. aureus</i> Erythromycin resistant Group A <i>Streptococcus</i> Clindamycin resistant Group B <i>Streptococcus</i>

**Urgent Threat:** Carbapenem-Resistant Enterobacteriaceae (CRE): Include Enterobacteriaceae group (E coli, Klebsiella, Salmonella etc.) resistant to many antibiotics including carbapenems. People acquire this in hospital or other medical care facility. IV catheters and scopes use are common risk factors upto 50% of

CRE infected subject may die. New Delhi metallo-beta-lactamase – 1 (NDM-1), KPC etc. falls under this group.

**Urgent Threat: Neisseria gonorrhoeae:** Gonorrhea (an STD) can effect hundreds of thousands of people. Some people do not have symptoms –hence high risk of transmission without being aware of the existence of infection. Earlier it was treatable by antibiotic easily, but currently it has acquired multiple drug resistance. Untreated, gonorrhea can lead to infertility in men and women. It also increases risk for HIV and other STDs. Rarely, it can cause life-threatening blood infections though.

**Urgent Threat: Clostridioides difficile:** Commensal bacteria in the gut, often overgrows and replaces all other commensals in gut killed after a prolonged antibiotic therapy causing serious diarrheal disease. A problem of medical care facility, it needs very urgent diagnosis and prompt treatment by select group of antibiotics. As per CDC 14,000 people a year die from it, most of them older adults. In severe cases, surgery may be needed to remove part of the infected intestine. Even after control of an outbreak/incidence in a healthcare facility, spores may be left behind in bathrooms, on linens, or on clothing with a risk of future transmission. Emergence of drug resistant (e.g. fluoroquinolones etc.) has been a major concern.

**Risk Factors (17):**

The risk of infection increases among elderly and immune-suppressed patients, and also patients with:

- An existing severe illness
- An underlying disease or condition (e.g., diabetes, CKD)
- Previous prolonged use of antibiotics
- Invasive procedures/medical devices (e.g., dialysis, catheters)
- Repeated contact with the healthcare system (e.g., multiple hospital admissions)
- An extended hospitalization
- Previous colonization with a MDRO

**How To Control The Menace Of Drug Resistance?**

The first and foremost step to control the menace of drug resistance is by strengthening the system of surveillance of antibiotic usage in a country and the burden of drug resistance present there and produce an area defined database. The European Union (EU)

has a well-defined system of monitoring in the European nations. Antibiotic use is reported as daily drug dose (DDD) per 1000 inhabitants per day according to pharmacy records, and resistance data are reported by sentinel laboratories using standard methods. (18,19) It has been noticed that there is a dramatic correlation between magnitude of antibiotic usage and prevalence of resistance in a particular area. By restricting the inappropriate use of antibiotic/ antibiotic abuse, the problem of drug resistance can be effectively controlled. (5)

Strict restriction has to be also made in the use of antibiotics in agriculture, livestock and restrict its use only when indicated. Government including the department of agriculture, fishery, animal husbandry should formulate guidelines limiting use of antibiotics in animal rearing clearly stating the indications and if indicated proper dosage has to be mentioned. Many countries have now rules and regulations restricting the indiscriminate use of antibiotic in these areas. The FDA has already announced a ban on cephalosporins for growth promotion in certain livestock in 2012. (5,20)

Strengthening of infection control practices in health care set ups plays a pivotal role in controlling resistance as hospitals and other health care set ups are centerpiece for development of superbugs due to prolonged and wide spectrum use of antibiotics. It is often seen in developing countries like India, strict adherence to infection control practices (like hand washing, waste disposal etc) is lacking. This leads to the spread of these superbugs into the environment and general population. (21)

CDC defined "Antimicrobial stewardship" (ASP) as: the right antibiotic, at the right time, with the right dose, by right route, for the right patient, optimal drug selection, dosage, and duration of antimicrobial treatment resulting in the best clinical outcome with minimal toxicity and resistance.(22) Aggressive promotion of hospital based ASP is the need of the hour as it leads to significant reduction in total antibiotic consumption, duration, and inappropriate use of antibiotics. Every hospital should have their own evidence based antibiotic protocol to optimize and narrow down the use of antibiotics according to syndrome/disease. 2,5 Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials, improves patient outcomes, reduces microbial resistance, and

decreases the spread of infections caused by MDR bacteria. (19)

Steps should be taken to upgrade the microbiology laboratory facility for diagnosis of infectious diseases from older phenotype-based methods to newer molecular based techniques. Newer point of- care molecular methods helps in identification of wide range of virus and bacteria and also their resistance pattern and thereby promotes pathogen-based treatment and replace empirical antibiotic therapy.<sup>5</sup> However for underdeveloped countries like India majority of the population cannot afford these techniques hence government and other funding agencies should come forward to strengthen diagnostic laboratories.

Antibiotic discovery and development programs by the Pharma industry should be revamped and the launching of initiatives by public Institutions can launch the initiative. Recently, WHO has drawn up a plan for controlling the menace of antibiotic resistance and identified development of newer drugs against emerging multi-drug resistant pathogens (superbugs) as major aspect in this plan. (23) They have identified 3 categories of priority pathogens for which newer agents needs to be researched and rolled out in the market urgently.

#### **Priority 1: Critical**

1. Acinetobacter baumannii, carbapenem-resistant
2. Pseudomonas aeruginosa, carbapenem-resistant
3. Enterobacteriaceae, carbapenem-resistant (KPC, NDM-1 etc), ESBL-producing

#### **Priority 2: High**

4. Enterococcus faecium, vancomycin-resistant
5. Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
6. Helicobacter pylori, clarithromycin-resistant
7. Campylobacter spp., fluoroquinolone-resistant
8. Salmonellae, fluoroquinolone-resistant
9. Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

#### **Priority 3: Medium**

10. Streptococcus pneumoniae, penicillin-non-susceptible
  11. Haemophilus influenzae, ampicillin-resistant
  12. Shigella spp., fluoroquinolone-resistant
- Drug resistant phenotypes of M. tuberculosis is excluded from this list as the need for new antibiotics

to treat DR TB has already been designated the highest priority earlier – as per WHO release.

Thus, realizing the global threat of antibiotic resistance, WHO had shown a red signal to the whole medical fraternity on Health Day 2011 by declaring the theme “Combat Drug Resistance” and declared that the problem “threatens the achievements of modern medicine. If urgent steps are not taken to combat this world-wide problem unitedly by everyone, we are very soon heading towards “A post-antibiotic era”— in which even common infections and minor injuries can kill. (2)

Infectious Diseases Society of America (IDSA) has launched a new collaboration titled the “10 × '20” initiative to support the development of 10 new systemic antibacterial drugs through the discovery of new drug classes as well as exploring possible new drugs from existing classes of antibiotics by 2020.(24)

## Conclusion

Thus, to fight the menace of drug resistance and to curb its tentacles from further spreading in hospital and community setting a cumulative effort has to be taken by government, health professionals, industry, civil society as well as the general public.

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## Tables

**TABLE 1 - TIMELINE OF INTRODUCTION OF ANTIBIOTIC USE AND APPEARANCE OF RESISTANCE:**

Antibiotic-Year introduced	Bacteria developing resistance	Antibiotic resistance identified
Penicillin -1940s	<i>Staphylococcus</i>	<b>1942</b>
Tetracycline-1950	<i>Shigella</i>	<b>1959</b>
Methicillin- 1960	<i>Staphylococcus</i>	<b>1962</b>
Penicillin	<i>Pneumococcus</i>	<b>1965</b>
Erythromycin-1953	<i>Streptococcus</i>	<b>1968</b>
Gentamicin -1967	<i>Enterococcus</i>	<b>1979</b>
Ceftazidime- 1985	<i>Enterobacteriaceae</i>	<b>1987</b>
Vancomycin-1972	<i>Enterococcus</i>	<b>1988</b>
Levofloxacin -1996	<i>Pneumococcus</i>	<b>1996</b>
Imipenem 1985	<i>Enterobacteriaceae</i>	<b>1998</b>
<b>XDR tuberculosis</b>		<b>2000</b>
Linezolid-2000	<i>Staphylococcus</i>	<b>2001</b>
Vancomycin	<i>Staphylococcus</i>	<b>2002</b>
<b>PDR-Acinetobacter and Pseudomonas</b>		<b>2004/5</b>
Ceftriaxone	<i>Neisseria gonorrhoeae</i>	<b>2009</b>
<b>PDR-Enterobacteriaceae</b>		<b>2009</b>
Ceftaroline 2010	<i>Staphylococcus</i>	<b>2011</b>
<i>XDR- Extensively Drug Resistant</i>	<i>PDR-Pan Drug Resistant</i>	

**TABLE 2 - COMMON BACTERIAL ISOLATES AND THEIR INTRINSIC INNATE RESISTANCE TO ANTIBIOTICS (13,14)**

Intrinsic innate resistance to -Antibiotic	Bacteria
<b>Aminoglycosides</b>	Anaerobic bacteria, <i>Enterococci</i>
<b>Metronidazole</b>	Aerobic bacteria
<b>Aztreonam</b>	Gram positive bacteria, <i>Acinetobacter baumannii complex</i>
<b>Vancomycin</b>	Gram negative bacilli
<b>Ampicillin</b>	<i>Klebsiella, Acinetobacter baumannii complex</i>
<b>Trimethoprim, Sulfonamides</b>	<i>Pseudomonas aeruginosa</i>
<b>Tetracycline</b>	<i>Pseudomonas aeruginosa</i>
<b>Imipenem</b>	<i>Stenotrophomonas maltophilia</i>
<b>Amoxicillin, Ampicillin-sulbactam, Aztreonam, Ertapenem, Chloramphenicol</b>	<i>Acinetobacter baumannii complex</i>
<b>Amoxicillin, Ampicillin-sulbactam, Amoxicillin-Clavulanate, Cefotaxime, Ceftriaxone, Ertapenem, Chloramphenicol</b>	<i>Pseudomonas aeruginosa</i>