Introduction

The discovery of Antibiotics was probably the most path-breaking event after Pasteur disproved the theory of spontaneous generation, in the history of Infectious Diseases. Penicillin, the wonder drug, saved millions of lives in the 2nd World War and many mothers were saved from puerperal sepsis. After the discovery of the tubercle bacilli and the anthrax bacilli by Koch in 1882, the different bacteria that caused the most horrible infections that inflicted mankind, like Diphtheria, Tetanus, whooping cough etc were discovered. In a similar manner, after Penicillin was discovered accidentally in the year 1928, and mass production started in 1943, there was a deluge of antibiotics entering the market. As if proving Darwin’s theory of “survival of the fittest”, the bacteria underwent a rapid hitherto unprecedented evolution to circumvent this new menace to their survival. Being single-celled and endowed with the ability to multiply rapidly, the change was almost natural and spontaneous. Mutation is a natural phenomenon that occurs in all living beings, including viruses, with DNA/RNA as genetic material. In a normal population of bacteria a few mutants are soon overgrown, but put them in a highly competitive environment like a hospital with all the latest antibiotics being used as soon as they are discovered, and the mutants gain the upper hand. Imagine looking at a welding arc with normal eyesight. Your retina is immediately burnt. When a blind person looks at it, he is not harmed, but in a normal environment he is handicapped due to his blindness. In the same way, mutant bacteria generally have some defects by which they are able to survive in an antibiotic environment, like inability to take up some nutrients from the environment. The antibiotic is also not taken up and they survive.

A surgeon is taught that, how to do a surgery well will take a few years of experience, when to do it will take longer, while when not to do it will take a lifetime. It is the same with antibiotics. The most difficult decision to take is when not to give antibiotics, or when to stop antibiotics.

Unwittingly, microbiologists have contributed a lot towards development of antibiotic resistance. This is because, as of now, there is no unified code for sensitivity reporting in Microbiology. There are many recommendations of which the most reliable ones are those by the Central Laboratory Standards Institute (CLSI), which has to be subscribed to and is too expensive for developing countries. The British Society for Antimicrobials and Chemotherapy (BSAC) also issues guidelines, which are updated yearly, and is free but is unknown to most Indian microbiologists.

In this scenario, let us try to understand this great concern regarding antimicrobial resistance and what can be done to overcome it.

Mechanisms of resistance and its transfer

Table no.1 gives the most common mechanisms of resistance to different groups of antibiotics. As can be seen antibiotics always belong to a group and the mechanism of action of those that belong to a group are similar. This is also true of the pharmacodynamics, i.e. drug uptake and distribution in the body, e.g. all beta lactams are excreted through kidney, achieve good urinary levels and are inhibited by enzymes called beta-lactamases.

Every new drug in a group will be an improvement on the older ones, either in spectrum of action or reduction in side effects or easier dosage schedule. However it is to be specifically emphasized here that when a new drug is introduced to overcome resistance, it should be used only on the resistant strains, proved by culture and sensitivity tests. For sensitive strains, the first line drug to which it is sensitive is the best drug and has the most rapid action. This means that for Staphylococcus aureus sensitive to Penicillin, that is the drug of choice. Vancomycin and Linezolid act better on resistant strains, but act less efficiently and slower than Penicillin on a sensitive strain. The modern trend to give the latest drugs to sensitive strains is counter productive and delays healing, finally leading to a really resistant isolate.
Mutation leads to Resistance encoding genes and resistance is transferred by the three methods of genetic transfer in bacteria, namely Transformation (naked DNA from dead bacteria), transduction (by phages) and conjugation (F factor). The latest in genetic transfer is the Transposon, which jumps from bacteria to bacteria, carrying chains of resistance genes leading to Multi Drug Resistance or MDR organisms.1

Empiric use of antibiotics
From the clinician’s perspective, a rapid decision is needed to start antibiotics and the choice, duration, dosage etc are not well thought out, even when there is enough time to do so, largely because all antibiotics are seen to be a single entity and starting one is expected to give a quick relief to the patient. The outcome is generally favourable, as all antibiotics have some action on all pathogens and the immune system of the body has its own ways of getting rid of unwanted infective agents.

The problem arises when:

- The infective agent is not a bacteria
- The infection is deep-seated and the antibiotic given does not get there
- Initial relief with an inappropriate agent or low dose or short duration leads to recurrence
- Antibiotics are used for prophylaxis rather than for treatment.

Factors in Selection
1. Site of infection: Skin infections, Gastro-intestinal infections, Pneumonia, meningitis, sinusitis, Urinary infections etc. have different bacteria as the common pathogens. It is well to have an idea of the organism before starting antibiotics, rather than just giving cover for all known bacteria (excessive spectrum coverage). Some infections like pneumonia and meningitis have well defined regimes which are available at authentic sites of CDC, WHO, NHS, BSAC etc. and can be followed, since they are updated every year.

2. Bacteriostatic or cidal: Generally both types are effective, but in situations like Infective endocarditis, CNS infections and osteomyelitis, cidal drugs have an advantage. It is also seen that a combination of static and cidal may even have an antagonistic effect (e.g.Crys.Penicillin + Chloramphenicol in Pneumococcal meningitis).

3. Intravenous vs. Oral: For severely ill patients IV route is preferred. Oral medication is possible through the naso-gastric tube. Meningitis, osteomyelitis etc. which have a prescribed regimen are given IV, while typhoid is a disease where oral administration helps to clear infection from the Peyer’s patches effectively.

### TABLE 1 - Eight Major Mechanisms of Resistance by Antimicrobial Class

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>β-Lactam</th>
<th>Aminoglycoside</th>
<th>Chloramphenicol</th>
<th>Macrolide</th>
<th>Sulfonamide</th>
<th>Tetracycline</th>
<th>Trimethoprim</th>
<th>Quinolone</th>
<th>Glycopeptide</th>
<th>Lincomycin, Steptomycin</th>
<th>Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymatic alteration</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+ (GN)</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Decreased permeability</td>
<td>+ (GN)</td>
<td>+ (GN)</td>
<td>+ (GN)</td>
<td>+ (GN)</td>
<td>−</td>
<td>+ (GN)</td>
<td>+ (GN)</td>
<td>+ (GN)</td>
<td>+ (GN)</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Efflux</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+++</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Alteration of target site</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+ (H. pylori)</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Protection of target site</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Overproduction of target</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Bypass of inhibited process</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Bind-up antibiotic</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

+++, most common mechanism; ++, common; +, less common; −, absent; GN, gram-negative; H. pylori, Helicobacter pylori.
4. **Dosing and tissue levels**: Some antibiotics may show an in vitro sensitivity but do not reach the site, e.g. Aminoglycosides in Meningitis. Intrathecal administration may be necessary if this is the only effective drug for the isolate. Pus anywhere has to be drained. Bone penetration is also an issue in osteomyelitis. An adequate dose has to be ensured, with strict compliance to the dosing schedule. In some hospital pharmacies quality of the available drug is another major factor.

5. **Topical antibiotics**: In eye and ear infections, a plethora of antibiotics are available as drops and ointments. It will be good to first ensure that there is bacterial infection and not just an allergic reaction, before prescribing antibiotic drops. A specimen of the pus from conjunctivitis, keratitis, dacryocystitis, endophthalmitis etc. before administering the drops can prove the bacterial aetiology and the empirical therapy can be modified accordingly. Uveitis is an entity where culture is not possible.

6. **Resistance Potential of an antibiotic**: This is a topic that is gaining ground recently. Some antibiotics have been proved to increase resistance in the ICU setting if used for prolonged periods or regularly on all patients. Cefazidime and Ciprofloxacin (and to a lesser extent, other quinolones) increase the prevalence of Methicillin resistance in staphylococci.²

### The Practice of Clinical Microbiology

Evidence based treatment has gained recognition all over the world. However, clinical examination remains the basis of diagnosis even after all the technical advances that have occurred in radiology and the laboratory services. Clinical microbiology is a science that combines the advantages of both.

Bacteria are ubiquitous and the mere presence of a bacterial species in a specimen does not prove that the infection is due to that bacteria. When you add to this the fact that in vitro susceptibility testing now has its own rules and interpretation criteria, the presence of a clinically trained microbiologist with a basic medical degree has become an essentiality. When there is a microbiology lab, which communicates effectively with the clinician and guides antibiotic therapy, the tendency to use antibiotics randomly reduces markedly. The areas where this kind of interaction is needed are:

1) **Intensive Care Units** – Significantly more samples are taken from ICU patients both for ruling out infection and for confirming it. They also receive significantly more antibiotics leading to colonization with MDR organisms. A ward round will help to identify potential outbreak situations early, tailor antibiotics according to need and give speedier preliminary findings.

2) **Management of positive blood cultures and CSF** – Sepsis and meningitis are medical emergencies where smear examination and prompt sub culture with direct sensitivity testing can reduce the time for a definite result, with an informed suggestion for antibiotic therapy. This has to be connected to an on-call service and a 24hr Microbiology lab for effective implementation. This will reduce blind empiric treatment which clinicians are reluctant to stop even after the real sensitivity is known.

3) **Proper interpretation of antibiotic sensitivities** – This can be done only by a Clinical Microbiologist who takes into account updates provided by the BSAC or CLSI, clinical response of the patient and always adheres to the principle of first line antibiotics first

4) **Hospital Infection Control** – The Clinical Microbiologist is generally the Infection control Doctor in the Infection Control Team, which liaisons with the Administration for effective control measures like procurement of material, conducting classes and waste disposal arrangements.

5) **Clinical Microbiological multi-disciplinary meetings** – Clinical Microbiologists with expertise in specific areas may coordinate with specialties like Ophthalmology, Orthopedics etc. to have an educational discussion on cases on a weekly basis.

6) **Public Health** – Public Health professionals can join hands with Microbiologists and Primary health care workers to tackle epidemics in the community.

This kind of set-up needs highly qualified technical staff who can be relied upon to take independent decisions regarding how to identify an isolate or which antibiotics are to be tested. This frees the clinical microbiologist to take the reports to the bedside and offer solutions to the clinician. When the colonizers and commensals are correctly identified and treatment is given more accurately with less of prophylactic antibiotics being used, the problem of the NDM bug will cease to exist.³

The scenario in India has to change dramatically with doctors and scientists and technicians taking their rightful places in the microbiology laboratory working together in perfect harmony, generating useful information to the clinician for more efficient patient care.

### References

2. Cunha B A. Antibiotic Selection and control of resistance in the Critical Care Unit. Infectious diseases in the critical care unit. 2008; Chapter 31: 609-13