CHAPTER

1

Basics of Prescribing Antimicrobial Drugs

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INTRODUCTION

Alexander Fleming at his 1945 Nobel Prize lecture so rightly predicted, "The time may come when penicillin can be bought by anyone in the shops. There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

In 2010, India was the world's largest consumer of antibiotics for human health at 12.9 x 10^9 units (10.7 units per person). The next largest consumers were China at 10.0 x10^9 units (7.5 units per person). Seventy-six percent of the overall increase in global antibiotic consumption between 2000 and 2010 was attributable to BRICS countries, i.e., Brazil, Russia, India, China, and South Africa.

Antimicrobial drugs are not antipyretics. It is high time that prescribing antimicrobial is taken seriously and not as knee jerk reaction for any febrile illness.

DEFINITION

The word antimicrobial was derived from the Greek words anti (against), mikros (little) and bios (life) and refers to all agents that act against microbial organisms. The term "antimicrobials" include all agents that act against all types of microorganisms – bacteria (antibacterial), viruses (antiviral), fungi (antifungal) and protozoa (antiprotozoal).

This is not synonymous with antibiotics. Antibiotic was derived from the Greek word anti (against) and biotikos (concerning life). Thus, the word "antibiotic" refers to substances produced by microorganisms that act against another microorganism. By strict definition, antibiotics do not include antimicrobial substances that are synthetic (sulfonamides and quinolones), or semisynthetic (methicillin and amoxicillin).

CHECK LIST BEFORE PRESCRIBING AN ANTIMICROBIAL AGENT

For a successful outcome of an infectious illness, however minor or major, apart from the right diagnosis, the right drug in the right dose and for the right duration is very crucial.

One must take in to account various factors: 1) Drug factors, 2) Bug factors, 3) Patient factors 4) Combination of antimicrobial drugs and 5) Implications of abuse and misuse of antimicrobial drugs.

1. DRUG FACTORS:

a. Which class to choose?

Classification of antimicrobial drugs based on

- Site / Mechanism of Action: e.g. drugs inhibiting the cell wall, drugs inhibiting protein synthesis, drugs inhibiting nucleic acid synthesis or function.
- Molecular structure: Drugs having beta lactum ring (BL), beta lactamase inhibitors (BLI), aminoglycoside ring, macrolide ring, etc.
- Spectrum of activity: Gram positive, Gram negative, Aerobic, Anaerobic.

b. Spectrum of antimicrobial activities:

i. Bacteriostatic or Bacteriocidal,

In immuno-competent patient and in minor illness bacteriostatic drugs are as good as bactericidal drugs.

- Bactericidal drugs are those that kill target organisms. e.g. aminoglycosides, cephalosporins, penicillins, and quinolones.
- Bacteriostatic drugs inhibit or delay bacterial growth and replication. e.g. tetracyclines, sulfonamides, and macrolides.
- Some antibiotics can be both bacteriostatic and bactericidal, depending on the dose, duration of exposure and the state of the invading bacteria. e.g. aminoglycosides, fluoroquinolones, and metronidazole exert concentration-dependent killing characteristics; their rate of killing increases as the drug concentration increases.

ii. Broad spectrum or Narrow spectrum

Broad spectrum anti bacterials are active against both Gram-positive and Gram-negative organisms e.g. tetracyclines, phenicols, fluoroquinolones, third and fourth generation cephalosporins.

Narrow spectrum anti bacterials have limited activity and are primarily useful against particular species of microorganisms e.g. glycopeptides are only effective against Gram-positive bacteria, Polymixins are active against Gram negative bacteria.

Aminoglycosides and sulfonamides are effective against aerobic organisms, and nitroimidazoles are effective against anaerobes.

c. Indication of prescribing: Prophylactic or Therapeutic?

The dose and duration of antimicrobial drugs are different when given for prophylaxis than when given for therapeutic indications. Discussion about therapeutic indications is beyond the scope of this review.

Surgical antimicrobial prophylaxis should be given as per the national guidelines, taking in to account the local antibiogram.

- Antimicrobials have to be administered within one hour before the incision
- Cefazolin (2 gm) or Cefuroxime (1.5 gm) or Cefaperazone + Salbactum (2 gm) are recommended for the most surgeries.
- Single dose is recommended. Consider second intra-operative dose in prolonged surgery.
- Duration of prophylaxis should not extend beyond 24 hours except for cardiothoracic surgery where up to 48 hours of prophylaxis is permissible.

d. Pharmacokinetics (Pk) and Pharmacodynamic (Pd) parameters (Figure 1)

- Pk= What body does to a drug

Pharmacokinetics of a medicine deals with the movement of a drug from its administration site to the place of its pharmacologic activity and its elimination from the body.

Remember: We must be conversant with ADME (Absorption, Distribution, Metabolism, Elimination) of every drug that we use.

- Pd= What a drug does to body

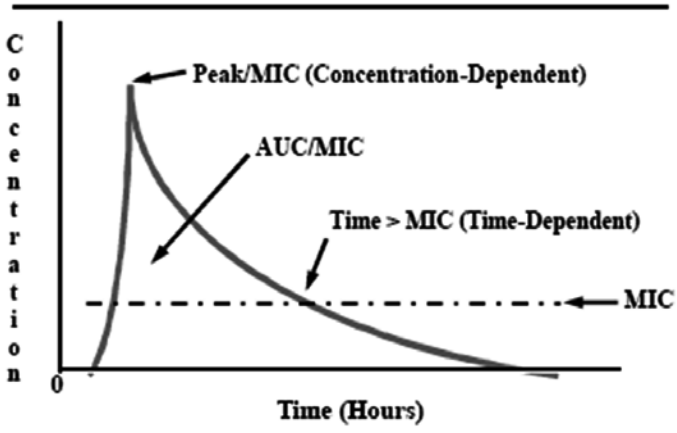

Fig. 1: Graph explaining drug distribution

Pharmacodynamics of a medicine correlates the concentration of the drug with its pharmacological or clinical effects. For an antibiotic, this correlation refers to the ability of the drug to kill or inhibit the growth of microorganisms. Antibiotics elicit their activity against bacteria by binding to a specific protein or structure in the organism.

Remember: We should know RPC (Receptor binding (including receptor sensitivity),

Post-receptor effects and Chemical interactions) of every drug that we use.

Antimicrobial drugs bring about their activities either by Concentration-dependant effect or by Time-dependant effect on organisms.

Concentration-dependant effect of antibiotics: Give High, Single daily dose: OD dose: Azithromycin, Levofloxacin, Aminoglycosides. Please do not prescribe. Azithromycin or Levofloxacin in twice a day dose.

Time-dependant effect of antibiotics: these drugs need to be given in divided doses:

BD, TDS or QDS doses e.g. Amoxicillin, Cephalosporin, Carbapenem. When given intravenously, one should give infusion over 2 to 4 hours every 6 to 8 hourly.

2. BUG FACTORS (Table 1)

a. Anticipated Organism(s) and choice of Antimicrobial Agents:

Every effort should be made to reach to the final diagnosis of the causative organism, pending which empiric antimicrobial may be started with provisional diagnosis of causative organism.

b. Is the infection by one organism or multiple organisms (polymicrobial)?

Most infections can be treated with one drug. However polymicrobial infections may require combination of different class of antimicrobial drugs or drugs working at synergistic or sequential manner.

3. PATIENT (HOST) FACTORS

a. Immuno-compromised or Immuno-competent host

Patients having HIV infection, diabetes mellitus,

Table 1: Empirical choice of antibiotics till final reports are available

Gram Positive organisms	Gram Negative Organisms	Anaerobic organisms
Penicillin	Aminoglycosides	Metronidazole
1st / 2nd gen. Cephalosporines	Quinolones	Clindamycin
Macrolides	Extended spectrum	Penicillin
Tetracycline	2nd/3rd/4th generation cephalosporines	
Newer Quinolone	Aztreonam	
Linezolid	Imipenem	
Vancomycin	Choramphenicol	

receiving steroids or Immune-suppressant drugs should be considered as immuno-compromised host and should be treated accordingly

b. Special situations : pregnancy, children, renal failure, liver impairment

Special precautions have to be taken when antimicrobials are prescribed to pregnant women, children, elderly, and in presence of renal and hepatic impairment

While prescribing antimicrobial to a pregnant woman or one who could be pregnant, one should be extremely careful in selecting a drug and must search for "Pregnancy Category" for prescribing such drug. In general prescribe only Category A and B drug. Reserve Category C drug for serious maternal infection.

c. History of recent antibiotic exposure

Antimicrobial Stewardship Program places patient who has received antibiotics in previous 8 weeks in higher category and requires to be treated differently.

d. Best time to take Antimicrobials?

Most antimicrobials are absorbed better when taken on empty stomach

Food, Antacids and Iron tablets reduce absorption of antibiotics.

4. COMBINATION OF ANTIMICROBIAL DRUGS

Antibiotic combinations required and are life-saving when indicated in situations such as

- Seriously ill patients
- Polymicrobial infections: burns, diabetic foot…
- To achieve synergism
- To prevent emergence of resistance as in case of Tuberculosis (TB)
- Immunocompromised or Neutropenic patient with bacteremia

Rational combinations (Proven additive or synergistic effects)

- Sulfonamide + Trimethoprim
- Amoxicillin + Clavulanate / Salbactum
- Piperacillin + Tazobactum

Irrational combinations (Irrational Pk/Pd parameters or No proven evidence)

- Quinolone + Metronidazole / Tinidazole
- Cefixime + Clavulanate
- Cefixime + Ofloxacin
- Cefpodoxime + Ofloxacin
- Linezolid(600mg)+ Cefixime (200mg)
- Azithromycin + Cefixime

5. IMPLICATIONS OF ABUSE AND MISUSE

Unlike Nonsteroidal anti-inflammatory agents (NSAID) or other drugs which cause damage to individual patients and affect their families, misuse or abuse of antibiotics affect the society as a whole. Important implications for the same may be as follows:

- Adverse effects / Drug – Drug interactions
- Extended hospital stay
- Escalation of cost
- "Collateral damage": Ecological adverse effects of antimicrobial therapy

Selection of drug-resistant organisms & unwanted development of colonization or infection with MDR organisms

- Cephalosporins → ↑ risk of infection with VRE, ESBL, Acenatobacter & C. difficile

Quinolones → ↑ risk of infection with MRSA, Pseudomonas aeruginosa

- Super-infection: Clostridium difficile
- Resistance

A new era began in 2009, when New Delhi Metallo-beta lactamase (NDM1) enzyme was isolated from Klebsiella pneumonie organisms. Later blaNDM1 gene was discovered which conferred resistance to carbapenems and all most all antimicrobial drugs. The resistance quickly spread to other organisms. NDM-1 began to be isolated from several other parts of India. Emergence of such bacterial species may be lethal for an individual patient and may lead to dangerous epidemics for society as a whole. Avoiding use of unnecessary antibiotics in upper airway disease will be a great service to the society

CONCLUSIONS

Antimicrobial drugs are our treasured weapons to combat war against infectious agents. We must use our armaments judiciously and prudently. Prescribing antimicrobials for viral URTI and Gastroenteritis must be discouraged. Only rational combination of antimicrobial drugs should be prescribed. Always keep in mind Pk and Pd parameters. If we miss the bus we have to blame our selves only. Save antimicrobials for our generation and more importantly, the next generation.

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