Rational Use of Antibiotics

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Rational use of antibiotics

- Aim :
  - Maximum treatment effectiveness
  - Minimum resistance development to the antibiotics

Rational use of antibiotics

- Discovery of effective antimicrobial agents are the most important development of modern medicine.

- Until 19th century, the therapy for infections strictly remained emprical.
  - Heavy metals (arsenic, bismuth used for syphilis)

Rational use of antibiotics

- Initial clinical use of sulfonamides 1936
- Discovery therapeutic value of the penicillin and streptomycin in 1940.
- 1950, golden age of antimicrobial agent

Rational use of antibiotics

Using Correct Antibiotic

- Do you have a proven of microbiological infection?
  - Treatment
- Is there any infection with inevitably-developed or likely to have an infection?
  - Empirical
- Is it possible to develop an infection which can be done prevention?
  - Prophylaxis

Rational use of antibiotics

Using Appropriate Antibiotic

- Prevent the both development of the resistance to endogenous flora and nosocomial infection
- Improve patient care (The best efficacy / less toxicity)
- If you have multiple options, choosing of the cheapest and most effective as a pharmacodynamic.

Rational use of antibiotics

Current State of the World and in Turkey

- One of the best-selling drug groups in Turkey
- In general, the rate of % 40 -50 is used incorrectly
- More than % 20 of the annual drug consumption are antibiotics
- The problem is not only the problem of backward countries
- URTI, %50-70 of them are being prescribed in the USA

Rational use of antibiotics

- The average time for the submission of a new antibiotic on the market is 14 years
- 85 million dollars of money spent for a new antibiotic

Rational use of antibiotics

Why antibiotics used exseccive or bad ?

- Physicians who wish to apply the best treatment patients do mistake to thought that
  - the best antibiotics is the most expensive and broad-spectrum antibiotics
  - If small doses are effective, the assumption is that long term using high doses will be more effective

Rational use of antibiotics

Why antibiotics used exseccive or bad ?

- Physicians who wish to apply the best treatment patients do mistake to thought that
  - Including the unusual microorganisms, using the multiple and broad-spectrum antibiotics
  - Inability physician the level of knowledge about the diagnosis and treatment of infectious diseases
  - Immediately asked to be taken control of the infection

Rational use of antibiotics

How is the bad using of antibiotics ?

- Using antibiotics for the diagnosis without necessary evaluation
- Infection without the use of antibiotics
- Selected antibiotic is incorrect
- Inadequate or excessive dose
- Inappropriate interval of dose
- Cheaper antibiotic / expensive antibiotic

Rational use of antibiotics

Where antibiotics are using sometimes extremely busy and exhausted ?

- Hospitals
- Policlinics
  - First Step Physician
  - Emergency service
  - Pediatrics policlinics
  - ENT policlinics
- Pharmacies / without a prescription

Rational use of antibiotics

What are the major results intensive and overuse of antibiotics in hospitals?

- Selecting resistant organisms are the dominant flora of hospital
- Increase in infections due to resistant microorganisms
- Increasing in mortality and morbidity
- Increase in the cost of treatment

Rational use of antibiotics

What can be done to use the correct antibiotic?

- Education
  - Continuously
  - One to one, face to face
- Restriction Methods
  - Formulary of the hospital
  - Restricted antibiotic statement
  - Using restricted application

Rational use of antibiotics

What can we do to use the correct antibiotic?

- Treatment, prophylaxis, and the creation of empirical treatment protocols
- Monitoring and notification the results of antibiotic susceptibility to clinician
- Monitor the impact of using antibiotics to patient care
- Prevent the wrong promotions (especially unethical promotions) of the Pharmaceutical companies

Rational use of antibiotics

Factors affecting selection of antibiotics

- Properties of Infections
  - The location and characteristics of the infection
- Properties of Patients
  - Age
  - Allergy
  - Underlying disease (liver, renal failure)
  - Pregnancy
  - Before used and now using antibiotics

Rational use of antibiotics

Factors Affecting Selection of antibiotics

- Properties of Antibiotics
  - Spectrum
  - Mechanism pharmocologically
  - Interval of dose
  - Route of administrationTiming
  - Drug interactions
  - Side effects
  - Cost

Rational use of antibiotics

- **Antibiotics** = a natural substance produced by a micro-organism to kill another
- **Antiinfectives/ Anti-microbial** = any agent (natural or synthetic) that kills pathogens microorganism
- Needs to kill the microbial cell and not to be toxic to normal healthy human cells

Rational use of antibiotics

- Antibiotics are a large and diverse group of drugs which combat infections by suppressing the growth and reproduction of bacteria.

- However, many bacteria are now resistant to antibiotics and some are resistant to all known agents.

- New drugs are continuously being introduced to combat evolving patterns of resistance.

Rational use of antibiotics

General principles:

- Establish the need for antibiotic therapy
- When not to prescribe
  - Viral or minor bacterial disease
  - Viral diarrhea
  - Sore throat
  - Sinusitis
  - Common cold / SELF LIMITING DISEASES

Rational use of antibiotics

Antibiotic treatment can be :

- **Treating bacterial infections** in accordance with culture and sensitivity testing or knowledge of prevalent organisms.
- When the cause of an infection is confirmed, **directed** therapy is aimed at the specific pathogen.
- **Prophylactic** antibiotics prevent serious infection in specific situations (e.g. preventing the spread of meningococcal disease, surgical procedures).
- **Empirical** antibiotic therapy — which is aimed at the likely causative organism — to manage an infection until microbiological culture and susceptibility results are known

Rational use of antibiotics

Microbiology guides therapy wherever possible

Indications should be evidence-based

Narrowest spectrum required

Dosage appropriate to the site and type of infection

Minimise duration of therapy

Ensure monotherapy in most situations

Rational use of antibiotics

- Antibiotics discriminate the differences between bacterial and human cells

- They prevent the renewal of the bacterial cell wall and inhibit protein formation

Rational use of antibiotics

- Bacteriostatic (Inhibit growth without death) Bactericidal (Killling bacteria)
  - Dosage related?
    - Streptomycine
    - Eriytromycin
    - Lincomycin
    - Chloramphenicol
- Mechanism of action (see later)
- Spectrum of Activity:
  - Broad or Narrow

Rational use of antibiotics

- Bacteriostatic allows for natural immunity to deal with the microorganism
  - Antibodies, Phagocytosis etc

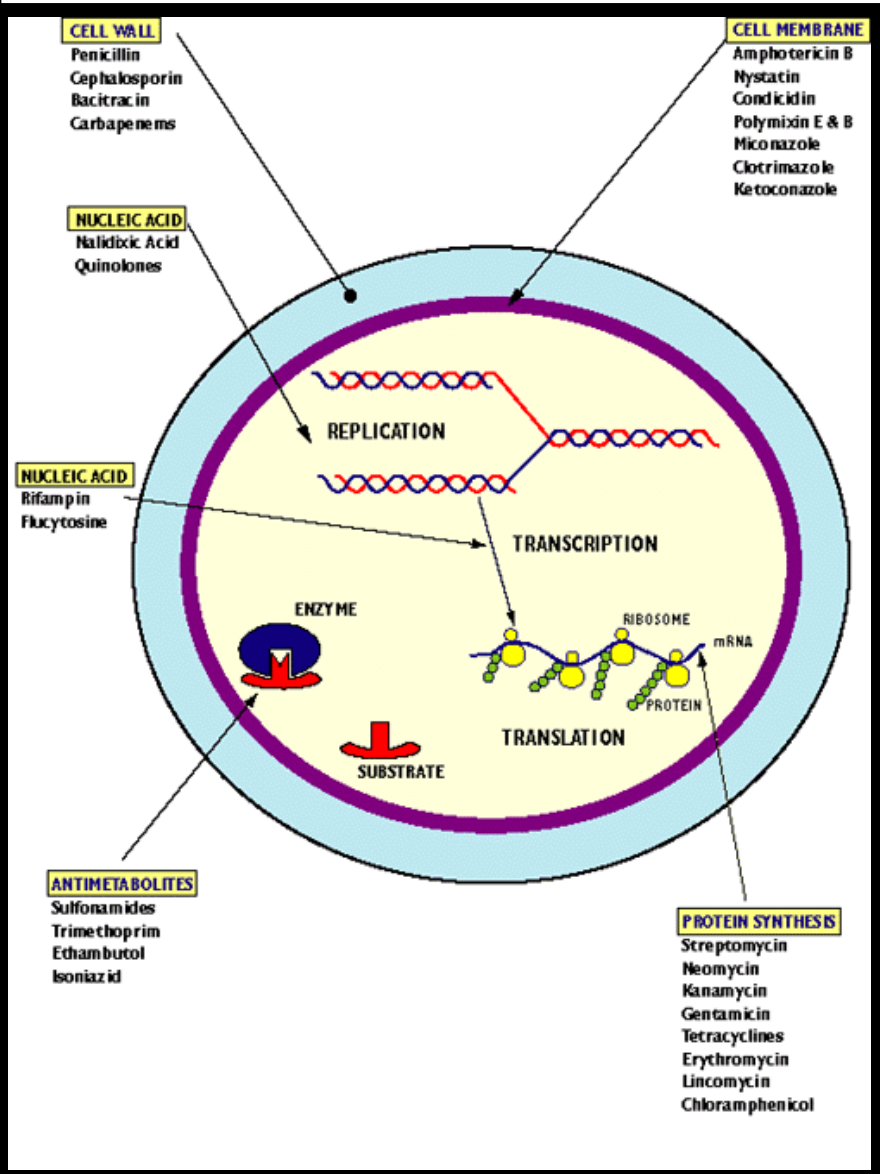
- Bactericidal may lead to release of toxins and microbial contents leading to subsequent illness and inflammatory responses.

Rational use of antibiotics

SPECTRUM OF ACTIVITY :

- Relates to the number of microbes that are susceptible to the action of the drug
  - Narrow (limited number) / Broad (wide)
- Penicillin G is a narrow spectrum drug as it is only effective against gram-positive microbe
- Tetracyclines are effective against gram-positive and gram-negative microbes (Broad)

Rational use of antibiotics



- **Mechanism of Action:**
  1. Inhibition of Cell Wall Synthesis
  2. Disruption of Cell Membrane
  3. Inhibition of Protein Synthesis
  4. Interference with Metabolic Processes

Oral administration

Antibiotic	Problem	Precaution
Tetracyclines, Quinolones	Absorption impaired by iron, zinc or calcium in the stomach	Taken either 1 hour before or 2 hours after tablets containing these minerals or dairy products.
Doxycycline Minocycline	Oesophageal or gastric irritation	Taken with food and a full glass of water
Ampicillin Erythromycin Rifampicin	Absorption reduced by food in the stomach	Taken 1 hour before or 2 hours after meals
Amoxycillin	Absorption reduced by high fibre diets, e.g. bran or bulk laxatives e.g. methylcellulose	Dose increases may be required
Most antibiotics	Absorption impaired by antacids, particularly those containing magnesium and aluminium	Antibiotic taken 1 hour before or 2 hours after antacids

Problem associated with all antibiotics-1

Problem	Precautions
Resistance	**Minimise antibiotics unless bacterial sensitivity is known.** **Ensure adequate doses.** **Complete course.** **Avoid spreading infection by observing hospital policies for hand-washing, asepsis, and single-use equipment.** **Try to prevent contact between MRSA and vancomycin-resistant *Enterococci* by separating patients harbouring these bacteria. Such contact could allow development of vancomycin-resistant MRSA.**
Hypersensitivity **1-10% of patients are hypersensitive to penicillins.**	**Thorough patient history.** **Pre-therapy assessment of breathing pattern and skin to facilitate detection of any changes.** **Administer intravenous therapy slowly.**

Problem associated with all antibiotics-2

Problem	Precaution
Superinfection	**Minimise use of broad-spectrum antibiotics.** **Monitor fluid and electrolyte balance if diarrhoea and vomiting occur and be alert for *Chlostridium difficile* infections.** **Small frequent meals may alleviate gastro-intestinal disturbance.** **Stomatitis may be alleviated by ice cubes and mouth care.** **Monitor for infections due to fungi (e.g. Candida), Pseudomonas, Enterobacteria.** **If aminoglycosides are administered, monitor for worsening of TB and Herpes infections.**
Therapeutic failure	**Ensure adequate doses and prompt administration.** **Certain antibiotics, particularly aminoglycosides, have a narrow margin between therapeutic dose and toxicity.**

Toxicity associated with antibiotics-1

Site	Antibiotic	Precaution
Brain: **Convulsions** **Confusion**	**Penicillins** **Cephalosporins** **Quinolones** **Aminoglycosides**	**Avoid intrathecal route.** **Caution in patients with histories of convulsions and/or renal failure.** **Avoid co-administration of quinolones and NSAIDs.**
Peripheral nerves: **pain, numbness, tingling**	**Aminoglycosides**	**Monitor. Alternative drugs may be needed.**
Inner ear **(hearing & balance)**	**Gentamicin** **Vancomycin** **Rarely:** **Erythromycin**	**Avoid other drugs affecting the ear.** **Avoid in pregnancy and breastfeeding, if possible.** **Ensure patient can hear and balance is not affected.** **Mobilise carefully.** **Monitor tinnitus.** **Administer intravenous therapy slowly.**

Toxicity associated with antibiotics-2

Site	Antibiotic	Precaution
Growing bones & teeth	Tetracyclines	Avoid in pregnant women & children.
Liver	Erythromycin Rifampicin Isoniazid Rarely: Tetracyclines Cephalosporins Co-amoxiclav	Undertake liver function tests if use prolonged. Avoid in people with history of alcoholism.
Pancreas	Cotrimoxazole	Be alert for severe vomiting and pain radiating to the back. Check blood glucose concentration.

Toxicity associated with antibiotics-3

Site	Antibiotic	Precaution
Kidney	Gentamicin Vancomycin Cotrimoxazole Rarely: Cephalosporins Penicillins Tetracyclines	Check serum creatinine and urea to assess renal function before and during therapy. Seek alternative drug in those over 65. Ensure adequate hydration,
Skin (photosensitivity)	Tetracyclines, Quinolones	Avoid prolonged exposure to sunlight.
Bone marrow	Chloramphenicol Cotrimoxazole Rarely: Cephalosporins Aminoglycosides	Avoid in patients with history/ family history of bone marrow problems or taking other drugs potentially toxic to the marrow (e.g. carbimazole, carbamazepine, antipsychotics). Check full blood count routinely

Rational use of antibiotics

- **Ideal antibiotic using :**
  - Correct antibiotic
  - Best way (IV,IM,PO)
  - Effective dosage
  - Optimal timing
  - Appropriate period
  - After correct diagnosis

Rational use of antibiotics

- Antibiotics are not antipyretic drug
- Only fever is not indication to use antibiotic
- Treatment with antibiotic for 3-4 days if there is no answer
  - Drug is wrong
  - Drug does not reach enfective area (abcess)
  - Identified microorganism wrong
  - Fever due to antibiotic usage
  - Second infection agent

Rational use of antibiotics

- Several methods for identification of pathogen microorganisms
- Gram stain
  - Simplest
  - Cheapest
  - Most useful (bacteria, fungus)
- Immunologic methods
  - ELİSA
  - Latex agglutination
- Molecular techniques
  - PCR (Viruses RNA-DNA, bacteria and other microorganisms)
- Culture
  - Definitive identification of pathogenic microorganisms

Rational use of antibiotics

- In some cases, it is impossible determine infecting organism before to institution of antimicrobial therapy.

- In these cases, the use of bacteriologic statistics may be particularly helpful.

Rational use of antibiotics

- Bacteriologic statistics refers to organisms most likely cause of infection.
- For example:
  - A person with normal host defense
  - Cellülitis on arm
  - Most likely pathogen agent
    - Staphylococcus aureus
    - Group A Streptococci (S.pyogenes)

Rational use of antibiotics

- Different organisms vary in their susceptibility to microbial agents
- If the pathogen is isolated from a culture, it can be subjected to direct susceptibility testing
- The widespread use of antibiotics has resulted many strains resistance of bacteria.

Rational use of antibiotics

- It is important geographic differences in pattern of susceptibility of organisms when choosing antimicrobial agent.
- There may be variations in susceptibility patterns between
  - Hospital-community
  - Neighboring hospital
  - Even among units of hospital

Rational use of antibiotics

For example : **MRSA**

- Many years accepted hospital acquired infection
- But that has changed recent years
- Community acquired MRSA infections in persons who have had a no contact with health care systems have been documented in a number of countries.

Rational use of antibiotics

- It is clearly important to determine identity and susceptibility of the organisms causing to the infection

- However, optimal therapy is impossible depends of host factors , that may influence the efficacy and toxicity of antimicrobial agent

Rational use of antibiotics

- Simply obtained adequate history of patients, may prevent inadvertent administration of antimicrobial agent to which patient is
  - Allergic
  - Otherwise intolerant

Rational use of antibiotics

- Age of patients is a factor choosing of antibiotics, gastric acidity varies with age.
- The pH of gastric secretions is higher in young children (<3 years) and achlorhydric elderly patients.
- The absorbtion of number of antibiotics via the oral route depends on their
  - Acid stabilty
  - pH of gastric secretions

Rational use of antibiotics

- For example : Oral absorbtion of Penicillin G
  - Markedly reduced by gastric acid
  - Hoewever, in young children and elderly patients, the absorbtion of the drug is markedly enhanced

Rational use of antibiotics

- Renal function varies with age
- Premature and newborn children renal function reach to adult level between 2-12 monts of age
- Antibiotics which are excreted by the kidneys may be considerably increased in neonates
  - Penicillin and derivates
  - aminoglycosides

Rational use of antibiotics

Creatinine clearence (GFR):

CrCl: ~~Urine Creatinine (mg/dL) X Urine volume (mL/dk)~~

Plasma Creatinine (mg/dL)

Rational use of antibiotics

- Creatinine clearance may be significantly reduced in older patients even thoug they have normal urea and serum creatinine level
- In wiev of this high doses of antibiotics
  - Penicillins
  - Cephalosporins
  - Carbapenems must be given with caution
- High serum levels which may produce severe neurotoxic reactions
  - Myoclonus
  - Seizures
  - Coma

Rational use of antibiotics

- GFR : glomerular filtration rate
  - Normal : > 100 ml/min
  - Light : 40-60 ml/min
  - Middle : 10-40 ml/min
  - Serious : < 10 ml/min

Rational use of antibiotics

- Hepatic function in the neonate is underdeveloped by adult standarts
- Chloramphenicol inactivated by glucronyl transferase in the liver
- If you give large doses chloramphenicol to neonates, high serum levels resulted with GRAY SYNDROME (shock,cardiovasculer collapse and death)

Rational use of antibiotics

- Hepatocellüler destroy
  - Ampicillin
  - Choloramphenicol
  - Clindamycin
  - Sulfonamides
  - SXT
  - İNH,PAS,PZA,RİF
  - Etionamid
  - Zidovudin
- Cholestasis
  - Erytromycine
  - Cephalosporins
  - SXT
  - Amoxcilline-clavulanic acid
  - Cloxacillin
  - Nitrofurantoin

Rational use of antibiotics

- Tetracylines are avidly bound to the teeth and developing bones

- They may cause adverse effects ranging from purplish to brownish discoloration of teeth and enamel hypoplasia

Rational use of antibiotics

- The quinolones have been shown to cause cartilage damage and arthropathy in young animals
- As a result, they had not been recommended for use in children

Rational use of antibiotics

- The presence of genetic and metabolic abnormalities may also have significant effect on the toxicity of a given antimicrobial agent
- Individuals with G6PD deficiency, if they use
  - sulfonamides,
  - dapsone,
  - nitrofurantoin,
  - anti malarial drugs resulted with hemolysis

Rational use of antibiotics

- Metabolic disorders such as diabetes mellitus may also pose problems in antimicrobial therapy.
- Fluroquinolones have been associated with dysglicemic reactions (hypo and hyper glicemia) and tendon rupture

Rational use of antibiotics

- Cephalosporins
- Chloramphenicol
- Isoniasid
- Nalidixic acid
- Nitrofurantoin
- Penicillin
- Streptomycine
- Sulfonamides
- Tetracylines

- This antibiotics can all cause false-positive test result in urine glucose test when urine sugar determined

Rational use of antibiotics

- The absorbtion of intramuscularly administered antibiotics may be impaired in diabetic patients
- Diabetic patients with endocarditis gives bad result, if penicillin use IM way
- But same dose penicillin administered İV way, eradicated endocarditis

Rational use of antibiotics

- Chloramphenicol delayed reticulocyte response to Vit B12 or iron therapy in patients with pernisious anemia or deficiency anemia

- Rifampin may incraese the hepatic metabolism and therefore decrease the effect of oral anticoagulants

Rational use of antibiotics

- All antimicrobial agents cross the placenta in varying degrees
  - Penicillin
  - Cephalosporins
  - Meropenem,ertapenem,doripenem
  - Clindamycine
  - Ertyromycin,azitromycine
  - Nitrofurantoin
  - Metranidazol can be use in pregnant women

Rational use of antibiotics

- For antimicrobial therapy to be effective an adequate concentration of the drug must be delivered to the site of infection.
- In most cases, this means that the local concentration of the antimicrobial agent should at least equal the MIC of infecting organism

Rational use of antibiotics

- The penetration of antimicrobial agent into interstitial fluid and lymps is related to protein binding
- Binding to serum proteins may effect both the tissue distribution and the activity of antimicrobial agent in the blood

Rational use of antibiotics

- The presence of foreign bodies also has a profound effect on the activity of antibiotics

- Thus it is often necessary to remove foreign material to cure infection (prosthetic heart valve, joint implant)

Rational use of antibiotics

- Local alterations in pH, such as abscesses and urine, may have an important effect on the activity of a number of antimicrobial agents.
- In acid pH are more active
  - Methenamine
  - Nitrofurantoin

Rational use of antibiotics

- Alkalinization enhances the activity of
  - Erythromycin
  - Azithromycin
  - Clarithromycin
  - Lincomycin
  - Clindamycin
  - Aminoglycosides.

Rational use of antibiotics

- Most infections with normal host defenses can be treated with a single antimicrobial agent
- The physician is often tempted to use combination two or more antimicrobial for the sense of security
- However, inappropriate use of antimicrobial combination may have significantly effects

Rational use of antibiotics

- When two antimicrobial are combined invitro they may demonsrate one of the three types of interactions against a given organism
  - Additive
  - Synergism
  - Antogonism

Rational use of antibiotics

Using Combine Antibiotics

- **Additive effect:** Used in combination from the individual effect of these drugs is the sum of the effects of drugs
- **Synergy:** The influence of drugs combination, these drugs is the sum of the effects that result from using only a single one
- **Antagonistic effect:** Drugs used in combination from the individual effect of these drugs is less than the sum of the effects of them

Rational use of antibiotics

Using Combined Antibiotic

- Expanding the antimicrobial spectrum
- Polymicrobial infection
- Serious infections in neutropenic patients
- Prevent the development of bacterial resistance
- Synergistic effect

Rational use of antibiotics

- Antimicrobial combinations in case of
  - Neutropenic patient
  - Critically ill patient
  - Brucellosis
  - Tuberculosis
  - Polymicrobial infections
  - Pseudomonal infections
  - Endocarditis
  - Foreign body infected staphylococcus

Rational use of antibiotics

- Neutropenic and critically ill patient treatment begin with broad spectrum antibiotics,
  - Gr(+) and MRSA
  - Gr(-)
  - Switch to single drug after the result of culture

Rational use of antibiotics

Undesirable Effects of Combination Antibiotic

- Antogonizm
- Colonisation of resistance microorganism and superinfection
- Toxicity and increasing side effect
- Increasing cost

Rational use of antibiotics

Making monitoring and if necessary the appropriate amendment responded to antibiotic treatment

- Evaluation of Clinical and Laboratory
  - İmprovement of clinical
  - Fever
  - CRP, Sedimentation,
  - Leukocyte
  - Culture

Rational use of antibiotics

Questions to Consider Before Using Antibiotics

- Is there an indication that require antibiotics?
- Is the materials suitable for the diagnosis before starting treatment?
- What are the causative microorganisms?
- What is the most appropriate antibiotic? Why?
- What are the characteristics of selected antibiotics?
- What are the characteristics of the patient?
- Do you need a combination of antibiotics**?**


Wash your hands!
YOU
know where they've been!