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 empirical.
  – 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
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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
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• 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
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Why antibiotics used excessively 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 excessive 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
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Where antibiotics are using sometimes extremely busy and exhausted?

- Hospitals
- Policlinics
  - First Step Physician
  - Emergency service
  - Pediatrics policlinics
  - ENT policlinics
- Pharmacies / without a prescription
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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
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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
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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
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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 pharmacologically
  – Interval of dose
  – Route of administration
  – 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

**M**icrobiology guides therapy wherever possible

**I**ndications should be evidence-based

**N**arrowest spectrum required

**D**osage appropriate to the site and type of infection

**M**inimise duration of therapy

**E**nsure 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  (Killing bacteria)
  – Dosage related?
    • Streptomycine
    • Erytromycin
    • 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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Problem</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines, Quinolones</td>
<td>Absorption impaired by iron, zinc or calcium in the stomach</td>
<td>Taken either 1 hour before or 2 hours after tablets containing these minerals or dairy products.</td>
</tr>
<tr>
<td>Doxycycline, Minocycline</td>
<td>Oesophageal or gastric irritation</td>
<td>Taken with food and a full glass of water</td>
</tr>
<tr>
<td>Ampicillin, Erythromycin, Rifampicin</td>
<td>Absorption reduced by food in the stomach</td>
<td>Taken 1 hour before or 2 hours after meals</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>Absorption reduced by high fibre diets, e.g. bran or bulk laxatives e.g. methylcellulose</td>
<td>Dose increases may be required</td>
</tr>
<tr>
<td>Most antibiotics</td>
<td>Absorption impaired by antacids, particularly those containing magnesium and aluminium</td>
<td>Antibiotic taken 1 hour before or 2 hours after antacids</td>
</tr>
<tr>
<td>Problem</td>
<td>Precautions</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Resistance</td>
<td>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 <em>Enterococci</em> by separating patients harbouring these bacteria. Such contact could allow development of vancomycin-resistant MRSA.</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity 1-10% of patients are hypersensitive to penicillins.</td>
<td>Thorough patient history. Pre-therapy assessment of breathing pattern and skin to facilitate detection of any changes. Administer intravenous therapy slowly.</td>
<td></td>
</tr>
</tbody>
</table>
### Problem associated with all antibiotics

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<tr>
<td>Superinfection</td>
<td>Minimise use of broad-spectrum antibiotics. Monitor fluid and electrolyte balance if diarrhoea and vomiting occur and be alert for <em>Chlostridium difficile</em> 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), <em>Pseudomonas</em>, <em>Enterobacteria</em>. If aminoglycosides are administered, monitor for worsening of TB and Herpes infections.</td>
</tr>
<tr>
<td>Therapeutic failure</td>
<td>Ensure adequate doses and prompt administration. Certain antibiotics, particularly aminoglycosides, have a narrow margin between therapeutic dose and toxicity.</td>
</tr>
</tbody>
</table>
## Toxicity associated with antibiotics

<table>
<thead>
<tr>
<th>Site</th>
<th>Antibiotic</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain: Convulsions Confusion</td>
<td>Penicillins</td>
<td>Avoid intrathecal route. Caution in patients with histories of convulsions and/or renal failure. Avoid co-administration of quinolones and NSAIDs.</td>
</tr>
<tr>
<td></td>
<td>Cephalosporins Quinolones Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Peripheral nerves: pain, numbness, tingling</td>
<td>Aminoglycosides</td>
<td>Monitor. Alternative drugs may be needed.</td>
</tr>
<tr>
<td>Inner ear (hearing &amp; balance)</td>
<td>Gentamicin Vancomycin Rarely: Erythromycin</td>
<td>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.</td>
</tr>
</tbody>
</table>
## Toxicity associated with antibiotics

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<tr>
<th>Site</th>
<th>Antibiotic</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growing bones &amp; teeth</td>
<td>Tetracyclines</td>
<td>Avoid in pregnant women &amp; children.</td>
</tr>
<tr>
<td>Liver</td>
<td>Erythromycin, Rifampicin, Isoniazid, Rarely: Tetracyclines, Cephalosporins, Co-amoxiclav</td>
<td>Undertake liver function tests if use prolonged. Avoid in people with history of alcoholism.</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Cotrimoxazole</td>
<td>Be alert for severe vomiting and pain radiating to the back. Check blood glucose concentration.</td>
</tr>
</tbody>
</table>
## Toxicity associated with antibiotics-3

<table>
<thead>
<tr>
<th>Site</th>
<th>Antibiotic</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>kidney</td>
<td>Gentamicin</td>
<td>Check serum creatinine and urea to assess renal function before and during therapy. Seek alternative drug in those over 65.</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Ensure adequate hydration,</td>
</tr>
<tr>
<td></td>
<td>Cotrimoxazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rarely: Cephalosporins Penicillins Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>skin (photosensitivity)</td>
<td>Tetracyclines, Quinolones</td>
<td>Avoid prolonged exposure to sunlight.</td>
</tr>
<tr>
<td>bone marrow</td>
<td>Chloramphenicol Cotrimoxazole</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Rarely: Cephalosporins Aminoglycosides</td>
<td></td>
</tr>
</tbody>
</table>
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 effective 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
  – ELISA
  – 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 to determine the infecting organism before the 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
  – Cellulitis 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 in 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 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 absorption of number of antibiotics via the oral route depends on their
  - Acid stability
  - pH of gastric secretions
Rational use of antibiotics

• For example: Oral absorption of Penicillin G

  – Markedly reduced by gastric acid

  – However, in young children and elderly patients, the absorption 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 months of age
• Antibiotics which are excreted by the kidneys may be considerably increased in neonates
  – Penicillin and derivates
  – Aminoglycosides
Rational use of antibiotics

Creatinine clearance (GFR):

\[ \text{CrCl} = \frac{\text{Urine Creatinine (mg/dL)} \times \text{Urine volume (mL/dk)}}{\text{Plasma Creatinine (mg/dL)}} \]
Rational use of antibiotics

• Creatinine clearance may be significantly reduced in older patients even though they have normal urea and serum creatinine level

• In view 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 standards
- Chloramphenicol inactivated by glucronyl transferase in the liver
- If you give large doses chloramphenicol to neonates, high serum levels resulted with GRAY SYNDROME (shock, cardiovascular 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 dysglycemic reactions (hypo and hyperglycemia) 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 absorption 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 IV way, eradicated endocarditis.
Rational use of antibiotics

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

- Rifampin may increase 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
  - Ertymycin, azitromycine
  - Nitrofurantoin
  - Metranidazol can be used 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

- Alkalization 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 demonstrate one of the three types of interactions against a given organism
  - Additive
  - Synergism
  - Antagonism
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 Antibiotic

• Antagonism
• 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
  – Improvement 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!