Team Medicine

35#

Use of antibiotics

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Introduction

Antimicrobials are the 2nd most common drugs prescribed by office-based physicians.

In USA, 1992: 110 million oral antimicrobial Rx written by office based physicians.

Annual antimicrobial drug use rate = 439 /1,000 population.

In Saudi Arabia, there is a 1 in 2 persons has been prescribed to take antibiotics.There are so many antibiotics out there, and organisms are becoming resistant with time. The reason for that is because of antibiotic abuse by either inappropriate choice of antibiotics or the antibiotic itself used without an indication.

Classes of antibiotics are many but these are some of them:

- **Beta lactams: (Inhibit Cell Wall Synthesis; via competitive inhibition of the transpeptidase enzyme)**

1) Penicillins. (30 to 40 antibiotics)
2) Cephalosporins:
- 1st generation: work against gram +ve bacteria.Ex. Cefazolin and Cephalexin
- 2nd generation: work against gram +ve and few of gram –ve bacteria.
Ex. Cefoxitin, Cefaclor and Cefuroxime.
- 3rd generation: work against gram –ve and few of gram +ve bacteria and it is the most used type.Ex. Ceftriaxone, Cefotaxime&Ceftazidime.
- 4th generation: work on the majority of gram –ve.Ex. Cefepime

- **Protein Synthesis inhibitors:**

3) Aminoglycosides: Quinolones.
4) Macrolides:Clarithromycin, Azithromycin.

- **Folic Acid synthesis inhibitors:**

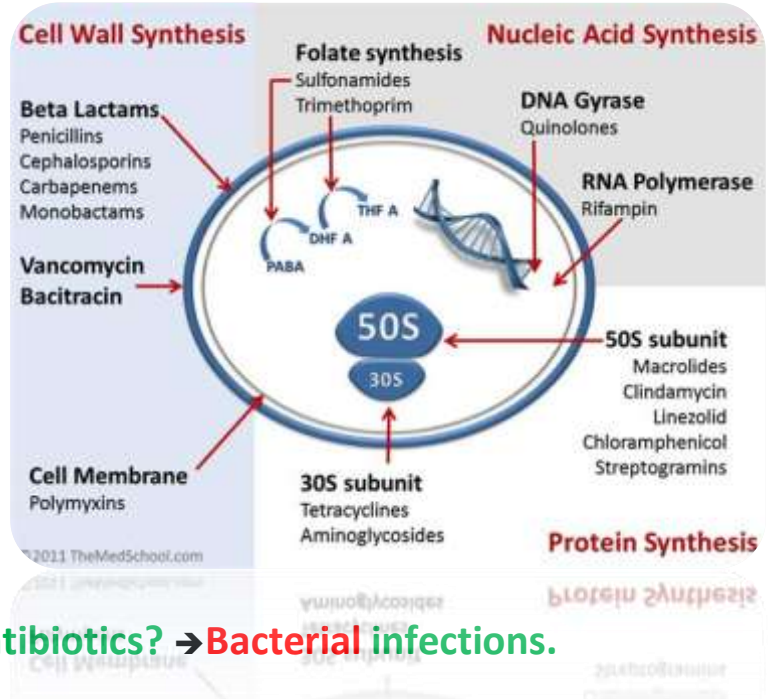
5) Sulfonamides.
Other: Trimethoprim

- **DNA Synthesis inhibitors:**

6) Fluoroquinolones (ex. Ciprofloxacin)
7) Metronidazole

- **RNA Synthesis inhibitors:**

8) Rifampin



❖ **What is the indication for antibiotics? ➔Bacterial infections.**

Case practice:

Would you use antibiotics for the following cases? Justify your answer.

- **A 21-year-old university student presents with fever, body aches, and sore throat.**
  ➔ No, because these symptoms are suggestive for a viral infection (Influenza), the use of antibiotic won't be affective. Moreover, by using antibiotics you will make the patient prone to a complicating resistant bacterial infection.
- **A 54-year-old lady complains of dysuria, frequency, loin pain and fever.**
  ➔Yes, because these symptoms are suggestive for upper urinary tract infection, which is almost always a bacterial infection.
- **A 36-year old man presents with cough, sputum, shortness of breath and fever.**
  ➔ Yes, because shortness of breath indicates that this is a serious infection despite the fact that you do not know if this was a bacterial or not. Why? Serious infections are one of the indications of antibiotics.

Indications for Antibioticsuse:

1. Definite or probable bacterial infection.

2. Serious infections. (Life-threatening infections like meningitis, septicemia and pneumonia; even if there is a probability that it is non-bacterial)

3. NOT FEVER !(Fever without any evidence of bacterial infection is NOT an indication for antibiotic use)

Where is the focus of infection? – Selection of Antibiotic:

1) **Clinical Assessment:**

Usually patients come to you with systemic manifestation of an infection, like; fever and fatigue and some of the focal symptoms of that infection.

Before giving antibiotics you should ask yourself where is the focus of this infection?

To determine the focus you should mainly do clinical assessment through history and physical examination. The chief complain usually determines the focus of this infection. (For example if a patient comes to you with fever and cough, coughs the main complaint. So, it is a probable chest infection like for example; pneumonia.)

The next step is to take samples from the site of infection. The samples needed are usually cultures and smears.

2) **What is the likely organism? - To determine the pathogen:**

1. **Determine the focus of infection.** **Ex. Meningitis is commonly caused by pneumococci and meningococci.**
2. **Type of the pathogen through gram stain.** **(Positive or negative)**
3. **Patient's age.** **Some infections are more common in certain ages, like meningitis of neonates is commonly caused by e-coli.**
4. **Epidemiological setting.** **Is it a community-acquired infection? Or a hospital acquired infection?**
5. **Prior culture data.** **If a patient comes to you with an infection (UTI for example) while having a previous history of an infection, it is assumed that it is because of the same organism (Relapse); you should start treat accordingly. However, a culture is still needed to confirm it.**

What is the commonest cause of the followings?! - Empiric Assessment -

- **Urinary tract infection:** **E.coli, staphylococcus, strep. Pyogenes and other gram –ve.**
- **Cellulitis:** **Staph. aureus or strep. aureus.**
- **Biliary infection:** **Mostly Gram –ve like: E.coli, klebsella, Protues, pseudomonas. You may also get anaerobes in old patients.**
- **Meningitis:** **N.menigitidis or pneumococcal. But remember viral causes also very common.**
- **Septic arthritis:** **Bone and joints commonly infected by Staph. aureus.**
- **Nosocomial pneumonia:** **Gram –ve bacilli pseudomonas.**

Before culture results treat with wide-spectrum antibiotics like Tazobactam, which will mostly cover every type [Empirical Treatment].

After the emergence of culture results …

After 48 hours ⇨ Check culture results ⇨ Start then to narrow the antibiotic coverage in order to reduce wide-spectrum antibiotics' complications and to prevent killing the normal flora.

Like what happens in *Clostridium difficile diarrhea* which is a result of using broad spectrum antibiotics (such as clindamycin, Fluoroquinolones, Cephalosporins…) that disrupt normal intestinal flora and competing bacteria in the gut leading to an overgrowth of C. difficile which is the most common cause of pseudomembranous colitis, and in rare cases this can progress to toxic megacolon, which can be life-threatening.

Infection Vs. Colonization:

An infection means that germs are in or on the body and make you sick, which results in signs and symptoms such as fever, pus from a wound, a high white blood cell count, or pneumonia.
Germs can also be in or on the body, but not make you sick. This is called colonization. People who are colonized will have no signs or symptoms!.

For example: MI Patient in ICU was intubated when they took a sample from his trachea it shows pseudomonas without any evidence of infection, signs and symptoms, this we call it colonization but not infection. So ➔ we don't treat him! Also, when we culture the skin or throat and we find staph aureus but the patient has no symptoms, this means he is colonized but not infected, thus we don't need to treat him.

So, Do NOT treat colorizations, always target infections only!

*** Exception! If the patient is immunocompromised, we should treat him using antibiotics.**

Other factors for antibiotic selection:

1. **Culture results.**
2. **Tissue penetration.** This is an important factor!
   For example, when a patient come to the ER with head trauma, and theinvestigations revealed that he is infected by gram-negative bacillus in the meninges, so he has a gram-negative meningitis, would you give him Aminoglycoside?
   ➔No, although it is good in treating gram negative bacilli, they do not penetrate the blood brain barrier, so they shouldn't be used in such a case.
   Thus, it is important to be sure that the antibiotic reach the site of infection in adequate concentration to kill the organism.
3. **Bactericidal Vs. Bacteriostatic.**
   "Bacteriostatic" means that the agent prevents the growth of bacteria (i.e., it keeps them in the stationary phase of growth), and "Bactericidal" means that it kills bacteria.
   It is not that important in general infections but it is important if the infection in a site where the neutrophils can't reach in adequate quantities (like in CNS infections, Endocarditis, Neutropenia…) in these cases bactericidal is more preferable to use.
4. **Renal disease.**
   We should avoid drugs the primarily excreted by the kidney. (Ex. Aminoglycoside, vancomycin…)
5. **Liver disease.**
   We should avoid drugs the primarily excreted by liver through the bile. (Ex. clindamycin, INH, tetracycline, rifampicin, chloramphenicol…)
6. **Pregnancy & lactation.**
   We must avoid drugs that are toxic to the fetus.
   Beta lactams generally SAFE to use in pregnancy.

- **FDA Pregnancy Categories:**
  The FDA has established five categories to indicate the potential of a drug to cause birth defects if used during pregnancy.
  1. Category A: The possibility of fetal harm appears remote. Extremely few drugs exist in this category (e.g. multiple vitamins).
  2. Category B: If there is a clinical need for a drug in this category they are considered safe to use. Examples: acetaminophen, amoxicillin.
  3. Category C: These drugs should be given only if the potential benefit justifies the potential risk to the fetus. Examples: Fluoroquinolones, gentamicin, saccharin, aspirin.

4. **Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk. They should only be used in pregnancy when the alternatives are worse. Examples: tetracyclines, ACE inhibitors, most antineoplastics.**
5. **Category X: The risk of use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are, or may become pregnant. Examples: thalidomide, oral contraceptives, statins.**

Dosing of antibiotics depends on:

1. **Minimum inhibitory concentration (MIC): is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism, and it is used not only to determine the amount of antibiotic that the patient will receive but also the type of antibiotic used, which in turn lowers the opportunity for microbial resistance to specific antimicrobial agents.**
2. **Half-life of drug: The time required for the concentration of a drug to fall to half of its initial concentration after reaching its peak.**
3. **Patient factors: Age, gender, etc. (For example in elderly patients we cut down the dose because creatinine clearance tend to decline with age).**

Duration of therapy:

We should complete the duration of using the antibiotic in order to prevent relapses. For Example: Upper UTI needs 10 days while lower UTI 3-5 days, bone infections and endocarditis need about 6 weeks. The duration depends on the site of infection not the organism causing it, but there is special organisms that need long duration of therapy like TB; pulmonary TB usually needs 6 months while extra-pulmonary (Brain, bone..) between 9-12 months.

Antibiotic combinations:

- **Indications:**
  1. **Sepsis of unclear etiology.**
  2. **Febrile neutropenia.**
  3. **Prevent emergence of resistance. (like what we do in TB, we start with 4 drugs assuming that the organism resistant to one of them, then we cut them down into two)**
  4. **Polymicrobial infection.**
  5. **Synergy. (Ex. Endocarditis will require combination of penicillin and beta lactam inhibitors)**

- **Disadvantages:**
  1. **Elimination of normal flora.**
  2. **Colonization by resistant organisms. (Usually, when we take a blood sample from patient using multiple antibiotics and we culture it, we find candida which is hard to be treated).**
  3. **Drug toxicity.**
  4. **Cost.**

Failure of therapy:

- **Patient factors:**
  1. **Poor compliance.**
  2. **Complications of the disease that prevent the response (for instance; in pneumonia, there are two complications that make the patient not responding to the antibiotic: (1) Bronchial obstruction that preventsinflammatory exudates and pus from coming out and if the patient had a closed abscess it cannot be treated by antibiotics and instead by surgical drainage. (2) Empyema (pus in pleura) when patient develop this complication, he will never respond until we put a chest tube and drain it.**
- **Drug factors:**

  Inadequate penetrationof the infection site is one of the principal factors related to failure of antibacterial therapy. The active drug needs to reach the bacteria in appropriate body fluids and tissues at concentrations necessary to kill or suppress the pathogen's growth.

- **Organism factors:**

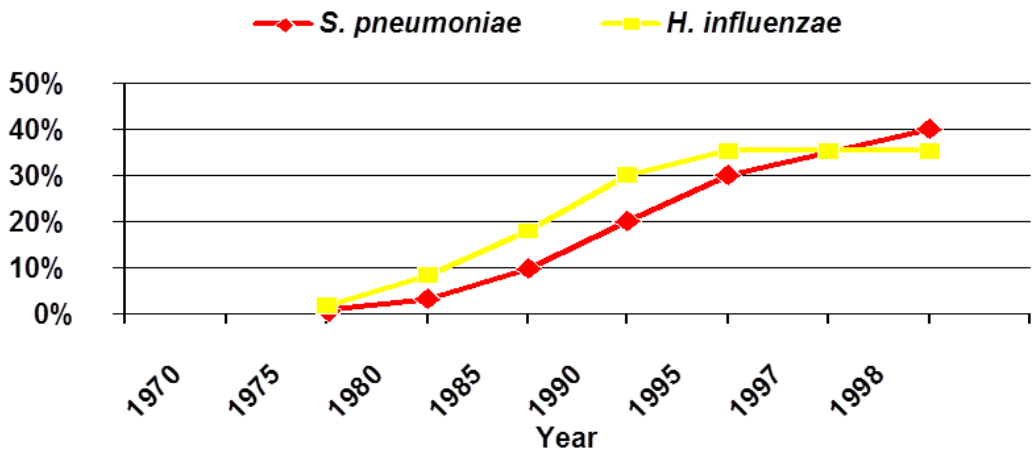
  Resistance to the antibiotics.

History of Resistance:

Antibiotic	Discovered	Introduced into Clinical Use	Resistance Identified
Penicillin	1940	1943	1940
Streptomycin	1944	1947	1947
Tetracycline	1948	1952	1956
Erythromycin	1952	1955	1956
Vancomycin	1956	1972	1987
Gentamycin	1963	1967	1970

From the table, comparing between discovered year and when resistance identifies, we can see that the resistance developed rapidly within just few years.

Increasing Antibiotic Resistance:



A study done at KKUH shows that the resistance of pneumococci increased into about 45% to penicillin among infected patients.

Antibiotic Resistance:

- **Current problems with antibiotic resistant bacteria include:**
  1. **MRSA:**
     37% of all bloodstream isolates of S. aureus are now MRSA.
  2. **Resistance in respiratory pathogens:**
     2.2% of S. pneumoniae are penicillin-resistant. ~15-20% of H. influenzae are amoxicillin-resistant.
  3. **Multi-resistant Gram-negative bacilli:**
     Extended-spectrum β-lactamase producers.
  4. **Glycopeptide-resistant enterococci:**
     21.6% of bloodstream isolates of E. faecium. 3.3% of E. faecalis.
  5. **MDR-TB:**
     6.2% of M. tuberculosis isoniazid-resistant. 1% is true MDR strains.

When to stop treatment?

1. **When infection is treated.**
2. **When infection is not diagnosed.**
3. **When infection is unlikely.**

Hospital control:

Monitor and evaluate empiric, therapeutic & prophylactic use;

1. **Prescriptions include type of treatment: E/T/P**

⇢ **Time limits:**

- **Empiric: 3 days.**
- **Prophylactic: 2 days.**
- **Therapeutic: 7 days.**

2. **Extension requires justification written by the prescribing physician.**

Restriction of Drugs classified as:

A. **Uncontrolled: available for treatment by all physicians.**
B. **Monitored: available but usage monitored through system.**
C. **Restricted: available only after consultation with ID specialist or limited list of MD.**

Summary

Classes of antibiotics are many but these are some of them:

- **Beta lactams**: Inhibit Cell Wall Synthesis (Penicillins, Cephalosporins), **Protein Synthesis inhibitors** (Aminoglycosides, Macrolides), **Folic Acid synthesis inhibitors** (Sulfonamides, Trimethoprim), **DNA Synthesis inhibitors** (Fluoroquinolones, Metronidazole), **RNA Synthesis inhibitors** (Rifampin)
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Indications for Antibiotics use:

1. Definite or probable bacterial infection. 2. Serious infections. 3. NOT FEVER !

Selection of Antibiotic:

1- **Clinical Assessment2- What is the likely organism?** (Determine the focus of infection, gram stain, Patient's age, Epidemiological setting, Prior culture data)
- You should know ***the commonest cause of the infections*** to be able to start the ***empirical treatment*** (for this we usually use broad-spectrum antibiotics).
- After 48 hours >> Check culture results >> Start then to narrow the antibiotic!
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Infection Vs. Colonization:

- Infection >> signs and symptoms >> **treat**.
- Colonization >>**NO** signs and symptoms >>**DON'T treat**(except in immunocompromised pts.).
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Other factors for antibiotic selection:

-Culture results. -Tissue penetration (e.g. BBB). -Bactericidal Vs. Bacteriostatic (low neutrophils or if they are unable to reach the infection >> bactericidal is preferable) -Renal disease. -Liver disease -Pregnancy & lactation (category A to X).

Dosing of antibiotics depends on:

1- Minimum inhibitory concentration (MIC)>>**to avoid resistance.**
2- Half-life of drug
3- Patient factors: Age, gender, etc.

Duration of therapy: mainly depends on the site of infection and sometimes depends on the organism.

Antibiotic combinations:

Indications:1. Sepsis of unclear etiology. 2. Febrile neutropenia. 3. Prevent emergence of resistance.4. Polymicrobial infection. 5. Synergy.

Disadvantages: 1. Elimination of normal flora. 2. Colonization by resistant organisms. 3. Drug toxicity. 4. Cost.

Failure of therapy:

- **Patient factors:** (Poor compliance, Complications of the disease).
- **Drug factors:** (Inadequate penetration).
- **Organism factors:** (Resistance to the antibiotics).

- **Stop the treatment when the infection is treated, not diagnosed or unlikely.**

Restriction of Drugs classified as:

A.**Uncontrolled**: available for treatment by all physicians.

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Questions:

1/ Which of the following is the best definition of 'Antibiotics'?

A. Chemicals produced by microbes that inhibit or kill other microorganisms
B. Chemicals produced by microbes that inhibit or kill other microorganisms but are relatively harmless to eukaryotes
C. Chemicals that inhibit or kill microorganisms
D. Chemicals that inhibit or kill bacteria
Explanation: Whilst often used interchangeably with the term 'Antibacterial', the word 'Antibiotic' actually refers specifically to naturally produced antibacterial chemicals. If the substance is also harmful to eukaryotes it is still an 'antibiotic' in this sense, though not a clinically useful one!
(Answer:A)

Q2/Penicillin and Gentamycin, two different classes of antibiotic, have been shown to engage in _____ with each other in certain infections

A. Indifference
B. Antagonism
C. Synergism
Explanation: These two antibiotics display synergism when given together in certain infections - increasing their effectiveness to a level greater than the sum of their parts (Answer:C)

Q3/ Which of the following B-lactam antibiotics has the broadest spectrum?

A. Benzylpenicillin
B. Meropenem (Imipenem)
C. Amoxicillin
D. Cefuroxime
(Answer:B)

Q4/ The main problems with the B-lactam antibiotics is/are

A. Bone marrow depression / neutropenia
B. Renal impairment
C. Allergic reactions
D. Narrow therapeutic window
(Answer:C)

Q5/ Treatment for MRSA

A. Flucloxacillin
B. Metronizadole
C. Benzylpenicillin
D. Vancomycin
(Answer:D)

Q6/ Which of the following is NOT true regarding Benzylpenicillin

A. It is also known as Penicillin G
B. It must be administered parentally
C. It is mainly effective against gram positive bacteria
D. It is a broad spectrum antibiotic
(Answer:D)

Q7/ Which of the following would be most effective in treating a gram negative infection?

A. Amoxicillin
B. Gentamicin
C. Vancomycin
D. Daptomycin
(Answer:B)

Q8/ Which of the following would be safe to give in patients with a severe penicillin allergy?

A. Aztreonam
B. Co-Amoxiclav
C. Cefalexin
D. Flucloxicillin
Explanation: On the whole, cephalosporins should be avoided in patients with serious penicillin allergies (10% will also be allergic to cephalosporins) but Aztreonam is considered safe as it does not have a bicyclic nucleus (Answer:A)

Q9/ What is the first-line treatment for MRSA?

A. Methylpenicillin
B. Doxytetracycline
C. Gentamicin
D. Vancomycin
(Answer:D)