

Use of Antibiotics

435 medicine teamwork

[**Important** | **Notes** | Extra | **Editing file**]

lecture objectives:

⇒ not given

Done By: Dalal Al Huzaimi & Nouf
Alabdulkarim

Edited By: Rawan Aldhuwayhi

Revised By: Omar Alsulaiman

References: Doctors' Slides

Antibiotic use

Important considerations when prescribing antibiotics:

1	Obtain accurate diagnosis of the infection. (logically don't prescribe antibiotics if you are not dealing with infection)
2	Empiric "expectation with background and experience" and definitive therapy.
3	Identifying opportunities to switch to narrow-spectrum. (After starting with broad spectrum you will shift them to a narrow spectrum after you know what you are dealing with).
4	Cost-effective oral agents for the shortest duration necessary. (if the price was cheap this will encourage the patient to continue the whole course).
5	<p>Understanding drug pharmacodynamics and efficacy at the site of infection. (knowing that this antibiotic cover the causative bacteria is not enough you have to know whether this antibiotic reaches the site of it colonization "bone, brain, peritoneum... etc.")</p> <p><u>Examples:</u></p> <ul style="list-style-type: none"> A- in staphartharitis both cefazolin "1st generation cephalosporins" and cloxacillin are covering staph, but which one of them goes to the joint? B- gentamicin and gram negative bacterial infection in the brain? gentamicin is one of the best drugs covering gram negative bacteria but it doesn't cross the BBB.).
6	Host characteristics that influence antimicrobial activity. (if the patient has renal failure or liver disease, you should adjust the dose of the antibiotic in accordance with their case).
7	Adverse effects of antimicrobial agents on the host. (warning the patient that they might have side effects and in such case they have to stop the AB because some of these side effects are very serious).

1 Obtaining an Accurate Infectious Disease Diagnosis

- Determining the site of infection (from the features of his presentation through taking a good Hx and Ex)
- Defining the host (e.g., immunocompromised or immunocompetent)
- Establishing, when possible, a **microbiological diagnosis**
 - especially for: Endocarditis, septic arthritis, meningitis "in these 3 emergency cases you have to dig in the Hx of the patient and don't go with empirical AB before taking a specimen? Because if you start a broad spectrum AB and then you do culture you won't get anything".
- Additional investigations to exclude noninfectious diagnoses (you need to be good in medicine to know that the fever of some patient is noninfectious).
- Microbiological diagnosis : Bacterial or fungal culture or Serologic testing
- Frequently the "Most likely" microbiological etiology can be inferred from the clinical presentation:
 - Cellulitis (streptococci or staphylococci) **No need for positive culture.** "never diagnose a pt. with Cellulitis based on culture it's costly and no need for it".



Is An Antibiotic Indicated?

Clinical diagnosis of bacterial infection.
 Pneumonia (CAP) can also be treated empirically— Macrolide or fluoroquinolone antibiotic—without performing specific diagnostic test
 pts. with CAP from minute one in the ER put them in AB and no need for culture because it either caused by streptococcus or atypical and no need for sputum culture with most cases that doesn't need admission".



Timing of Initiation of Antimicrobial Therapy:	
<u>Urgent:</u>	<u>Non-urgent:</u>
<p>1) Acute meningitis 2) Septic shock 3) Febrile neutropenia.</p> <p>Empiric therapy should be initiated immediately after or concurrently with collection of diagnostic specimens.</p> <ul style="list-style-type: none"> - They can't wait. 	<p>Febrile and stable patient with fever for several days with no clue to diagnosis.</p> <p>In more stable clinical circumstances, hold antibiotics until appropriate specimens have been collected and submitted.</p> <p>Example: subacute bacterial endocarditis\ multiple sets of blood cultures.</p>

►CASE SCENARIO:

a 16 year old boy who presented with 3 days H/O of high grade fever and severe headache. examination revealed T: 39 and neck stiffness, otherwise fully conscious and has no neurological deficit : What is the most appropriate steps of approach:

- A) Start combination of antibiotic and arrange for CSF study
- B) Arrange for urgent CT-scan brain
- C) Perform urgent Lumbar Puncture and give the first dose of antibiotics
- D) perform urgent LP and if CSF is abnormal ,start RX

..... A OR C

- Depending on the time and the facility that you have. Giving AB should be your first concern rather than doing LP "to know the organism so u can decide the course the AB"
- Empirical AB in such case might change the culture but it definitely won't change the gram stain,
- Physician aim in meningitis is to save the patient's life before getting a diagnosis.
- Incase the pt. was febrile for long time and he is stable why would you start with empirical AB, you have to wait and see him after week like subacute bacterial endocarditis.
- Draw the specimen that you need before giving AB in non urgent cases
- **Any AB that is NOT indicated is contraindicated.**

Patient was prescribed a dose of : ceftriaxone and vancomycin; urgent LP was done:

- Results:
 - o WBC : 1230 cells/mm...90% polymorph..
 - o RBC : NIL
 - o Gram stain: Gram positive intracellular diplococci..
- What you will do? To continue the same antibiotics? Yes or No. "the answer is No, we have to take out the unnecessary AB (ceftriaxone cross the BBB, vancomycin used to cover other organisms "some pneumococcal are resistance to ceftriaxone which is known by knowing the epidemiology of the hospital from the microbiology through annual report about the sensitivity of the bacteria to all Abs in KSA".
- Premature initiation of antimicrobial therapy, **any harm** ?
 - o can suppress bacterial growth
 - o May preclude the opportunity to establish a microbiological diagnosis
 - o Requires several weeks to months of directed antimicrobial therapy to achieve cure.

2 Empiric and definitive therapy:

- Microbiological results do not become available before **24 to 72 hours**.
- Empiric and guided by the **clinical presentation**.
- Inadequate therapy for infections in critically ill, hospitalized patients are associated with **greater morbidity and mortality** "any patient dies from an infection is mismanaged, either they come late or they aren't given the right care: right AB in the right Dose and Duration".
- **Use broad-spectrum** antimicrobial agents as initial empiric therapy "giving a narrow spectrum AB as empiric therapy will leave the patient with huge number of organisms that might kill him".

What organisms are likely to be responsible?

- Based on: Hx & P.E. You might have a clue to DX.
- Epidemiological data: Hospital-acquired vs. community-acquired, Prior antibiotic use
- Examples:
 - Patient with dyspnoea and cough: Streptococcal pneumonia and atypical organism
 - Patient with fever and urinary symptoms : E.coli
 - Patient with erythema over the right leg associated with pain and tenderness: Group A Streptococcus and Staphylococcus
 - **The most common causative organism of septicarthritis in western university aged patients is gonorrhea. However, in adults worldwide it is staph.**

Hospital-acquired infections

Related to the presence of invasive devices and procedures: “mostly catheter related”

- A. Catheter related bacteremia: **Coagulase negative staph** “most common, followed by Coagulase positive staph”, Methicillin-resistant Staphylococcus aureus [MRSA] “treatment of choice for MRSA if it is in the community is vancomycin, but in if it was hospital acquired It doesn’t respond to any AB”,
- B. Catheter related UTI: Gram negative (eg, Pseudomonas aeruginosa) if in the community it is mostly caused by E.coli.

3 Identifying opportunities to switch to narrow-spectrum

Once:

- 1) Microbiology have identified the etiologic pathogen
- 2) Antimicrobial susceptibility data are available

⇒ Then every attempt should be made **to narrow the antibiotic spectrum:**

- It can reduce cost and toxicity.
- Prevent the emergence of antimicrobial resistance in the community.

Interpretation of Antimicrobial Susceptibility Testing Results:

Antimicrobial Susceptibility Testing (AST):

- Antimicrobial susceptibility testing **measures the ability of a specific organism to grow in the presence of a particular drug in vitro: susceptible, resistant, or intermediate** “in vitro testing”.
- Data are reported in the form of **minimum inhibitory concentration (MIC)**: The lowest concentration of an antibiotic that inhibits visible growth of a microorganism. “how much dose do I need to kill the bacteria”.
- Susceptible: indicates that the isolate is likely to be inhibited by the usually achievable concentration of a particular antimicrobial agent when the recommended dosage is used
- Different antibiotics has different MIC,
- LIMITATION.

►CASE SCENARIO:

a 23 years old man who has done a surgery at the base of the skull After trauma “organism is most likely to be staph”. Presented few days later with meningitis, CSF has revealed: WBC 1200 mainly poly, Culture: **staph aureus**, RX: cephazolin it does not achieve therapeutic concentrations in the CSF. “the site is the 1st information that u have to know”.

Bactericidal vs Bacteriostatic Therapy:

Bactericidal:

Causes death and disruption of the bacterial cell.

Drugs act on:

- The cell wall: β -lactams
- Cell membrane: Daptomycin
- Bacterial DNA: Fluoroquinolones

Preferred in the case of **serious infections** such as **endocarditis**, **pneumonia** & **meningitis** to **achieve rapid cure**.

Bacteriostatic:

Inhibits bacterial replication without killing the organism.

Act by inhibiting protein synthesis, such as:

- Sulfonamides,
- Tetracycline,
- Macrolides.

Quick Hit about Antimicrobial Combinations (Why & When to use it):

Why to use it? Exhibits **synergistic activity**.

When? it is used in the treatment of serious Infections:

A. **Rapid killing is essential:**

Endocarditis caused by Enterococcus species with a combination of penicillin and gentamicin: bactericidal activity.

B. **shorten the course:**

Endocarditis due to viridans group streptococci, A combination of penicillin or ceftriaxone with gentamicin for 2 weeks can be as effective as penicillin or ceftriaxone alone for 4 weeks).

C. **critically ill patient:**

Give Empiric therapy for **Septic shock**, blood cultures are reported to be **growing gram-negative bacilli**, it would be appropriate to provide initial therapy with 2 agents that have activity against gram-negative bacilli, particularly P aeruginosa

D. **Polymicrobial Infections:**

Antimicrobial combinations, such as a **third-generation cephalosporin** or a **fluoroquinolone** plus **metronidazole**, can be used as a potential treatment option in these cases and can sometimes be more cost-effective than a comparable single agent (eg, a carbapenem).

4 Cost-effective oral agents for the shortest duration necessary:

- **Candidates for treatment of mild to moderate infections.**
- **well-absorbed oral antimicrobial agents:**
 - A. Pyelonephritis → Fluoroquinolones
 - B. Community-acquired pneumonia → Augmentin and macrolides coverage.
- **Bioavailability:** The percentage of the oral dose that is available unchanged in the serum.
 - Examples of antibiotics with excellent bioavailability are: Trimethoprim-sulfamethoxazole.

5 Understanding drug pharmacodynamics and efficacy at the site of infection:

▲ **NOTE:** The efficacy of antimicrobial agents depends on: their capacity to achieve Concentration equal to or greater than the MIC (minimum inhibitory concentration) at the site of infection

Ocular fluid, CSF, abscess cavity, prostate, and bone are often much lower than serum levels, For example:

- A. First- and second- generation cephalosporins do not cross the blood-brain barrier.
- B. Aminoglycosides: are less active in: 1- low-oxygen, 2- low-pH type of **Abscesses**
- C. Fluoroquinolones: achieve high concentrations in the prostate,
 - preferred oral agents for the **treatment of Prostatitis**.
- D. Moxifloxacin: does not achieve significant urinary concentrations, therefore **not suitable** for treatment of **UTIs**.

6 Host characteristics that influence antimicrobial activity:

Host Factors to Be Considered in Selection of Antimicrobial Agents:

1] Renal and Hepatic Function,

2] Pregnancy and Lactation:

Special considerations .. **teratogenicity** or otherwise **toxic** to the fetus:

Drug	Risk
Sulphonamides:	A risk to develop kernicterus , especially <u>preterm infants</u> .
Tetracycline:	Staining of the teeth see here
Fluoroquinolone:	Cartilage damage to the fetus.
Thalidomide: very effective antiemetic that was used to: - <u>treat morning sickness</u> - <u>emesis in pregnant women</u> .	Phocomelia: The biggest man-made medical disaster ever, Over 10,000 children were born with a range of <u>severe</u> and <u>debilitating malformations</u> . see here .

3] History of Allergy or Intolerance:

- **Penicillin** and anaphylaxis.

4] Consider Special Host Factors:

- Genetic e.g. G6PD
- Renal function,
- Liver function,
- Drug interaction.

Assessment of Response to Treatment:

Response to treatment of an infection:

- a. Clinical parameters.
 - i. **improvement of symptoms and signs:** (eg, fever, tachycardia, or confusion)
- b. laboratory values.
 - i. **decreasing leukocyte count.**
 - ii. **radiologic decrease in the size of an abscess.**

Antimicrobial Agents as Prophylactic:

1. Presurgical Antimicrobial Prophylaxis:

- used to reduce the incidence of postoperative surgical site infections.
- A single dose of a **cephalosporin** (such as **cefazolin**) administered within 1 hour before the initial incision is appropriate for most surgical procedures

2. Prevent Transmission of Communicable Pathogens to Susceptible Contacts:

- **ciprofloxacin** for close contacts of a patient with **N.meningitidis**.

3. Antimicrobial Prophylaxis Before Dental Procedures:

- Prosthetic valves, Rheumatic heart.. to prevents Endocarditis.

Non Infectious Causes of fever:

Some Examples:

Adult onset Still disease | Drug induced fever | fever associated with pulmonary embolism | lymphoma.

Treatment of a Positive Clinical Culture in the Absence of Disease:

- **Colonization** without any associated manifestation of disease occurs frequently in certain populations:
⇒ Colonization of:
 - 1- Old women with indwelling urinary catheter: Active infection are absent (asymptomatic bacteriuria).
 - 2- Endotracheal tubes in mechanically ventilated patients.
 - 3- chronic wounds.

The Appropriate Dose :

- The **lowest dose** that is **effective**.
- Avoid sub-therapeutic doses.

Determined by	Modification Principles
<ul style="list-style-type: none">○ Serious vs non-serious infections○ Site of infection○ Drug PK/PD properties○ Other host factors (e.g. renal function ... etc.)	<ul style="list-style-type: none">○ Narrow vs broad spectrum agents,○ Least toxic agent○ Cheaper.

New VS Current Antimicrobial Agent:

Know:

- approved indications.
- advantages vs disadvantages.
- basic pharmacokinetics
 - serum T $\frac{1}{2}$
 - activity at various site
- common adverse effects.

Criteria for Use of New Agent:

- Antimicrobial activity is superior,
- Have a therapeutic advantage,
- Better pharmacokinetics
 - Site penetration
 - Longer t $\frac{1}{2}$
 - Shorter duration
- Less toxic.
- Better tolerance.

The Four Moments of Antibiotic Decision-Making:

1. Does my patient have an infection that requires antibiotics?
2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?
3. A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy?
4. What duration of antibiotic therapy is needed for my patient's diagnosis?

Conclusion:

Appropriate use of antimicrobial agents involves:

- Obtaining an accurate diagnosis,
- Determining the need for and timing of antimicrobial therapy,
- Understanding how dosing affects the antimicrobial activities of different agents,
- Tailoring treatment to host characteristics,
- Sign for the narrowest spectrum and shortest duration of therapy, and: switching to oral agents as soon as possible.
- Non-antimicrobial interventions, such as abscess drainage, are equally or more important in some cases and should be pursued diligently in comprehensive infectious disease management.

MCQs

1 - An 18 years old boy presented to the family physician complaining of fever, headache, painful throat, vocal hoarseness, dry cough, running nose, general malaise 3 days ago. An oral temperature was measured to be 38.8 C. The physician immediately prescribed a combination of penicillin and gentamicin for 2 weeks. 1 week later, the boy came with worsening symptoms and persisting fever. What was the mistake the physician committed?

- A - Antibiotics shouldn't be combined at all.
- B - He prescribed antibiotics that must not be used at the age.
- C - Inappropriate use of empirical antibiotics without an evidence of a bacterial infection.
- D - The physician started an oral preparation while it should be administered intravenously.

2 - Which one of these cases is not a clear indication for the use of prophylactic antimicrobial agents to reduce the risk of developing infection?

- A - A 68 year - old male with a prosthetic heart valve who will undergo an invasive dental procedure.
- B - A susceptible close contact person with a meningitis patient infected with Neisseria meningitides.
- C - A 35 year - old woman with a central venous catheter placed to deliver chemotherapy for treatment of breast cancer.
- D - A 70 year old woman with a brain tumor, which is going to be removed surgically tomorrow .

3 - A three year old girl presents to the emergency department with a two day history of headache, nausea, vomiting and fever. She was seen by a physician two days ago who diagnosed otitis media. At ED She was conscious, alert and complains of pain over the neck area. On examination she has pain on flexion of the neck, a clinical diagnosis meningitis has been made. What is the most appropriate action to do in this case?

- A - Start a regimen of empirical antibiotics then do a lumbar puncture later.
- B - Start an empirical regimen of antibiotics immediately after or concurrently while taking a diagnostic CSF specimen by a lumbar puncture.
- C - Start Ceftriaxone + Vancomycin immediately and LP is not needed since the clinical scenario is clear for Neisseria meningitides and S.pneumoniae especially this age group.
- D - Lumbar puncture and bacterial culture should be done first to select the antimicrobial regimen based on the results.

4 - Which of the following is the most important cause of the widespread emergence of antimicrobial resistance?

- A - The lack of commitment in following the guidelines in selecting the appropriate agents.
- B - The common use of broad spectrum antibiotics in urgent cases that need the use of empirical agents.
- C - The use of antimicrobial agents for short courses .
- D - The inappropriate use of antimicrobial agents.

1-The answer is (C),antibiotics use should be absolutely limited for cases with clear evidence of an infection either clinically such as in case of community acquired pneumonia or by a laboratory confirmation with a microbiological diagnosis. In this case, the patient is complaining of typical upper respiratory tract symptoms which is most of the time caused by a self-limiting viral infections. Thus the use of antibiotics here is inappropriate due to the absence of clear evidence.

2-The answer is (C),according to guidelines, prophylactic use of antibiotics is indicated before dental operations such as in A, as well as in close contacts for meningitis patients such as in B,and in pre-surgical patients to prevent surgical site infection such as in D, while there is no indication to use prophylactic antibiotics before the use of central venous catheter. In this case, following the hygiene guidelines and using sterilized instruments would be enough.

3-The answer is (B),in cases of unstable and extremely ill infected patients, the delivery of empirical antibiotics should be started immediately just after taking the specimen as it can be lethal if delayed. At the same time you need to do a microbiological diagnosis to narrow the spectrum of antibiotics once the lab results are ready. Therefor the most appropriate action would be starting the antimicrobial agents immediately after collecting the specimen. Whenever the lab results are ready, empirical agents can be exchanged by narrow spectrum agents.This should be applied in septic shock and febrile neutropenia as well.

4-The answer is (D),the inappropriate use of antibiotics has largely contributed to the emergence of antimicrobial resistance. Bacteria are able to undergo mutations aiming to be resistant against the type of antibiotic used inappropriately. Inappropriate use of antibiotics include using them with no indications such as in viral URTIs, using them in long courses and the use of broad spectrum antibiotics while they are not needed.