Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

# Use of Antibiotics

## Objectives :

No objectives were found.

## Done by :

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# Antibiotics

Chemical produced by:

1) A microorganism:

Antibiotics are secondary metabolites produced by microorganism such as bacteria, fungi, and actinomycetes as their natural defense system against other microbes living in their vicinity.

2) Synthetics:

that kills or inhibits the growth of another microorganism.

-Isolation of antibiotics from microorganism is much easier than chemical synthesis of these compounds.

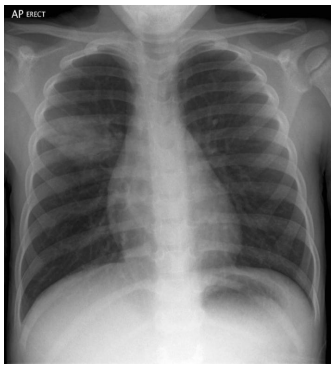
# Important considerations when prescribing antibiotics:

1. Obtain accurate diagnosis of infection.
2. Empiric and definitive therapy.
3. Identifying opportunities to switch to narrow-spectrum. Specific to organism
4. Cost-effective oral agents for the shortest duration necessary.
5. Understanding drug pharmacodynamics and efficacy at the site of infection. E.g. can cross BBB?
6. Host characteristics that influence antimicrobial activity. Renal impairment? Liver disease?
7. Adverse effects of antimicrobial agents on the host.

# Obtaining an Accurate Infectious Disease Diagnosis:

- Determining the site of infection
- Defining the host (e.g., immunocompromised)
- Establishing, when possible, a microbiological diagnosis.
- Especially for: Very serious conditions, need to know the organism
  - **Endocarditis**
  - **Septic arthritis** (staph most common)
  - **Meningitis**
- Additional investigations to exclude noninfectious diagnoses
- Microbiological diagnosis :
  - Bacterial or fungal culture or Serologic testing
  - Swab is not as effective as pus ,body fluid or tissue culture
- Frequently the Most likely microbiological etiology can be inferred from the clinical presentation: Cellulitis (streptococci or staphylococci) No need for positive culture. In less serious cases like cellulitis, use antibiotics against the most common organism.

## Use of antibiotics:




- Is an antibiotic indicated?
  X-ray shows consolidation (pneumonia), either hospital or community acquired.
- Clinical diagnosis of bacterial infection.

Pneumonia (CAP):

usually caused by streptococcus pneumoniae or by atypical organism such as: legionella, mycoplasma

Can be treated empirically:
(macrolide for atypical organism or fluoroquinolone for streptococcus pneumoniae antibiotic) without performing specific diagnosis test.

## Timing of Initiation of Antimicrobial Therapy:

| Urgent situation: | Non urgent |
|---|---|
| - Acute meningitis<br>- Septic shock<br>- Febrile neutropenia<br><br>In these cases ALWAYS use empirical treatment (according to epidemiology of hospital) you might lose the patient if you don't act quickly. | - In more stable clinical circumstances.<br>- febrile and stable patient with fever for several days with no clue to diagnosis.<br>- subacute bacterial endocarditis, must take multiple sets of blood cultures |
| Empiric therapy should be initiated immediately after or concurrently with collection of diagnostic specimens | Hold antibiotics until appropriate specimens have been collected and submitted |

## Urgent vs Non urgent?:

16 year old boy who presented with 3 days H/O high grade fever and severe headache, examination revealed T: 39 and patient has 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 LP and give the first dose of antibiotics.
D) Perform urgent LP and if csf is abnormal ,start RX.

Symptoms highly suggest meningitis, which, as mentioned above, is an emergency condition that required immediate empirical treatment.
Ans: A or C

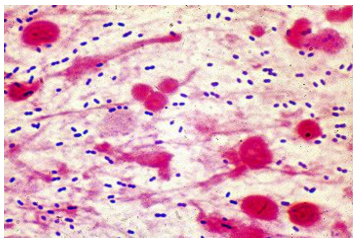
NB. never do a lumbar puncture (LP) when there is suspicion of an abscess of space occupying lesion.

# Use of antibiotics:

- Patient was prescribed a dose of:

Ceftriaxone and vancomycin (start broad then tailor antibiotics to organism) and urgent LP is done:

- Result:
  - **WBC**: 1230 cells/mm, 90% polymorph.
  - **RBC**: NIL.
  - **Gram stain:** Gram positive intracellular diplococci.



- What you will do?
- Continue the same antibiotics? Yes or No
- Stop Vancomycin and continue with Ceftriaxone

- <u>Premature initiation of antimicrobial therapy any harm?</u>

- Can suppress bacterial growth
- Preclude prevent the opportunity to establish a microbiological diagnosis. Therefore can't narrow down the antibiotics
- Require several weeks to months of directed antimicrobial therapy to achieve cure.

# Empiric vs Definitive Antimicrobial Therapy:

- Microbiological results do not become available
- for 24 to 72 hours
- Empiric and **guided by the clinical presentation**
- Inadequate therapy for infections in critically ill, hospitalized patients is associated with greater morbidity and mortality
- Use **broad-spectrum antimicrobial** agents as initial empiric therapy

# Best Educated Guess?

What organisms are likely to be responsible?
Based on:

- History & physical examination.. You might have a clue to diagnosis.
- Epidemiological data:
  1. Hospital-acquired vs community-acquired
  2. Prior antibiotic use

- ❖ Patient with dyspnea 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

## Hospital-acquired infection:

- Related to the presence of invasive devices and procedures
- Catheter related bacteremia:
  - Coagulase negative staph
  - Methicillin-resistant Staphylococcus aureus [MRSA]
- Catheter related UTI:
  - Gram negative (eg, Pseudomonas aeruginosa nosocomial organism)

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:

1) It can reduce cost and toxicity
2) Prevent the emergence of antimicrobial resistance in the community

Antibiotics are very toxic to normal flora and may disturb their physiological balance.

## Interpretation of Antimicrobial Susceptibility Testing Results:

- 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
- Data are reported in the form of minimum inhibitory concentration (MIC):
  - The lowest concentration of an antibiotic that inhibits visible growth of a microorganism.

## Antimicrobial susceptibility testing (AST):

- **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. (minimum inhibitory concentration)

Case Scenario:
23 years old man who has surgery at the base of the skull after a trauma. Presented few days later with meningitis

- CSF has revealed:
  - WBC 1200 mainly poly
- Culture:

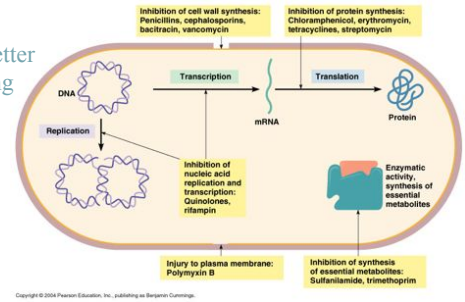
-staph aureus

- Treatment:

-cefazolin

- It doesn't achieve therapeutic concentration in the CSF

# Bactericidal vs Bacteriostatic Therapy:

| Bactericidal<br>ALWAYS use bactericidal for serious conditions!! | Bacteriostatic |
|---|---|
| - Cause death and disruption of the bacterial cell.<br>- Drugs act on :<br>1) The cell wall (b-lactams) eg penicillin, cephalosporins, carbapenems<br>2) Cell membrane (daptomycin)<br>3) Bacterial DNA (fluoroquinolones)<br><br>- Preferred in the case of serious infections such as:<br>- endocarditis<br>- meningitis to achieve rapid cure.. | - Inhibit bacterial replication without killing the organism.<br>- Act by inhibiting protein synthesis such as:<br>1) Sulfonamides<br>2) Tetracyclines<br>3) Macrolides eg erythromycin, azithromycin<br><br>Figure for better understanding<br>  |

# Use of Antimicrobial Combinations:

Use combination in patients likely to be infected with different organisms.

Exhibits synergistic activity 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:**

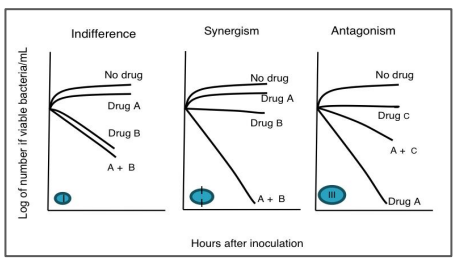
- Endocarditis due to viridans group streptococci
- A combination of penicillin or ceftriaxone with gentamicin for 2 weeks can be as effective as penicillin or ceftriaxone alone for 4 weeks).

**C) Critical ill patient:**

- Empiric therapy
- Septic shock and 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 combination, such as third-generation
- cephalosporin or a fluoroquinolones plus metronidazole
- can be used as a potential treatment option in these cases
- can sometimes be more cost-effective than a comparable
- single agent (eg, a carbapenem)

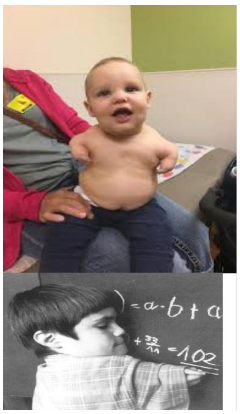


# Host Factors to Be Considered in Selection of Antimicrobial Agents:

1) Renal and Hepatic Function (Adjust dose)
2) Pregnancy and Lactation, special considerations, teratogenicity or otherwise toxic to the fetus:
   - **Sulphonamides**: A risk to develop kernicterus, especially preterm infants.
   - **Tetracycline**: Staining of the teeth
   - **Fluoroquinolone**: Cartilage damage to the fetus
3) History of Allergy or Intolerance.
   - **Penicillin** and anaphylaxis

- Consider Special Host Factors
- Genetic e.g, G6PD
- Liver function
- Pregnancy & Lactation
- Drug interactions

# Thalidomide-induced teratogenesis:



- Phocomelia:
- Thalidomide was released in the late 1950's
- It was very effective : antiemetic and used to treat morning sickness and emesis in pregnant women
- The biggest man-made medical disaster ever, over 10,000 children were born with a range of severe and debilitating malformations.

# Oral vs Intravenous Therapy:

- Candidates for treatment 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 as well as fluoroquinolones
- The efficacy of antimicrobial agents depends on their capacity to achieve:
  - Concentration equal to or greater than the MIC at the site of infection
  - Ocular fluid, CSF, abscess cavity, prostate, and bone are often much lower than serum levels
- For example:
  - **First- and second- generation cephalosporins do not cross the blood-brain barrier**
  - **Aminoglycosides**: are less active in the: *low-oxygen*, *low-pH*, of Abscesses
  - **Fluoroquinolones** achieve high concentrations in the prostate preferred oral agents for the treatment of **Prostatitis**.
  - **Moxifloxacin** does not achieve significant urinary concentrations therefore not suitable for treatment of UTIs.(Moxifloxacin is better for pneumonia, Ciprofloxacin is more suitable for UTIs )

## Antimicrobial Agents as Prophylactic:

1) Presurgical Antimicrobial Prophylaxis:
- is 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
    - Previous hx of infective endocarditis
    - Cardiac transplant with valvopathy
    - Unrepaired cyanotic Congenital heart disease including palliative shunt or conduit
    - Completely repaired congenital heart defects with prosthetic material or device , whether placed by surgery or by catheter intervention, during the first 6 months after procedure repair risk is only 6 m post procedure
    - Repaired congenital heart disease with residual defects at the site or adjacent to the site of the prosthetic device
    - Rheumatic heart.., removed from new guidelines

Eg. Patient presentation comatosed to the ER, temperature was 40 Celcius with an extensive purple rash on her legs. This is a case of meningitis due to Neisseria meningitidis. (any meningitis patient with rash is N.meningitidis). The patient passed away shorty. However antibiotics should be given to close contact of the patient eg. husband.

## Non Infectious Causes of Fever:

- 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:
    - Old women with indwelling urinary catheter: Active infection are absent (asymptomatic bacteriuria)
    - Endotracheal tubes in mechanically ventilated patients,
    - Chronic wounds.

Culture sample of pleural fluid is better than sputum

## 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.

In addition:

- 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.

## What is the appropriate dose?

- The lowest dose that is effective.
- AVOID sub-therapeutic doses
- Determined by:
  - Serious vs non-serious infections
  - Site of infection
  - Drug PK/PD properties
  - Other host factors (e.g. renal function… etc)

## Any Modification Needed?

Principles:

- Narrow vs broad spectrum agents.
- Least toxic agent.
- Cheaper.
- Single agent preferred.
- Switching iv to oral when possible.

## New VS Current Antimicrobial Agent:

Know:

- Approved indications
- Advantages vs disadvantages
- Basic pharmacokinetics
  - serum T ½
  - 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 ½
    - Short duration
- Less toxic
- Better tolerance

## Antibiotics use:

- Identification of infecting organism
- Determining antimicrobial susceptibility
- Host factors:
    - allergies, age, pregnancy, renal and hepatic function, site of infection (which is an indication to the most likely type of organism)
- Antimicrobial combinations:
    - indications, synergism, antagonism, cost, adverse effects
- Dosing:
    - route, regimen, monitoring response/effectiveness

## 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?

# Summary (from 436)

Antibiotic: Chemical produced by a microorganism that kills or inhibits the growth of another microorganism.

<table>
<tr><td>Antibiotic Indications</td><td colspan="2"><ul><li>Clinical diagnosis of bacterial infection.</li><li>Pneumonia (CAP) treated empirically (macrolide or fluoroquinolone antibiotic) without performing specific diagnosis test.</li></ul></td></tr>
<tr><td>Timing of Initiation of Antimicrobial Therapy</td><td><u>Urgent</u>:<br>1) Acute meningitis.<br>2) Septic shock.<br>3) Febrile neutropenia. Empiric therapy should be initiated immediately after or concurrently with collection of diagnostic specimens</td><td><u>Non Urgent:</u><br>Febrile and stable patient with fever for several days or months with no clue to diagnosis.<br>In more stable clinical circumstances, hold antibiotics until appropriate specimens have been collected and submitted.<br>Example: subacute bacterial endocarditis\ multiple sets of blood cultures</td></tr>
<tr><td>Organisms responsible</td><td colspan="2">Based on: Hx & P.E.<br>You might have a clue to DX.<br>Examples:<br>1- Patient with dyspnoea and cough: Streptococcal pneumonia and atypical organism. 2- Patient with fever and urinary symptoms : E.coli<br>3- Patient with erythema over the right leg associated with pain and tenderness: Group A Streptococcus and Staphylococcus.</td></tr>
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</table>

# Questions

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-A 35-year-old previously healthy man develops cough with purulent sputum over several days. On presentation to the emergency room, he is lethargic. Temperature is 39°C, pulse 110, and blood pressure 100/70. He has rales and dullness to percussion at the left base.There is no rash. Flexion of the patient's neck when supine results in spontaneous flexion of hip and knee. Neurologic examination is otherwise normal. There is no papilledema. A lumbar puncture is performed in the emergency room. The cerebrospinal fluid (CSF) shows 8000 leukocytes/µL, 90% of which are polys. Glucose is 30 mg/dL with a peripheral glucose of 80 mg/dL. CSF protein is elevated to 200 mg/dL. CSF Gram stain is pending. Which of the following is the correct treatment option?
A-Begin acyclovir for herpes simplex encephalitis.
B-Obtain emergency MRI scan before beginning treatment.
C-Begin ceftriaxone and vancomycin for pneumococcal meningitis.
D-Begin ceftriaxone, vancomycin, and ampicillin to cover both pneumococci and Listeria.

3-Formation of essential components of bacterium cell wall is inhibited by:
A-Tetracycline.
B-Erythromycins.
C-Penicillin.
D-both A and B.

4-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 .

5-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.

# Answers w/Explanations

**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).** This previously healthy male has developed acute bacterial meningitis as evident by meningeal irritation with a positive Brudzinski sign, and a CSF profile typical for bacterial meningitis (elevated white blood cell count, high percentage of polymorphonuclear leukocytes, elevated protein,and low glucose). The patient likely has concomitant pneumonia. This combination suggests pneumococcal infection. Because of the potential for beta-lactam resistance, the recommendation for therapy prior to availability of susceptibility data is ceftriaxone and vancomycin. Though herpes simplex can be seen in young healthy patients, the clinical picture and CSF profile are not consistent with this infection. The CSF in herpes simplex encephalitis shows a lymphocytic predominance and normal glucose. Listeria monocytogenes meningitis is a concern in immunocompromised and elderly patients. Gram stain would show gram-positive rods. Neisseria meningitidis is the second commonest cause of bacterial meningitis but rarely causes pneumonia (the portal of entry is the nasopharynx). Although penicillin G still kills the meningococcus, empiric therapy should cover all likely pathogens until Gram stain and culture results are available. Because the patient has no papilledema and no focal neurologic findings, treatment should not be delayed to obtain an MRI scan

**3-The answer is (C)**

**4-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.

**5-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 is long courses and the use of broad spectrum antibiotics while they are not needed.