

MEDICINE

432 Team

63 Use of antibiotics



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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

Not given

Cases

1. A 21 year old university student presents with fever, body aches, and **sore throat**.

No, because these symptoms are suggestive for a viral infection

2. A 54 year old lady complains of dysuria, frequency, loin pain and **fever**.

Yes, because these symptoms are suggestive of upper urinary tract infection (pyelonephritis), which is almost always a **bacterial infection**.

3. 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. (Most likely pneumonia) but it the differential it could be mycobacterium, or viral

Introduction:

- Antimicrobials are the 2nd most common drugs prescribed by office based physicians
- In USA1992:
 - 110 million oral antimicrobial rx written by office based physicians
- annual antimicrobial drug use rate
 - = 439 /1,000 population

Indications for use:

1. **Definite or probable bacterial infection**
2. **Serious infections compromising the pat**
3. **NOT FEVER:** because fever could be due to anything drug induced, lymphoma, collagen vascular disease, etc...

- Fever of 3 days most likely viral
- Sub-acute fever 1 week or longer ,you need to investigate
- Fever of Serious illness , give broad spectrum and investigate

Where is the focus of infection?

A. Clinical assessment

Do clinical assessment through history and physical examination. The next step is to take samples from the site of infection. The samples needed are usually cultures and smears.

B. Gram stain & cultures : from site of infection i.e. pneum=sputum, CNS=CSF, UTI=midstream urine

What is the likely organism?

1. Determine the focus of infection. E.g. Meningitis is commonly caused by pneumococci and meningococci , or in community acquired pneumonia its most likely strept.pneum or mycoplasma
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 but in adults pneumococci.
4. Epidemiological setting: Is it a community-acquired infection? Or a hospital acquired infection?
5. Prior culture data: because if the patient was positive for and infection in the past , it more likely the current one is a relapse

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

- Urinary tract infection: E.coli, staphylococcus, strep. Pyogenes and other gram -ve, klebsella, Protues.
- 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.meningitidis or pneumococcal. But remember viral causes also very common.

- Septic arthritis: Bone and joints commonly infected by (Staph. Aureus commonest non-specific) brucella and gonococcal .
- Nosocomial pneumonia: Gram -ve bacilli pseudomonas or staph or multidrug resistant

Note(s):

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

After the 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.
- Excessive consumption of broad spectrum antibiotic can kill normal intestinal flora which will lead to over growth of C. difficile that manifests as diarrhea. Also C. difficile it is the most common cause for pseudomembranous colitis and may complicate to toxic mega colon.

*In pneumococci when not resistant to penicillin, it should be your choice after the culture results

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. (always target infections only)
- Colonization: germs can also be in or on the body, but not make you sick. People who are colonized will have no signs or symptoms. (no need for treatment unless the patient is immunocompromised)
- In pregnancy when they screen the urine and they have a colony count of >100,000/ml If there are no puss cells that's contamination, if there is puss

cells without fever treat as LUTI for 3 days if there is fever treat as pyelonephritis for 14 days

- ICU patients who are intubated when you culture them they may have klebsella , the pus cells are low , these are colonized

Other factors for antibiotic selection:

1. Culture result.
2. **Tissue penetration. This is an important factor!**
For example, when a patient come to the ER with head trauma, and the investigations revealed that he is infected by gram-negative bacillus in the meninges, so he has a gram-negative meningitis, would you give him Aminoglycoside?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. **BBB, vitreous, and prostate are difficult sites to reach**
3. Bactericidal Vs. Bacteriostatic: if the infection in a site where the neutrophils can't reach in adequate quantities (i.e. **CNSinfections, Endocarditis**(low vascularity in the leaflets and so neutrophils can't reach it), **Neutropenia(<500),etc...**) in these cases **bactericidal is more preferable** .in other conditions Bacteriostatic are more preferred like in typhoid we give chloramphenicol
4. Renal disease: avoid drugs excreted by the kidney. **(Ex.Aminoglycoside, vancomycin...)**
5. Liver disease: avoid drugs the primarily excreted by liver through the bile. **(Ex.clindamycin, INH, tetracycline, rifampicin, chloramphenicol , metronidazole, clarithromycin , azithromycin) hepatotoxic**
6. Pregnancy & lactation: **Beta lactams generally SAFE to use in pregnancy.**

FDA Pregnancy Categories:

Category A: The possibility of fetal harm appears remote. Extremely few drugs exist in this category (e.g. multiple vitamins).

Category B: If there is a clinical need for a drug in this category they are considered safe to use. Examples: acetaminophen, amoxicillin.

Category C: These drugs should be given only if the potential benefit justifies the potential risk to the fetus. Examples: Fluoroquinolones, gentamicin, saccharin, aspirin.

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.

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. **MIC (minimal inhibitory concentration):** is the lowest concentration of antimicrobial that will inhibit the visible growth of a microorganism and development of resistance. You want the drug to be higher than the MIC all through dosing interval
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, meningitis 2 weeks, bone infections and endocarditis need about 6 weeks, chronic osteomyelitis is treated for 3 months. 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 extrapulmonary (Brain, bone..) between 9-12 months.

Indications for Anti-biotic Combination Therapy:

1. Sepsis of unclear etiology.
2. Febrile neutropenia.
3. Prevent emergence of resistance. (e.g. in TB, we start with 4 drugs assuming that the organism resistant to one of them, then we cut them down into two . another is pneumococcus)

4. Polymicrobial infection: Perforated colon with peritonitis (gm-ve , enterococci(strep.feacalis only responds to ampicillin and vancomycin) ,and anaerobes
5. Synergy: means one drug potentiating the action of the other (e.g. Endocarditis will require combination of penicillin and beta-lactam inhibitors to aminoglycosides in case of strep viridans and enterococcal endocarditis)

Disadvantages of Anti-biotic:

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.

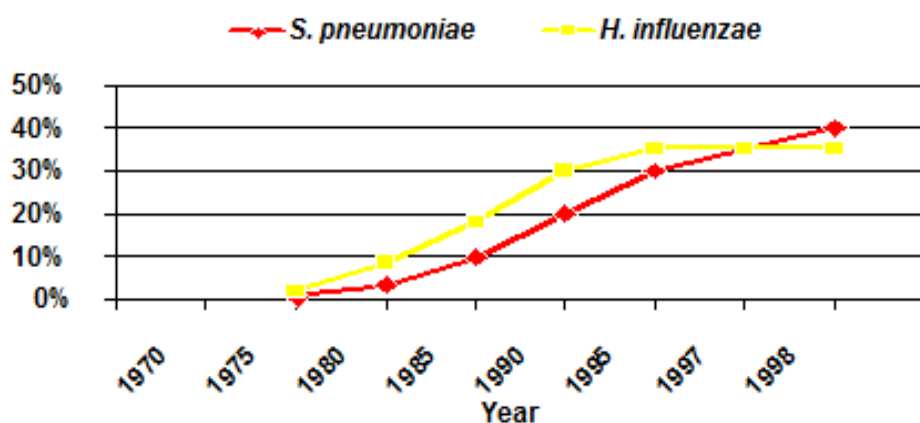
Failure of the therapy:

1. Patient factors: Poor compliance and Complications of the disease that prevent the response. For example in pneumonia 1) Bronchial obstruction that prevents inflammatory 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) (para-pneumonic effusion) when patient develop this complication, he will never respond until we put a chest tube and drain it. *this is seen with bronchogenic carcinoma co-existing with pneumonia
2. Drug factors: Inadequate penetration of 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.
3. Organism factors: Resistance to the antibiotics.

*in pneumonia we give the patient with ceftriaxone (to cover pneumococci and h.influenzae and gm-ve(klebsella))and azithromycin will cover atypical i.e mycoplasma

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

*Resistance was there ever since antibiotics were discovered . *check the penicillin*



Before 1980 resistance of pneumococci was very low but now it increased to almost 40%

It causes pneumonia and meningitis and we don't treat with penicillin unless sensitive usually we give ceftriaxone

Antibiotic Resistance: Current problems with antibiotic resistant bacteria include:

- **MRSA:**
 - 37% of all bloodstream isolates of S. aureus are now MRSA → **only vancomycin**
- **resistance in respiratory pathogens:**
 - 2.2% of S. pneumoniae are penicillin-resistant
 - ~15-20% of H. influenzae are amoxicillin-resistant

- multi-resistant Gram-negative bacilli (extended-spectrum β -lactamase producers-ESBL)
- resistant to all beta-lactams and the only drug that can kill them is imipenem or Carbapenems and aminoglycosides
- glycopeptide-resistant enterococci
- 21.6% of bloodstream isolates of *E. faecium* and 3.3% of *E. faecalis*
- *Drug of choice is ampicillin if resistant vancomycin*
- MDR-TB
- 6.2% of *M. tuberculosis* isoniazid-resistant
- 1% are true MDR strains

Stop Antimicrobial Treatment:

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

Hospital Control:

- 1- Monitor
- 2- Evaluate empiric, therapeutic & prophylactic use
 - Prescriptions include type of rx: E/T/P
 - Time limits
 - Empiric: 3 days
 - Prophylactic: 2 days → one dose before and one after in case of surgery
 - Therapeutic: 7 days
 - Extension requires justification written by the prescribing physician
 - Requiring MD to justify prescriptions ↑ proper usage.
- 3-Restriction of Drugs classified as:
 - Uncontrolled: available for rx by all physicians
 - Monitored: available but usage monitored through system
 - Restricted: available only after consultation with ID specialist or limited list of MD

This is just for your reference and to freshen your memory (taken from 432 team work)

Antibiotics class	Examples	Mechanisms	Spectrum of Activity	S/E
INHIBITION OF CELL WALL				
(β-Lactam) Penicillins	Natural: penicillin G Semi-synthetic: oxacillin, ampicillin- clavulanic acid, ampicillin- sulbactam	Inhibit peptoglycan synthesis necessary for cell- wall formation	Bactericidal-most active against gram +; synthetic and potentiated penicillin have improved gram – coverage	Hypersensitive, anaphylaxis GIT
(β-Lactam) CEPHALOSPORINS	1 st generation: cephalothin, cephalexin , 2 nd generation: Cefuroxime 3 rd generation: ceftriaxone , ceftazidime 4 th generation: Cefepime		Bactericidal 1 st gen: Gram +, limited Gram – 2 nd gen: Gram +, improved Gram – and some anaerobes. 3 rd gen: limited Gram+, excellent Gram- and anaerobes	
Glycopeptides	Vancomycin		Bacteriocidal; Gram+ve bacteria only MRSA	* Red man syndrome *Neprototoxicity
Inhibition of protein synthesis (bind to ribosomes)				
Aminoglycosides <small>"Cannot be used for anaerobes"</small>	Gentamicin , amikacin, tobramycin, neomycin	Bind 30S ribosomal subunit; inhibit peptide elongation	Bactericidal; Gram-, including <i>Pseudomonas</i> and <i>Mycobacterium</i> , <i>Streptococcus</i> and anaerobes are resistant	Ototoxicity Nephrotoxicity " More important than Vancomycin"
Tetracyclines <small>"Cannot be used for pregnant and children under 8 year"</small>	Tetracyclines , doxycycline	Bind 30S subunit; inhibit RNA function	Bacteriostatic; Gram+ and Gram –; <i>Rickettsiae</i> , <i>Mycoplasma</i> , <i>Chlamydothila</i>	Teeth discoloration GIT photosensitivity
Chloramphenicol	Chloramphenicol	Bind 50S subunit; inhibit protein synthesis	bactericidal; broad Gram+ and Gram- spectrum * used for meningitis	BM aplastic anemia
Macrolides And lincosamides	Erythromycin Azithromycin Clarithromycin Clindamycin	Bind 50S subunit; inhibit protein synthesis	Bacteriostatic; Gram+, <i>Legionella</i> , <i>Campylobacter</i> , <i>Mycoplasma</i> , <i>Chlamydothila</i> , <i>Rickettsiae</i> , *Clindamycin has good anaerobic spectrum	GIT pseudo- membranous colitis

INHIBITION OF NUCLEIC ACID SYNTHESIS				
1. QUINOLONES "Cannot be used for children under 18 year"	1 st generation: Nalidexic acid 2 nd generation: Fluoroquinolones Ciprofloxacin- 3 rd generation: Gatifloxacin 4 th generation: Moxifloxacin	Inhibits DNA gyrase, preventing supercoiling →DNA degradation	Bactericidal; Gram +ve and gram -ve, INCLUDING Pseudomonas at a higher dosage	Cartilage damage
2. Nitroimidazoles	Metronidazole * the only can cover Bactria and parasite	Metabolized by anaerobes to intermediates that prevent DNA synthesis	Bactericidal; anaerobes (Also antiprotozoal)	GIT
3. Rifampicin (used for TB)	Rifampicin	DNA degradation	Bactericidal; Gram +ve and gram -ve bacteria	Discoloration of body fluid hepatotoxicity
INHIBITION OF BACTERIAL GROWTH				
Sulfonamides	Trimethoprim-sulfadiazine, ormethoprim sulfa	Competitive analogue of para-aminobenzoic acid (PABA) →inhibits dihydrofolate reductase →blocks folic acid synthesis	Bacteriostatic → bactericidal when combined. Gram -ve Chlamydia, nocardia, protozoa and pneumocystic	Discoloration of body fluid hepatotoxicity
Anti-Tuberculosis Agents				
1. Anti TB isoniazide (INH)	Bacteriocidal All lung tissue	T.B treatment and prophylaxis	Hepatotoxicity peripheral neuropathy	
2. Ethambutol	bacteriocidal concentrated lung alveoli phagolysosome	TB treatment	Optic neuritis, Hepatotoxicity	
3. Pyrazinamide	Acid environment of macrophages	TB treatment	Hepatitis gouty arthritis, Hepatotoxicity	
ALTERATION OF CELL MEMBRANE				
Polymyxin "Cannot be used for pregnant"	Colistin	Alter cell membrane permeability For multi-resistant organisms (MRO)	Bacteriocidal; Gram -ve bacteria	

Questions (From 431)

Q1/ 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

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

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

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

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

Q5/ First-line treatment for MRSA?

- A. Flucloxacillin
- B. Metronidazole
- C. Benzylpenicillin
- D. Vancomycin

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

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

- A. Amoxicillin
- B. Gentamicin
- C. Vancomycin
- D. Daptomycin

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. Flucloxacillin

432 Medicine Team Leaders

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For mistakes or feedback: medicine341@gmail.com

Answers:

- 1-A
- 2-C
- 3-B
- 4-C
- 5-D
- 6-D
- 7-B
- 8-A