ANTIBIOTICS

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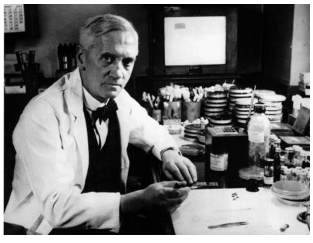
Introduction



- This is Alexander Fleming who discovered Penicillin in 1928.
- Penicillin is the first antibiotic to be discovered.
- Years later, Penicillin was available for use and since that time it saved millions of lives around the world.

Antibiotic Effect

- Bacteriostatic: Capable of inhibiting the growth or reproduction of bacteria until the patient's immune system takes care of the bacteria.
- Bactericidal: Capable of killing bacteria. Are used for;

-Immunocompromised patients

-For serious infections, like meningitis & infective endocarditis

- It's important to know that all B-lactams (Penicillin, Cephalosporin, Carbapenems and Monobactams) are bactericidal antibiotics.

Bactericidal	Ex. Bactericidal	Bacteriostatic	Ex. Bacteriostatic
Antibiotics that kill the bacteria.	B-lactams	Antibiotics that prevent the growth of the bacteria	Macrolides (clarithromycin)
Action is irreversible	Metronidazole	Action is reversible	Tetracyclines
Inhibit the cell wall formation of the bacteria	Rifampicin	Inhibit DNA replication and protein synthesis of the bacteria	Lincosamides (Clindamycin)
Do Not work with the	Glycopeptides	Work with the	

immune system of the host	(vancomycin)	immune system of the host	Fusidic Acid
	Quinolones		Chloramphenicol

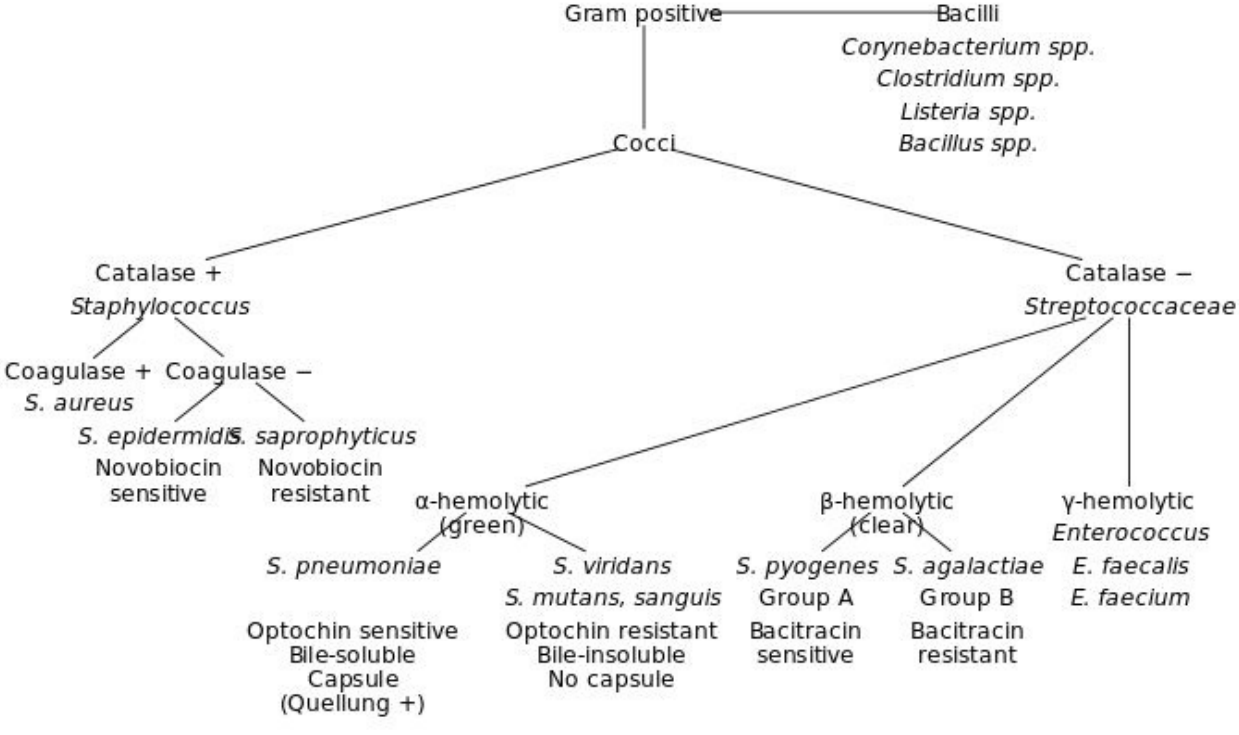
Gram Stain

- Gram stain usually shows the gram negative bacteria appearing like bacilli (rods in shape) which usually stained in **pink**, while the gram positive appears like cocci (round in shape) and usually stained in **blue** or **purple**,
- This is the usual, but there's some exceptions:

-Sometimes we have gram+ bacilli, like Listeria & Clostridium.

-Or gram- diplococci, like H. Influenzae.

Gram Positive Bacteria



Common Gram+ Microorganisms

1.Staphylococcus Aureus:

- More than 90% of cases in community acquired previously healthy patients caused by S. aureus.
- Divided into MSSA (Methicillin Sensitive S.aureus) & MRSA (Methicillin Resistant S.aureus).
- **Diseases:**

- The most common cause of Skin/Soft tissue/bone infections: Cellulitis, Abscess, Osteomyelitis, Septic Arthritis.

- Infections associated with foreign bodies (central line, VP shunt, Foley's catheter): **S.epidermidis** (causes gradual indolent not life-threatening infections) **S.aureus** (rapid acute and life threatening).

***S.aureus is the 2nd most common cause of central line infections after S.epidermidis**.

***S.epidermidis is the most common cause of central line infections & blood contaminants of blood culture.**

- Hospital acquired infections: mostly by **MRSA**. Also **pseudomonas Aeruginosa**, **Actinobacter**.

- Staph saprophyticus: is the cause of UTI infection in sexually active female adolescents.

2.Streptococcus:

- **α-Hemolytic**: a greenish discoloration and partial hemolysis of the red blood cells immediately surrounding colonies of some streptococci on blood agar plates.

ex1) **S. Pneumonia**: The most common cause of Pneumonia, meningitis (beyond neonatal period), otitis media, sinusitis, Mastoiditis, orbital cellulitis or (any -itis except cellulitis and osteomyelitis).

- The most common cause of bacteremia in some age group.

- Sensitive to penicillin and ceftriaxone but the drug of choice is Ceftriaxone.

***NOTE: KEEP IN MIND THAT S. PNEUMONIAE HAS 10% RESISTANCE TO PENICILLIN.**

- We have to add vancomycin in case of meningitis with resistance S. Pneumonia.

ex2) **Strep Viridans**:The most common cause of infective endocarditis in children (native valve endocarditis), and the second common cause of blood contamination.

*Viridans means green.

- **B-Hemolytic**: Sharply defined clear colorless zone of hemolysis surrounding colonies of certain streptococci on blood agar plates.

***It is important to know that B-Hemolytic S.coccus are 100% susceptible to Penicillin. The drug of choice for either group A or B is Penicillin or aminopenicillin.**

ex1) **S.Pyogenes (Group A strep)**: The most common cause of **Bacterial Tonsillitis** and can cause Skin/Soft Tissue Infections (Abscess, Cellulitis, Impetigo and Scarlet Fever).

*Group A Strep also cause **ACUTE RHEUMATIC FEVER** or **GLOMERULONEPHRITIS** as a squeal of TONSILLITIS.

***GROUP A STREP IS THE ONLY BACTERIAL ORGANISM THAT WE TREAT FOR TONSILLITIS.**
Previously we had DIPHTHERIA but we don't see it anymore due to VACCINATION, also we have GONOCOCCAL Tonsillitis around the world, but we don't have it in Jordan because it is a STD.

ex2) **S.Agalactiae (Group B strep)**: Neonatal Infections like, Neonatal Sepsis and Neonatal Meningitis (most common cause in neonates).

- **Gamma-Hemolytic (Enterococcus)**: Lack of hemolysis in the area around a bacterial colony. A blood agar plate displaying gamma hemolysis actually appears brownish.

-It is a known cause of endocarditis in children.

-The most common gram+ bacterial cause of UTI.

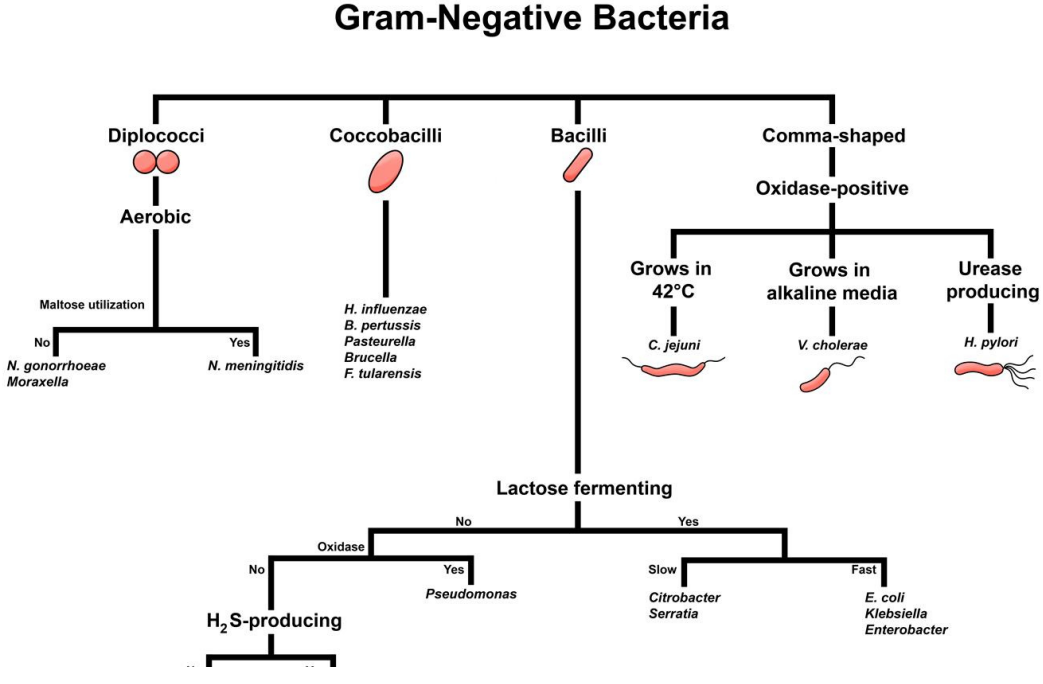
-Most of the time it is just a contamination of blood, except in two cases:

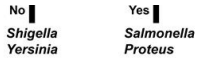
1-If the patient has a heart disease that predispose him for infective endocarditis.

2- Immunocompromised case leaded to sepsis.

*** We treat Enterococcus by: ampicillin or penicillin. If it resistance like enterococcus faecium we cover it by vancomycin and if it is not respond we use linezolid. (the sequence is v.important).**

Gram Negative Bacteria





Moises Dominguez

Common Gram- Microorganisms

- **Escherichia coli (E.coli):**

-Causes UTI and Intra-abdominal infections, like peritonitis as a result of a ruptured viscus.

-Intra-abdominal infections are caused by gram negative bacteria like, Klebsiella.

-The most common cause of UTI is E.coli, but the most common gram +ve cause of UTI is Enterococcus.

- **Pseudomonas aeruginosa:** -Opportunistic infections-

-Usually infects immunocompromised patients, like patients with fever and neutropenia due to chemotherapy, CF, DM.. etc.

-It is a known cause of hospital acquired infections.

- **Anaerobes:**

-A common cause of intra-abdominal infections because this bacteria come from the GI tract. For example: in case of peritonitis developed after a ruptured appendicitis, you have to think of anaerobic infection.

-Aspiration pneumonia, common especially in CP patients.

- Brain abscess, but not common.

- **Atypical Bacteria**:

-Mycoplasma Pneumonia, Chlamydia Pneumonia, Legionella.

-It is atypical because it does not have a cell wall.

-Causes Pneumonia in school age children (>5 yrs old) and it is called walking pneumonia (as it is mild so the patient doesn't stay in bed and comes walking).

-Atypical Pneumonia patient usually presents with cough and fever. Physical exam may reveal wheezes with no previous history of Asthma. On chest X-ray the most common pattern is diffused infiltrates.

***Treated with MACROLIDES not Fluoroquinolone or Tetracycline.**

***If the patient is older than 8 years of age an alternative of Macrolides will be Tetracycline.**

***Atypical bacteria lacks cell wall, so Beta lactams Antibiotics don't act on it.**

-Fluoroquinolone are contraindicated in children under 18 yrs because it leads to tendon rupture and interferes with the cartilage growth and causes permanent CNS inability. We may use it in children younger than 18 only if there are no safer options.

-Fluoroquinolone covers gram-negatives mainly, Pseudomonas aeruginosa. Newer Fluoroquinolones like, Levofloxacin also covers atypical bacteria and gram+.

-Tetracycline are not given for children under 8yrs because it leads to permanent staining of the teeth and bone.

-Tetracycline has potential coverage for MRSA as well as atypical organisms.

Multi-Drug Resistance

1. **Acinetobacter**: A hospital acquired infection and only Colistin (Polymyxin E) covers it.

If the bacteria become resistant to Colistin we call it **PAN RESISTANCE MICROORGANISM**.

2. **Extended Spectrum Beta-Lactamase (ESBLS)**: They respond only to Carbapenems.

Antibiotics Classification

Antibiotic Classes

Mechanism of Action

1. **Aminoglycosides** - Inhibit Protein Synthesis
2. **Cephalosporins** - Inhibit Cell Wall Synthesis
3. **Tetracyclines** - Inhibit Protein Synthesis
4. **Penicillins** - Inhibit Cell Wall Synthesis
5. **SulFOnamides** - Inhibit **FO**late Synthesis = **"FO"**
6. **FluoroQUINolones** - Inhibit DNA Replication = **QUIN**tuplets
7. **Macrolides** - Inhibit Protein Synthesis
8. **Carbapenems** - Inhibit Cell Wall Synthesis
9. **Lincosamides** - Inhibit Protein Synthesis
10. **Glycopeptides** - Inhibit Cell Wall Synthesis

MALT = Protein

- Macrolides
- Aminoglycosides
- Lincosamides
- Tetracyclines

Penicillin

- **Classification of PCN**:

1- Natural PCN: PCN G (IV) and PCN V (Oral).

*PCN G (IV) is not available in Jordan.

2- Synthetic PCN:

☐ Anti-staphylococcal penicillin (penicillinase resistant):

- Nafcillin, Oxacillin, Cloxacillin and Dicloxacillin. Effective ONLY against MSSA.

☐ Broad spectrum penicillin:

- Amino-PCN (Ampicillin IV, Amoxicillin PO): Extends to cover gram negative bacteria like E. coli (Ampicillin IV is not available in KAUH).

- Ureidopenicillins (Piperacillin IV, Carbenicillin and Ticarcillin): Against Pseudomonas.

- **Coverage & Use**:

1- Gram positive cocci: Group A strep, Group B strep, some Strep pneumonia and some enterococcus.

- The resistance rate of group A and group B β-hemolytic strep to penicillin (penicillin, amoxicillin, and ampicillin) is zero! So NO need for 2nd or 3rd line treatment, the DOC is always penicillin! As in tonsillitis caused by group A strep or in neonatal sepsis caused by strep agalactiae (group B strep) where the DOC is IV ampicillin or penicillin G (Benzylpenicillin IV route).

- S.pneumoniae infections have 2nd and 3rd line treatments, it has resistance to penicillin.

2- Mouth anaerobes (except Bacteroides, the intestinal anaerobes).

-Amoxicillin provides a very good coverage for mouth flora; therefore it can be used alone as a prophylaxis before dental surgeries.

3- Some gram negative bacteria.

4- MRSA gained its resistance through alteration in penicillin-binding protein (PBPs).

5- When you add beta-lactamase inhibitor: (Ampicillin and Sulbactam, Amoxicillin and Clavulanic acid , Piperacillin and Tazobactam), will extend to more gram negative bacteria like, Moraxella & Haemophilus which cause respiratory tract infections, and Anaerobes including Bacteroides and MSSA.

***AMOXICILLIN AND CLAVULANIC ACID = AMOCLAN**

*** PIPERACILLIN AND TAZOBACTAM=TAZOCIN**

Cephalosporins

- **Classification:**

- 1st generation (Cefazolin IV and Cephalexin PO).

- 2nd gen: (Cefuroxime IV and PO), include Cephamycin subgroup against Bacteroides (Anaerobes) (Cefoxitin and Cefotetan).

- 3rd gen: (Cefotaxime IV, Ceftriaxone IV, and Cefixime PO) against Pseudomonas aeruginosa (Ceftazidime IV).

*Cefixime PO: Suprax® *Ceftriaxone: Rocephin® *Ceftazidime is Not available in Jordan

- 4th gen: (Cefepime IV) Not available in Jordan.

- 5th gen: (Ceftaroline IV) Not used yet in children.

- **Coverage & Use:**

1-First generation: Covers most gram positive cocci (Except MRSA, Enterococcus) & Some gram negatives like, E. coli +Anaerobic pathogens except Bacteroides.

-Are very similar to Amoxicillin, but unlike Cephalosporin, Amoxicillin cannot cover MSSA.

-Usage: Skin/soft tissue infections, some UTI, Group A strep infections, preoperative prophylaxis.

2-Second generation: It is less active against gram positive cocci than the first generation but more active against gram-negative bacilli, Haemophilus influenzae and Moraxella catarrhalis.

Uses: Pneumonia, URTI & Pelvic inflammatory diseases

***Cefoxitin: more anaerobic coverage.**

3-Third generation: It is less active against gram positive organisms than the

first generation.

Uses: Community Acquired Meningitis (empiric therapy), to rule out Sepsis or occult Bacteremia, Pneumonia, UTI and many others.

***Ceftazidime has poor activity against gram positive organisms and should be reserved for use in proven or highly suspected P. aeruginosa.**

***Ceftriaxone causes the formation of "sludge" in the biliary tract and displacement of bilirubin from albumin causing hyperbilirubinemia.**

***Ceftriaxone is contraindicated in patients < 1 mo of age; Use cefotaxime IV instead.**

4-Fourth generation: Greater activity against the gram negative.

- Cefepime is as active against Pseudomonas aeruginosa (febrile neutropenia & Hospital acquired infections).

5-Fifth generation: Ceftaroline has a spectrum of activity similar to ceftriaxone but with improved gram positive activity (MRSA).

***Some organisms, including all Enterococci, Listeria, Atypical bacteria (Legionella, Mycoplasma, and Chlamydia) are ALWAYS resistant to Cephalosporin.**

- **Side effects:**

They're generally well tolerated. Oral cephalosporin may cause nausea, vomiting, & diarrhea.

- **NOTES:**

-From first to third generation increase gram negative coverage and decrease gram positive coverage, so the best one for gram positive Osteomyelitis is first generation and the best one for UTI is third generation.

-The second generation is used for respiratory tract infections like Otitis media and Pneumonia.

-2ed & 3rd generations are resistant to Beta-lactamases.

-Ceftazidime is the only third generation that covers Pseudomonas.

-The drug of choice for S.pneumoniae inpatients is third generation cephalosporin. For patients who are incompletely immunized, that includes the pneumococcal vaccine.

-Fourth generation is similar to third generation, covers gram negative. And similar to first generation covers gram positive in addition to that it covers Pseudomonas.

Glycopeptide

- Vancomycin, Teicoplanin.
- Inhibits cell-wall synthesis: Bactericidal (not βlactam drugs therefore isn't degrades by βlactamase).
- **Coverage & Use**:

-Gram positive including MRSA and Enterococcus.

-Meningitis (S. pneumonia).

-Hospital-acquired infections (Staph aureus).

-Foreign body associated infections (VPS prosthetic materials)(S.aureus & S.epidermidis).

-C. difficile (PO only)

-Vancomycin given orally only in case of C. difficile colitis (Pseudomembranous colitis). It is the second line to treat C.difficile in children, vancomycin is used mainly IV because it can't be absorbed from the intestine.

-Teicoplanin IV, used in adults.

- **Side effects:**

1. Red man syndrome: (affects both men and women).

***How to treat? Slow the infusion rate to over 2 hours and increase the dilution volume, Antihistamine & Steroids are given in severe cases.**

- It's not an allergic reaction, it causes a direct effect on mast cells and basophils which characterized by redness and itchiness in the whole body.

2. Extravasation will cause serious injury with possible necrosis and tissue sloughing.

3. Might cause nephrotoxicity.

Carbapenems

- Imipenem, Meropenem, Ertapenem, Doripenem
- have a very broad spectrum of activity.
- Inhibit bacterial cell wall synthesis.
- **Coverage & Use:**

-Active against many gram +ve ,-ve, anaerobic bacteria and stable to beta-lactamases including extended-spectrum beta-lactamases (ESBL).

***REMEMBER THAT CARBAPENEMS ARE THE ONLY AVAILABLE DRUG AGAINST ESBL.**

-Intra-abdominal infections (gram negatives & anaerobes).

-Nosocomial pneumonia (not first line).

-Febrile neutropenia (not first line, use Tazosyn instead).

- Carbapenems lack activity against Enterococcus faecium, MRSA and atypical microorganisms.

- Ertapenem lacks activity against Pseudomonas aeruginosa.

Lincosamide

- Bacteriostatic - disrupting protein synthesis.
- Ex) Clindamycin
- **Coverage & Use:**

- Anaerobic; Aspiration pneumonia

- Gram +ve; streptococcal and staphylococcal infections; Bone/Joint and skin/soft tissue infections including MRSA

- Toxic shock syndrome; it inhibits protein synthesis.

***Vancomycin doesn't stop the toxin production of Staph & Strep, therefore you should give Clindamycin with it in case of very ill patients.**

- **Side effects:**

The most common side effect is diarrhea.

Macrolides

- Bacteriostatic- Disrupts protein synthesis.
- Azithromycin, Erythromycin, Clarithromycin
- **Coverage & Use:**

-Gram positive (strep, staph) and atypical bacteria (Atypical pneumonia), Bordetella pertussis.

-Common substitute for patients with a penicillin allergy.

- **Side effects:**

Common side effect in neonates is **hypertrophic pyloric stenosis**.

Metronidazole

- Inhibits DNA Synthesis.
- AKA Flagyl.
- **Coverage & Use:**

-Anaerobic bacteria: Aspiration pneumonia, Intra-abdominal infections, lung abscess.

-Clostridium difficile infection.

-Protozoa: Amoebiasis, Giardia,Trichomonas.

Bactrim (Trimethoprim-sulfa)

- Bactericidal- Inhibit folate biosynthesis and metabolism)
- **Coverage & Use:**

-Gram-ve and most gram+ve (MRSA), no coverage for group A strep.

-Urinary tract infections.(because it cover gram -ve very well)

-Skin/soft tissue and bone/joint infections

-Treatment and prophylaxis of Pneumocystis jirovecii pneumonia (PCP) in HIV patients.

-Shigella

-Stenotrophomonas maltophilia ***An aerobic gram-ve bacilli which is uncommon pathogen in humans. usually incapable of causing disease in healthy hosts without the assistance of invasive medical devices that bypass normal host defenses. It's associated with pulmonary infections in Cystic Fibrosis patients.**

- **Side effects:**

-Not used in G6PD (causes hemolysis).

-Not used in neonates (displaces Bilirubin)

Aminoglycosides

***Bacteriostatic or bactericidal agents, Depending on their concentration.**

- Gentamicin, tobramycin, amikacin, neomycin (preoperative bowel preparation).
- Not available orally Must be given intrathecally in the treatment of meningitis
- **Coverage & Use:**

-Gram-negative aerobic bacteria, including pseudomonas, they are ineffective against anaerobes.

-Gram positive usually as synergistic effect. The synergistic effect between aminoglycosides and β-lactam antibiotics is well established against gram positives; (b

lactams destroy the cell wall then aminoglycoside enters and inhibit synthesis of proteins).

- Usually used for synergy or double coverage, or for UTI.

- **Side effects:**

Ototoxicity and nephrotoxicity are the most notable adverse effects.

***GENERAL NOTES:**

-**Anti-pseudomonas**: Aminoglycosides, Quinolones, Cephalosporins (Ceftazidime,

Cefepime), Antipseudomonal penicillins(Piperacillin), Carbapenems.

-**Anti-Anaerobic**: Metronidazole, Clindamycin, Penicillin (i.e. Ticarcillin, Ampicillin,

Piperacillin) and a Beta- lactamase inhibitor (i.e. clavulanic acid, sulbactam, tazobactam), Carbapenem.

-**Anti-Atypical**: Macrolides and Tetracyclines.

-**Anti-MRSA**: Vancomycin, Bactrim, Clindamycin, Doxycycline, Linezolid, ceftaroline.

-**Anti-C.diff**: Oral Vancomycin & Metronidazole.

- When a patient presenting with fever, send for blood culture.
- The best time to collect a blood sample is during or around temperature elevation.
- If you are suspecting UTI then do urine culture and analysis.
- If suspecting Meningitis do LP for CSF analysis and culture .
- You have to know the most common organism for each diseases like (pneumonia, UTI, meningitis, sepsis) and each age. This is useful for empirical therapy while choosing the proper antibiotic cultures take 2-3 days for results to appear. For example, school or preschool age children usually present with Atypical pneumonia so you have to give them macrolides (i.e Azithromycin) to cover atypical bacteria like mycoplasma pneumonia.
- Mycoplasma doesn't have a cell wall so avoid using cell wall synthesis inhibitors like Penicillins.
- Chloramphenicol is not used anymore due to aplastic anemia (dose dependent or synergic).