The third (and the last) part about the Antimicrobial drugs.

Tetracyclines:

1. This group is considered Bacteriostatic drugs
   Bacteriostatic drugs means: the effect of them is not killing, they just inhibit the replication of the microorganism. Then the body should later get rid of died cells or the few no. of cells which might survive from the infective tissue.

2. It (group) has two important functions against two specific target of the bacteria cell
   A. One in relation to the 30s of the bacterial ribosome
      It prevent the binding of amino-acyl transfer RNA (tRNA) to the 30s ribosome complex and this inhibit the protein synthesis (as a result inhibit but don’t kill the susceptible bacteria).
   
      B. Secondly, in relation to the accumulation of the drug within the cytoplasmic membrane
      Note: in this site there will be prevention for the access of the drug inside the bacteria cell
      I am not sure about this, but I think that dr. meant here that some bacteria cells develop a way of resistant against these drugs by a mean called (efflux).

   Efflux means: the cell membrane produce a form of prevention majors
   By blocking the channels which allow the tetracycline to flow inside the bacteria cytoplasm and instead it try to remove the drug outside of the cytoplasmic membrane as well as the cell wall.

3. It considered a wide spectrum antimicrobial drug
   It has a wide spectrum of activity against approximately 90% of all intestinal flora including some anaerobes, not all anaerobes but mainly facultative anaerobic bacteria,( gram –ve and +ve).
4. It often associated with developing of side effect.

A. This effect is related to the intestinal flora which might associate with

* developing of diarrhea
* lacking certain pro-vitamins due to the damaging of intestinal Flora
* the over growth of types of bacteria and yeast

***Yeast cannot be affected by tetracycline, so the few no. of yeast which is usually controlled by the presence of other intestinal flora or vaginal flora or oral flora.....ect. This flora will be reduced so the yeast will increase in no.

And this might be associated with developing of over growth of yeast Candida, especially in ladies associated with what we called vaginal discharge( which is a form of irritation in the mucosa and it is painful during urination )

***In addition the yeast covers the surface of the tongue in the oral cavity.

B. in addition tetracycline shouldn’t be given to the children up to age 8-10 years (mainly to adults), because in addition to the previously mentioned side effects, this drug interfere with the formation of the teeth and it might also color the teeth into yellow color.

Tetracycline, in fact, has been used in large amount, usually 2-4 g/day where as the new developed tetracycline, which is due to the change of the molecular structure of tetracycline (we have now Minocycline and Doxycycline)And this has changed the pharmacokinetics of the drug , so instead of use 4g/day now we are using just 1 or 2 g/day ......(note that any change in the structure result in some changes in pharmacokinetics and this relate to the administration of the drug)  

5. it effect certain type of bacteria considered usually not easily to be treated by other organism due to the lack of the cell wall or due to the presence of thin layer of peptidoglycan.
As example:

1. *Mycoplasma* (which associated with respiratory infection, genital infection ...)

2. *Chlamydia* infection

3. *Legionella* infection

Recently they have introduced a modification of tetracycline called Tigecycline.

Tigecycline is proved to be very effective drug in treatment of wide range of bacteria but on the other hand it proved to be susceptible to develop resistant by certain type of bacteria (ie. It is excellent drug but bacteria might produce resistant against it)

But despite this fact it is now used in treatment of certain serious infections which usually observed on hospitalized patients, like in relation to multiresistant pseudomonas and so on.....

The second drug which has similar wide spectrum of activity due its small molecular size is ((Chlramphenicol)).

Chlramphenicol and Tetracycline were introduced together in the mid of 50s and they are the most common used drugs in many developing countries include our country, because it is cheap and could easily be produced by small pharmacy companies.

Chlramphenicol has function related to the inhibition of protein synthesis (but instead of affecting the 30s it target the 50s of bacterial ribosome and then prevent the later transcription and the presence of the peptide bond.

In addition to that Chlramphenicol is a very small molecule so it can easily affect the intracellular organisms ((certain type of bacteria like Brucella, Salmonella typhi (causative agent of typhoid fever))

This type of infection required a type of drug that easily penetrate the intracellular compartment of our tissue (reaching the bacteria inside the tissue and easily reach the (CSF) by the crossing of the barrier of CSF reaching the causative agent)
But why Chlramphenicol is only used in certain type of infection?

Because: it is a very toxic drug especially for certain percentage of population, it associated with what we called Aplastic Anemia (affect the red blood cells, bone marrow ......etc.)

(((((But despite this fact, it considered

1. One of the best drugs in treatment the patients from the fever
2. And it contributes in recovering in short period more effective than any other drugs)))...... from the observations of (dr.shaker kandeel) during the treatment from Brucella and typhoid fever.

Macrolides:

1. composed of drugs which has a large lactone ring which usually composed of 12-14 or 16 rings associated with oxy ,hydroxyl group......etc.
2. affect the 50s of the bacterial ribosome preventing the developing of peptide chain (so it affect the mRNA → affect the protein synthesis)
3. macrolides represented by a very famous drug known as (Erythromycin)

Erythromycin:
- Introduced in the (1970s) to treat the infection especially by staphylococcus and streptococcus (in upper respiratory tract infection)
Especially in patients who are allergic to penicillin (ie, this drug has replaced the penicillin in treatment infections by these organisms)
- Erythromycin (like penicillin G, V and first generation of penicillin) cannot resist the developing of resistant but the resistance here is not related to the production of β-lactamase but it is more related to a change in the cytoplasmic membrane (specific proteins prevent the access of the Erythromycin).

-Despite that, it still a useful drug for treatment of certain types of infection related usually to: a. gram -ve bacteria not gram +ve (G-ve like, streptococcus pneumonia, staphylococcus infection, spectococcus infection group a,b,c and others.
b. in addition to another type of bacteria (which is covered by tetracycline) like *Chlamydia, Legionella*...... (*these considered as intracellular organisms and difficult to be treated by other organisms*)

- the classical form of Erythromycin, usually, should be given 4 times per day, now they have developed more active forms of it called (Clarithromycin and Azithromycin) and this is enough to be given twice per day (as 2 tablets or 1 per 24 hours)

- in relation to the Erythromycin we have another group of drug specialized in treatment staphylococcus infection but especially in certain area of our bodies (like in relation to the oral cavity, bone marrow) where Erythromycin and penicillin cannot penetrate well in the bone.

So we can say, they have developed these form of drug which cover gram+ve chronic bacteria and to some anaerobic bacteria which is not covered by Erythromycin, penicillin, tetracycline, Chloramphenicol .........etc. These drugs are presented by clindamycin, lincomycin.

Clindamycin and Lincomycin are effective mainly against gram +ve bacteria infections especially (staph) and in relation to specific infections especially in the bone. But treatment with these drugs has again side effect, due to the fact that these two drugs inhibit large number of anaerobic bacteria which found in our oral cavity and intestinal cavity. So, they change the ecology of our intestine HOW? By killing the majority of bacteria, and on the other hand by the direct support of spore forming bacteria (anaerobic spore forming bacteria) which belongs to the genus species (*Clostridium difficile*)

I.e. if the patient intestine tract carry the *Clostridium* spore forming bacteria , it will increase in no. resulting in production of a very potent toxins (known as *Clostridium difficile enterotoxin*) . This toxins affect the large mucosa of the intestine necrosis (i.e. Produce a damage associated with bleeding and these toxins also might be absorbed and reach the kidney and produce damage there).
Just a note: that show us how the antibiotics interfere with our body flora, and on the coast of an organism it might support the growth of another, and instead of treat the original problem we will develop a new type of diseases associated with endogenous flora)

Nalidixic acid:

This is the fourth type of antibiotics which related to the nucleic acid (whether DNR or RNA)

1. Nalidixic acid is a part of drug group known as (Quinolones)
2. It has a complex structure composed of 6 rings associated with oxy group, hydroxyl group, amino group ..etc. and it might be associated with flour atoms, Chlorine atoms..etc.

-the basic structure of Quinolones (Nalidixic acid) is found without the presence of flour
-Later they have modified this drug (Nalidixic acid)
- Nalidixic acid was mainly used for treatment of urinary tract infection caused by gram –ve bacteria (like, e-coli) but now it is less used.

-Due to the modification of in the structure of Quinolones, they have developed a new group of drugs called Fluoroquinolones (represented by Ciprofloxacin and norfloxacin ..etc).

# Fluoroquinolones (represented by Ciprofloxacin and norfloxacin ..etc) are very useful drugs introduced 30 years ago and they are Still widely used in treatment variety of infections.

3. Nalidixic acid considered as urinary tract drug
Used in association with urinary tract infections not associated with other infections. Why???
Because this drug excreted to 90% in the urinary bladder, so it has no used to treat other infections in the body.

4. In relation to the Nalidixic acid we have (Nitrofurantoin) which is again an excellent drug also used in treatment of gram –ve bacteria causing usually infection in the urinary tract.

4. The mechanism of action of Nalidixic acid and Fluoroquinolones is related to DNA JAIRAS:

DNA JAIRAS: is responsible for replication and super coiling of the DNA.
→→they prevent the double stranded developing so inhibit the nucleic acid production →so the growth of the bacteria.

Note:

① Fluoroquinolones is a wide spectrum affecting gram +ve and gram –ve bacteria. whereas, the Nalidixic acid affect gram –ve bacteria.
② Fluoroquinolones affect the intracellular organisms and this is very important (exactly like tetracycline).
③ Fluoroquinolones (approximately) accounting 50% of antimicrobial drug used in clinical medicine (because of its ability in treating urinary tract, respiratory tract, systemic infections .............)

④ But unfortunately bacteria again develop increasing resistance against this drug (40% of gram-ve bacteria associated with urinary tract infection and other infections considered to be resistant to Fluoroquinolones.

● In relation to Fluoroquinolones there is another type of drug called fusidic acid
Fusidic acid:
- it is the only steroid antimicrobial drug
- used in treatment of certain type of specific infections related to (staph).
- it prevents translocation of tRNA to ribosome.
- it is used as topical drug (in cases of infections of the skin eyes.....etc.).

Anti-tuberculosis drugs:

1. Special form of drugs used mainly to treat microbacteriotuberculosis And other type of micro bacteria which produce infection.

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<tr>
<td>Tuberculosis still a serious infection agent, kill each year at least 8 million persons around the world.</td>
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<td>The last few years we have seen cases of Tuberculosis (in Jordan as well as in other countries) caused by multiresistant micro bacteria, which cannot be treated with these anti-tuberculosis drugs. As as a result the patients will die or they have to use very expensive drug.</td>
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<td>The treatments of normal Tuberculosis need 6 months of using 2-3 drugs in combination (it is not treated using just one drug).</td>
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<tr>
<td>The treatment course using classical anti-tuberculosis drugs cost 1-2 hundred JD. On the other hand, the cost of multiresistant tuberculosis reach 10-100 hundred thousand $.</td>
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3. All antimicrobial drugs interfere in one way or another in the bacteria synthesis (whether DNA or RNA synthesis). In addition these antimicrobial drugs are directed to affect the cell wall of micro bacteria.
This micro bacteria (which cause tuberculosis) has special cell wall, which is not composed (like gram+ and gram –ve bacteria) from the outer membrane, peptidoglycan layer and oligosaccharides. **But it** composed of a special layer called (Mycolic acid) associated with huge amount of lipids. Which mean that (Tuberculosis) is not easily to be treated with other dugs because the cell wall is not accessible for these drugs.

**Examples of anti-Tuberculosis:**

- Rifamycin group, Isonized (INH), Ethambutol, Cycloserine....there is others but these are the most common ones.

**The treatment of this disease takes a long time (6-24) months.

**S** Rifamycin:

1. It can be used in treatment of other infections than tuberculosis
    - In certain cases used to treat the Chlamydia and Brucella (multifever, produce high fatality if the patient is not treated)
    - Note: Chlamydia and Brucella are considered intracellular organisms.

    **As a result:** Rifamycin mainly used in tuberculosis but it might be used in treatment of other infections especially in cases of Chlamydia infection and Brucella infection.

2. It can penetrate tissue, and inhibit the multiplication of these bacteria.

**Sulfa drugs:**

- The first chemical constructed drug, introduced in chemical medicine for certain gram +ve bacteria.
- They developed a new form of this drug like sulfanilamide.

**Sulfanilamide:**

- Belong to Sulfa drugs
- Very simple drug
c. Has a mechanism of action in relation to the production of folic acid

Note: folic acid is essential component in production of protein synthesis.

-Sulfa drugs (sulfanilamide) compete another precursor called Para- amino benzoic acid (PAPA) on an enzyme activity which is responsible for the conversion of dehydrofolic acid into folic acid. (Plz, check this info.)

This mean, at the end, that sulfa drug interfere with the production of protein synthesis producing a form of inhibition (not directly but through the folic acid which is important in protein synthesis).

-sulfa drug can be used in treatment of gram +ve and-ve bacteria and they found that if sulfa drug where combined with another drug called Trimethoprim to produce what we call (combination synergism reaction).

In synergism reaction we have an additive effectiveness against that microorganism (i.e. double effect of two types of drugs or chemical structures).

-Sulfamethoxazole with Trimethoprim together produce a drug called (Cotrimoxazole) .this new drug as combination is excellent in treatment a wide range of gram +ve and –ve bacteria in relation to the respiratory tract urinary tract...etc.

But now more than of 70% of clinically isolated e-coli considered to be resistant to this drug, so this drug, now, is less used despite the fact it is very cheap and easily to be used. Now, the use of it is limited on outpatient clinic in the first time developing infection.

§Metronidazol:

-used only in treatment of anaerobic infection as well as against certain parasites (protozoa).

-it is very valuable for Surgeons (they use it in association with another drugs like amino glycosides or retrophiencol) usually to control or prevent an infection by anaerobic bacteria.
Antibiotic susceptibility tests

It’s important if we have any clinical infection to:

(Clinical infection: infection in related to any part of our bodies from upper respiratory tract, skin GI tract...to the urinary tract...etc.)

1. Know, firstly, the causative agent (by isolation and identification of the causative agent)
   -for that we have some selective media and molecular techniques.
   -for example: in relation to the urinary tract we have to get a urine sample and to culture for the pathogen and once we isolate the organism in pure culture (not in a mixed) so we can do what we call antimicrobial or antibiotic susceptible disks.

2. Do, secondly, antimicrobial or antibiotic susceptible disks to know if the isolated agent is sensitive or resistant to a certain type of drug.

   - we have to use special medium called Mueller Hinton agar medium
   - the culture growth which used to test against the different type of antibiotic must be fresh (not older than 24 hours) and often, we prefer to be the logarithmic phase (during the rapid growth).
   - and then we plated definite amount (0.1 ml) which contain about 10^7 cells on the surface of the plate by using of the cotton swab
   - later, we place a number of disks (5-8), each one contain a definite amount of antimicrobial drug

   --this amount is not randomly put((they use an amount of a drug which can be later translated into a definite amount to be given to patients.))
   (Ie. They determine the concentration in vivo from the concentration in vitro)
   - each of these drugs, according to the activity, produce inhibition zone
surrounding the disk

- Note: the disk is a filter paper impregnated with these antibiotics.

- There are guide lines (managements) for these zones in the lab. (Ex. The cefoxitin (fox) in order to be sensitive to(e-coli)the zone must be at least 18 µm.......and so on.)

★-and then we record the results to the physician as this bacteria is (S) susceptible or (R) resistant

So by that we have isolated the organism and decided if it S,R.

The accuracy of the disk method (called the diffusion method) reaches up to 97-98%.

Not 100%→because under certain conditions the bacteria reported to be in vitro as (S bacteria) and appear as (R bacteria) in a patient [i.e. the patient doesn’t response to the drug].

So the report is just a guide line for the physician but there are other factors should be considered.

Sometimes there is some patients who has problems with their kidney function or liver function so, you have to use the least amount of the drug which can kill or inhibit the microorganism (this have a special test called e-test similar to the filter disk test but there is a gradient for concentration)

We can exactly measure the microgram/ml (ie. The amount of the drug which can be used in treatment of the infection and this help to select, in certain cases, the proper anti microbial drug.
Multi resistant:

● The definition (According to different references):

  Multi resistant bacteria: bacteria that resist 2 types of antibiotics or more.

  Multi resistant bacteria: bacteria that resist 3 types of antibiotics or more. (this one is better)

● 3 types mean 3 groups of drug (we consider the resistant as groups like penicillin group, chloramphenicol group....etc. except for second and third generations which have different considers).

● Misuse, overuse and wide use of drugs (no relation to the patients only but also to the community like in animal hospitality or in chicken farms) all of these control directly or indirectly developing of this resistant.

● Antimicrobial drugs cannot consider as personal drug, because this doesn’t affect him alone but also the community. For example, if you take this drug you may indirectly develop resistant in the intestinal flora which could distribute to other family or community members.

  ◆ Note: resistant is not a reversible process, if it is developed it will be stable for a long time.

Your colleague Laila Suboh