Antibiotics can be classified according to their effects on the biochemistry or molecular biology of pathogens:

1-ribosomal inhibitors (macrolides),
2-cell wall disrupters (B-lactams),
3-DNA disturbers (fluoroquinolones),
4-metabolic poisons (trimethoprim-sulfamethoxazole).

Antibacterial Agents

-Substances that **kill or stop the growth** bacteria **without** harming the host.

-History:

Arsenic: 1800s for **syphilis**.

Sulfonamides: 1935.: **synthetic** antimicrobial agents.[not used now due to resistant]

Penicillin(Antibiotics): 1940.

Antimicrobials have revolutionized the treatment of bacterial infections as well as enhanced the advancement of medical and surgical treatment.

#Patient's natural resistance plays a major role.

-Choosing an Antibiotic: [you need to think about]

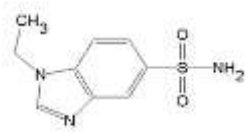
1-The infecting organism.
2-The correct antibiotic. **3**-Site of infection.
4-Route of administration. **7**-cost
5-Drug history of the patient.[if there is any allergy]
6-Complicating factors such as pregnancy.

-Problems associated →

1-Overprescribing due to patient demand
2-time pressure on clinicians
3-diagnostic uncertainty.

#Sulphonamides

Almost obsolete nowadays because of:[stopped now due to]



1-Bacterial resistance.
2-bacteriostatic
3-Toxicity:
a-Nausea. b-Rashes
c-Blood dyscrasia: the presence of abnormal material in the blood, usually applied to diseases affecting blood cells or platelets. Evidence of dyscrasia can be present with a **WBC count of over 1,000,000**.
4-Precipitation (crystallization) in urinary tract and stone formation.

Chemical features

-SO2NH2 group is not essential
-as such the important feature is that the sulfur is linked directly to the benzene Ring
-The NH2 group is essential.

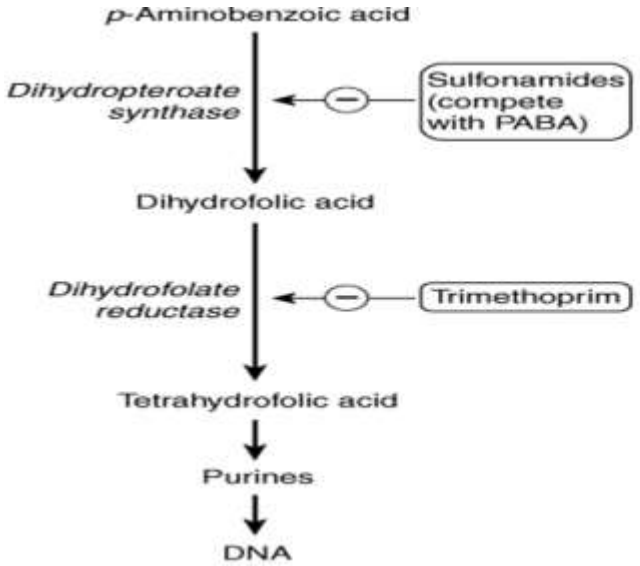
Sulphonamides... كلهم فيهم tri

Cotrimoxazole- Trimethoprim Combination→
other names(**Bactrim**, **Septrin**, **Balakatrin**):
One of the few, **still** used, sulfa drugs.
-**Very effective fixed combination**.
-**No resistance**.
-**Very useful** in UTI, RTI, treat Salmonella, and Pneumocystis pneumonia, an opportunistic infection in AIDS patients.

#التركيبة الوحيدة لحد الان تستخدم

-Mechanism of Action→

-Sulfonamides: structural analogs and competitive antagonists of para-aminobenzoic acid (PABA)
-Prevent normal bacterial utilization of PABA for the synthesis of folic acid



Sensitive microorganisms are those that must synthesize their own folic acid;
bacteria that can use preformed folate are **not affected like mamalin cells**

#Quinolones

Interfere with cell division of bacteria[stop the division.

1-Nalidixic Acid:

-Very old **urinary antiseptic**.[**for UTI**]

2-Norfloxacin:

Used **only for UTI**.

3 day course.

3-fluorinated 4-quinolones [famous] such as ciprofloxacin (CIPRO), mxifloxacin (AVELOX), and gatifloxacin (TEQUIN)

Ciprofloxacin:[famous}

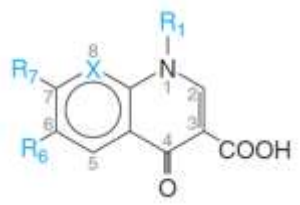
-Wide range of activity, even Botulinum.

-Expensive.[disadv.]

-Prophylaxis for meningitis.[in surgery]

Can cause g.i upset, and epilepsy

Quinolones available for use are containing **a carboxylic acid moiety at position 3 of the primary ring structure**



-end with **floxacin**

وعشان تتذكروا هم لشو

Fluor=floxacin

Note→Botulinum toxin is produced by Clostridium **botulinum** bacteria

#Nitrofurans (Nitrofurantoin)

Chemistry and Mechanism of Action

-A number of 5-nitro-2-furaldehyde derivatives, called nitrofurans, are used in the **treatment** and/or **prophylaxis** of microbial infections, primarily in the **urinary tract.**

-modify various bacterial macromolecules that affect a variety of biochemical processes (e.g., DNA and RNA synthesis, protein synthesis.)

It is presumed that the nitrofurans are selectively toxic to microbial cells because in humans→ the **slower reduction by mammalian** cells prevents high serum concentrations.

Nitrofurantoin is primarily **active against gram-negative bacteria** (**E. coli, P. mirabilis i**s variable) and some **susceptible gram-positive organisms**, such as **S. aureus** and **Enterococcus faecalis**

#note→resistant strains is virtually unknown

Clinical Use

The singular indication for nitrofurantoin is the **treatment** and **long-term prophylaxis** of lower UTIs caused by susceptible bacteria

it is not used as a bacterial suppressant.

It is often used prophylactically post intercourse in women with **chronic UTIs.**

The **bacteriostatic or bactericidal** activity of nitrofurantoin is **concentration** dependent; a urinary concentration **greater than 100 ug/mL ensures bactericidal** activity

Nausea and **vomiting** are the most commonly **observed adverse effects**.

Nitrofurans example : Methenamine

Methenamine (hexamethylenetetramine) is an **aromatic** acid hydrolyzed at an acid pH (less than 6) to **liberate ammonia and the active alkylating agent formaldehyde**

-formaldehyde denatures protein and is bactericidal.

Methenamine is usually administered **as a salt** this salt is either **mandelic** (Mandelamine) or **hippuric** (Hiprex, Urex) acid.

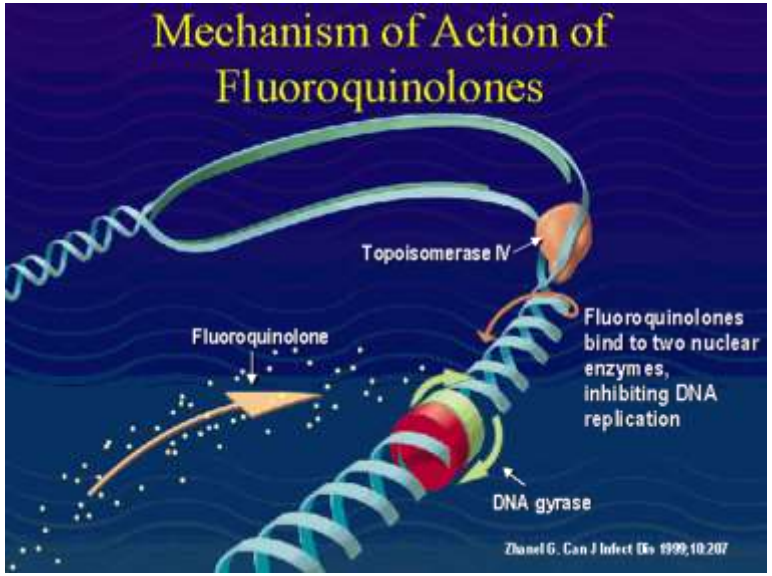
these acids **acidify** the urine, which is necessary to generate formaldehyde.

also, the resulting **low urine pH is by itself bacteriostatic for some organisms**

Methenamine...

Methenamine is **administered orally** and is well absorbed from the **intestinal tract**.
10 to 30% decomposes in the stomach unless the tablets are protected by an enteric coating.
The **inactive[ammonia mostly]** form (methenamine) is distributed to virtually **every bodyfluid.**
Almost all of the methenamine moiety is excreted into the urine by 24 hours

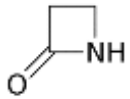
Methenamine is primarily used for the long-term **prophylactic** or suppressive therapy of **recurring UTIs**.
It is not a primary drug for therapy of acute infections.
It should be used to maintain sterile urine after appropriate antimicrobial agents have been employed **to eradicate the infection.**



Quinolones inhibit the nicking and closing activity of the gyrase and also block the activity of topoisomerase IV

Beta Lactam Antibiotics

All contain a beta lactam ring.
Work **to inhibit cell wall synthesis.**



The **beta lactam ring** is the **active functional group where antibiotic activity resides**

-Resistant bacteria produce a lactamase which **can break this ring.**

-**Penicillin G** → is the prototype for all antibiotics and all the **beta lactam antibiotics**.

Oldest antibiotics, but still growing and **new agents are still discovered** and added to the group.

→**β-lactamase inhibitors**:

1-Clavulanic acid
2-sulbactam
3-tozabactam

To avoid resistant by add new product work with antibiotic:

The Penicillins

Are the **most widely** used antibiotics.
Penicillin G was found very effective against the most common and important **Gram positive** bacteria like **Staph**, **Strept**, **Pneumococcus**, and many others..

-**Natural** produced from the fermentation medium used to culture Penicillium such as Penicillin G which is the only natural penicillin used clinically→ من فطر البنسلين

-**Semisynthetic**= Modified natural.

-**Synthetic**.

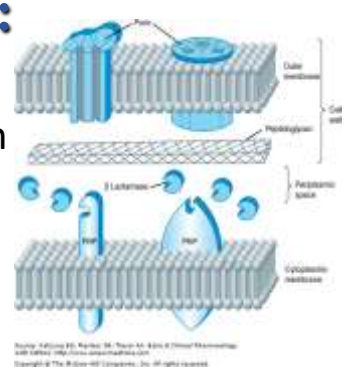
Side chains can be added that alter the susceptibility of the resulting compounds to inactivate enzymes (β-lactamases)

-Penicillinase, produced by resistant bacteria, inactivates penicillins by **breaking the beta lactam ring**.

-Clavulanic acid inhibits this enzyme, so **combined** with **ampicillin** to give good combination" **Augmentin".**

Penicillin Actions:

-The cell walls of bacteria are essential for their normal growth and development.
-Peptidoglycan provides **rigid** mechanical stability.



In gram-positive microorganisms, the cell wall is 50 to 100 molecules thick, but it is only 1 or 2 molecules thick in gram-negative bacteria

last step in peptidoglycan synthesis that is **inhibited by the β-lactam antibiotics**
Benzyl penicillin (Penicillin G):
-Deep **IM injection**.
-Highly active against sensitive strains of gram-positive cocci
-**hydrolyzed by penicillinase**
-**ineffective S. aureus**
-**Procain benzylpenicillin**: حل مشكلة الالم
Painless, **prolonged** action injection.
-**Phenoxymethyl penicillin**:
Oral, not **destroyed by gastric juice**.
-**Cloxacillin**, **Dicloxacillin**, and **Fluclocillin** :
Penicillinase resistant, for Staphylococcus.

The Penicillins…

#End with -cillin

Ampicillin:

Broad-spectrum penicillin, can cause **diarrhea**, due to **overgrowth** of normal flora, and **incomplete** absorption.

Frequently administered with a **β-lactamase** Inhibitor to avoid any resistant.

Amoxicillin:

Same, but more completely absorbed than ampicillin.

So, less diarrhea, and **longer acting than ampicillin.**

Azlocillin, **Pipercillin**, and **Ticarcillin**:

Have **extended spectrum**, e.g. Proteus, Pseudomonas,Klebsiella, and certain other **gram-negative** Microorganisms.

Adverse Effects:

Relativley **very safe drugs**; except:

Pain of injection. Abscess formation.

Allergic reactions:

1-Skin rash.2-Urticaria.3-Anaphylaxis.
4-rash 5-fever 6-bronchospasm,
7-dermatitis, Stevens–Johnson syndrome

→note:

1-**Anaphylaxis** is a serious allergic reaction that is rapid in onset and may cause death.

2-Stevens–Johnson syndrome, a form of toxic epidermal necrolysis, is a life-threatening skin condition, in which cell death causes the epidermis to separate from the dermis.

Management of the Patient Potentially Allergic to Penicillin.

Evaluation of the patient's history is the most practical way.

Most patients who give a history of allergy to penicillin should be treated with a different type of antibiotic.

Antistaphylococcal (penicillinaseresistant) Penicillins→

• including **Nafcillin**, **oxacillin**, **cloxacillin**, and **dicloxacillin** which are more **resistant to bacterial B-lactamases than is penicillin G.**

• Consequently, these antibiotics are effective against for MRSA and methicillin-resistant Staphylococcus epidermidis (MRSE).

Methicillin, is no longer marketed in the United States, is another penicillinaseresistant antibiotic similar to nafcillin and oxacillin.

• Many hospitals are reservoirs for MRSA and **methicillinresistant Staphylococcus epidermidis (MRSE).**

These pathogens are resistant in vitro to all B-lactam antibiotics.

• For parenteral therapy, nafcillin and oxacillin offer comparable efficacy and antimicrobial spectra of activity.

• Indications for nafcillin or **oxacillin** include severe staphylococcal infections like cellulitis, empyema, endocarditis, osteomyelitis, pneumonia, septic arthritis, and toxic shock syndrome.

B-Lactamase Inhibitor Combinations

Several **formulations combine a B-lactam antibiotic with a B-lactamase inhibitor such as**

- (**ampicillin-sulbactam** [Unasyn],
- **ticarcillin-clavulanic acid** [Timentin],
- **piperacillin-tazobactam** [Zosyn],
- **amoxicillin–clavulanic acid** [Augmentin]).

All of the B-lactamase inhibitor combinations except **amoxicillinclavulanic acid are parenteral formulations.**

- Elimination of the combination drugs occurs primarily by **renal excretion**

→all of the B-lactamase inhibitor combinations require dose adjustments in patients with renal insufficiency.

- The addition of the B- lactamase inhibitor significantly broadens the spectrum of antibacterial activity against Blactamase-producing organisms.
- Consequently, these drugs have clinical use in treating infections with known or suspected mixed bacterial flora, such as **biliary infections, diabetic foot ulcers, endomyometritis, and peritonitis**.

→note:

Gram-positive bacteria are bacteria that give a positive result in the Gram stain test. then appear to be purple-coloured .This is because the thick peptidoglycan layer in the bacterial cell wall retains the stain after it is washed away from the rest of the sample

- **Gram-negative bacteria** cannot retain the violet stain after the decolorization step; Their peptidoglycan layer is much thinner and sandwiched between an inner cell membrane and a bacterial outer membrane, causing them to take up the counterstain and appear red or pink.

The Cephalosporins

Came one decade later after the penicillins.

Rarely the drugs of first choice for any infection.

Mainly used for surgical prophylaxis.

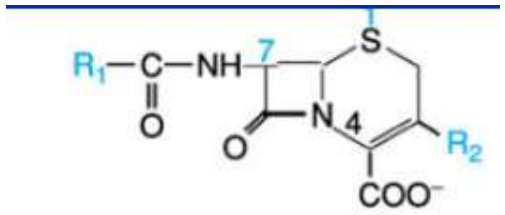
Expensive, especially the newer generations.

Same toxicity as penicillins.

Cross allergic with the penicillins.

Activity differs among the generations.

The generations differ in modifications in the R1 and R2 groups and is based on general features of antimicrobial activity.



Cephim nucleus

The Cephalosporins…

#**First Generation:** good activity against **gram-positive bacteria** and relatively modest activity against gram negative microorganisms.

-Cephalothin

-Cefazolin

#**Second Generation**: somewhat **increased activity against gram-negative** microorganisms

-**Cefamandole.**

-Cefoxitine.

#**Third Generation**: more active against the **Entero bacteriaceae, including β-lactamase-producing strains**

-Cefoperazone.

-Cefotaxime.

-Ceftriaxone.

#**Fourth-generation** **extended spectrum of activity and stability from hydrolysis**

-**Cefepime**

Lectures 2 to 5
Dr. Manar
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