Pharmacology

Subject :

Lec no : 29

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وَقُل رَّبِّ زِدْنِي عِلْمًا

*طب هسا ليه عم نحكي عن هدول العائلتين سوا رغم انهم ما الهم دخل ببعضchemically وهما من 2 different family لسببين :
١*انهم بشتغلو على ال DNA synthesis بس بطرق مختلفة
٢*انهم useful to treatment UTI

Folate Antagonists

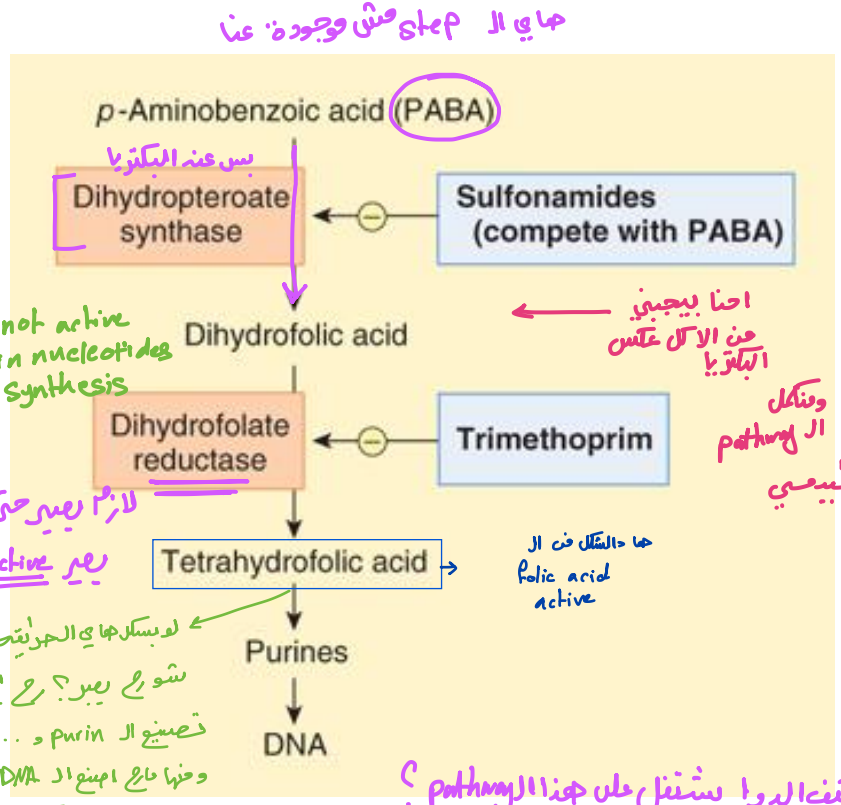
ملاحظة مهمة عن دور nucleotides اللي همه ال purines and pyrmidines في تكوين الdna:
يتم تصنيع ال purines وال pyrimidines في خلايا البكتيريا من خلال pathways معينة لتكوين ال nucleotides اللي بتشارك في تصنيع ال dna

Anti metabolites
بتدخل في جميع ال metabolic processes الخاصة بال folic acid

Folic Acid Antagonists

كل ال**metabolic pathways** الخاصة بتصنيعهم **depend on the folic acid cofactors** وتعتبر مهمة جدا لنمو البكتيريا وال **dna synthesis**

- Purine and pyrimidine synthesis requires folate-derived cofactors
- Folic acid is necessary for DNA replication and cellular growth
- Many bacteria are impermeable to folate →rely on de novo synthesis
- Folic acid must be converted into tetrahydrofolate



*some of bacteria → synthesis folic acid
*Eukaryote → can't do this (من الاكل جاهزه)

Sulfonamides

بتدخل مع اول عمليات تصنيع ال folic acid اللي بتظهر في denovo bacterial step

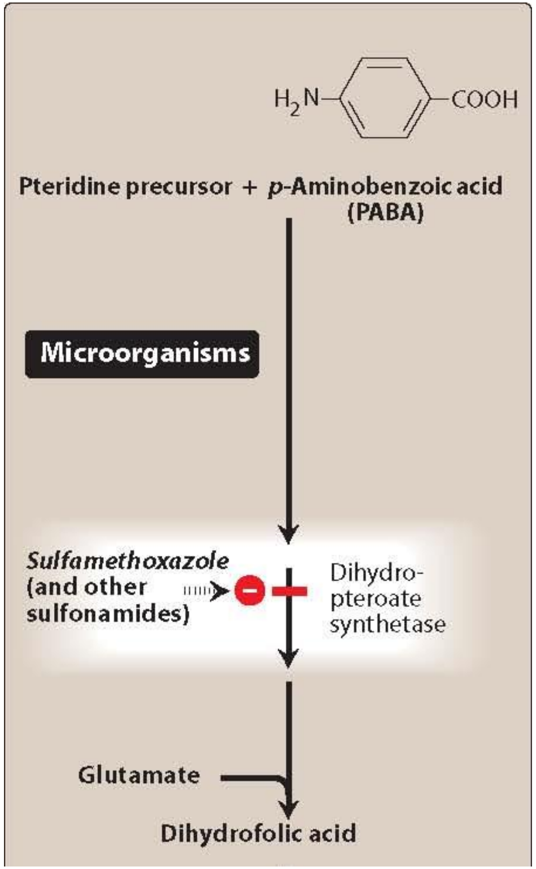
Sulfonamides

Mechanism of action:

- Sulfonamides are synthetic analogues of PABA
- PABA is used to synthesize dihydrofolate
- Sulfonamides inhibit *dihydropteroate synthetase*

Which block the folic acid synthesis and interfere with purines and pyramidine synthesis which lead to the bacterial DNA synthesis

- Bacteriostatic



Sulfonamides

Antibacterial spectrum

gram −

- Effective against Enterobacteriaceae causing UTIs
- Effective against H. influenza, streptococcus, staphylococcus spp.

Mechanisms of resistance

- Altered dihydropteroate synthetase
- Decreased cellular permeability
- Enhanced production of PABA

To sulfa drugs

INHIBITORS OF FOLATE SYNTHESIS

1. *Mafenide* SULFAMYLON
2. *Silver sulfadiazine* SILVADENE
3. *Sulfasalazine* AZULFIDINE

عن طريق يغير في ال bind ويقلل ال affinity لارتباط ال drug

ما في سرف

3 2 1

جرب انت بالمختبر وحط E.coli وعرضها ل low concentration to sulfonamides يوم بعد يوم في جزء رح تلاقي مات وجزء رح يلاقي طريقة تعمل فيها resistant وحدة من هاي الطرق انها تحسن وتزود انتاج PABA ليههه؟ لانو حكينا هو competition analogues يعني بس يزيد تركيز PAPA رح ينافس ال الدوا على المكان

Sulfonamides

Pharmacokinetics

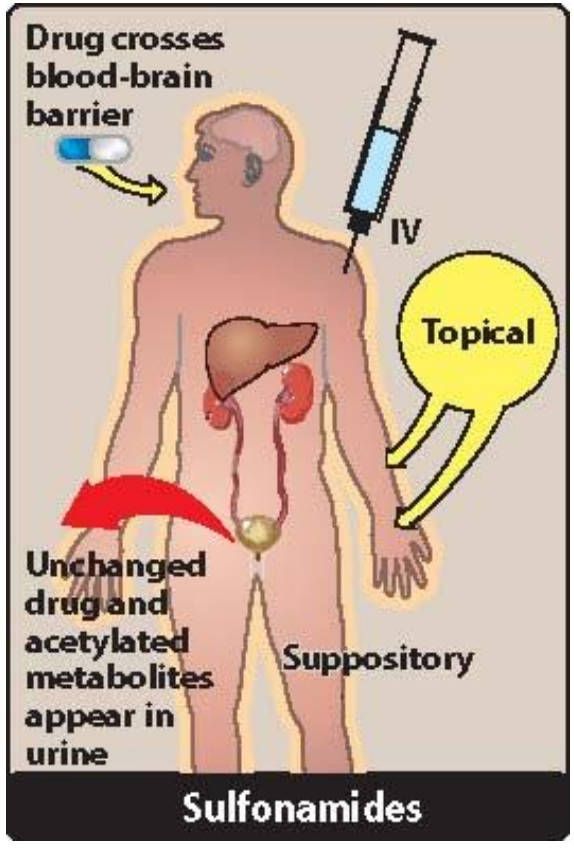
- **Absorption**

-oral: well-absorbed (except sulfasalazine) poorly absorbed

-how can you use sulfasalazine? سبشل

We use it to treat inflammatory not infection but autoimmune diseases like ulcerative colitis, rheumatoid arthritis

+ إلي تحت



Special Uses

toxoplasma gondii parasite عدوى سببها
ويتعدي الاشخاص منقوصين المناعة زي الـ AIDS

سبشل كمان

TOXOPLASMOSIS RX

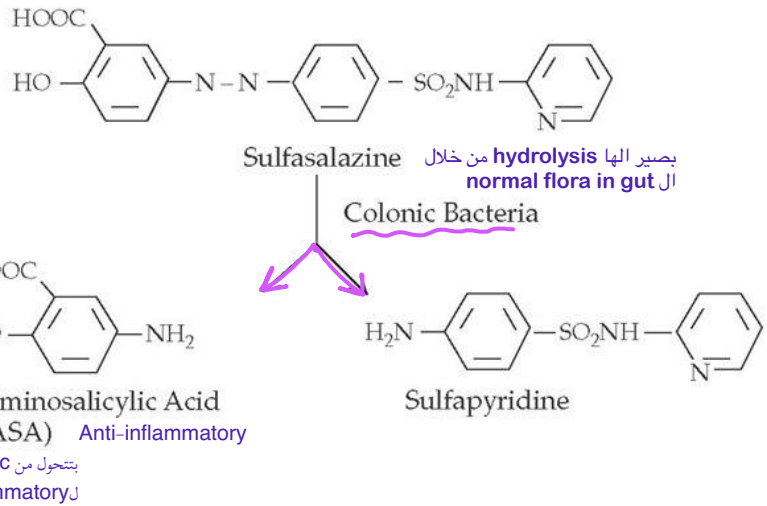
First Line	• Pyrimethamine (200mg-L/75C) + Sulfadiazine(6-8g/d -4d/d) till improve CD4 count • Pyrimethamine + Clindamycine

برضوهاي ملبتص سبشل

It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of chronic inflammatory bowel diseases.

يستخدم في الحروق لانه بمنع ال **colonization of bacteria at burn sites**

(بذكونا بد ايبرين)



بصير الها hydrolysis من خلال ال normal flora in gut

بتتحول من antibiotic ل anti-inflammatory

Sulfonamides

Pharmacokinetics

- **Distribution**

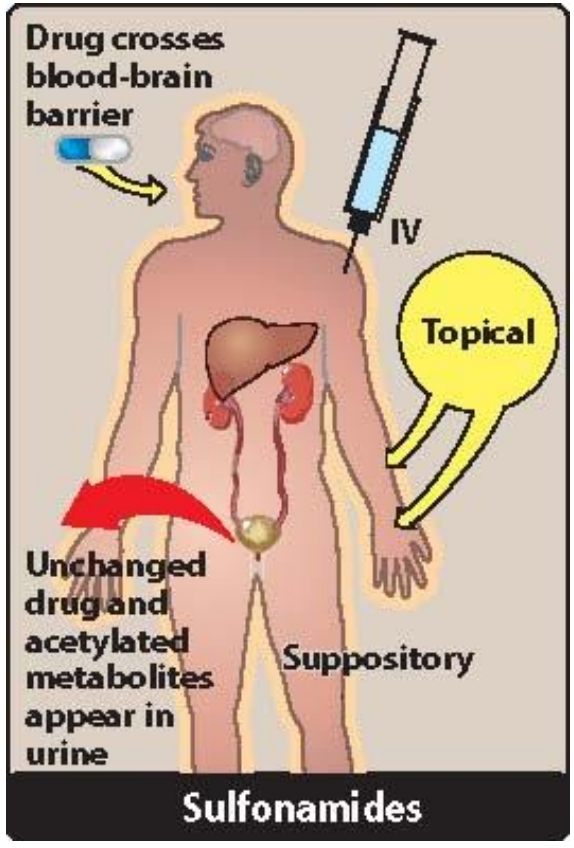
-highly-bound to serum albumin → warfarin زي أدوية

-distribute well through body fluids including CSF

-cross placenta

-eliminated in breast milk

It is a contraindicated treatment in lactating women



Sulfa drugs penetrate well into cerebrospinal fluid and cross the placental barrier to enter fetal tissues.

Sulfonamides

Pharmacokinetics

- **Metabolism**

بس يطلع من ال liver ويروح الkidney

-metabolized in the liver (acetylation and conjugation)

يترسبو ويسببو

-acetylated metabolites can crystalize in urine causing renal stones

(acidic urine)

يسبب ال pH

وهاي من ADE

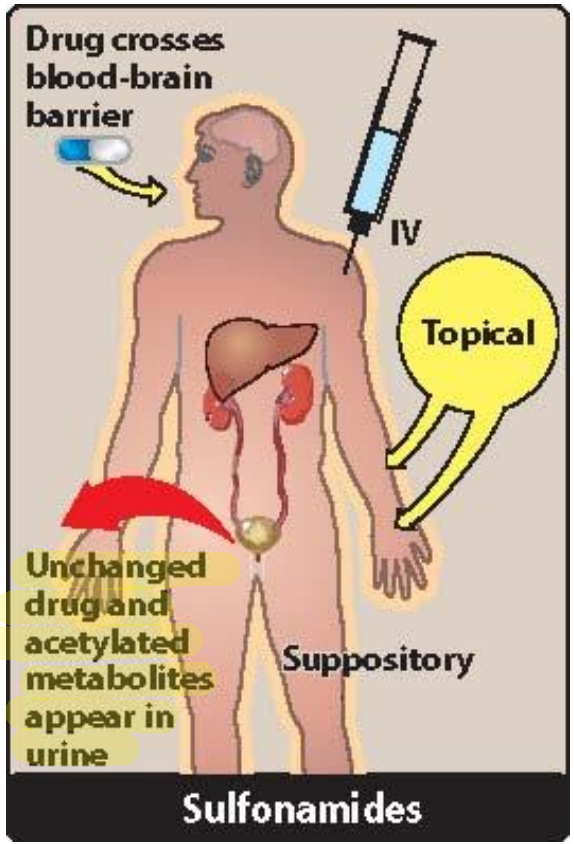
in kidney

كل ما زادت ال acidity زاد crystalize

ـ كيف نعلجها؟ عن طريق ال alkalin

- **Elimination**

-eliminated by glomerular filtration and secretion



Sulfonamides

Adverse effects

- **Crystalluria**

-nephrotoxicity **Damage of the urinary tract system**

-requires adequate hydration and urine alkalinization **Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization**

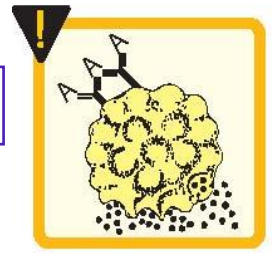
- **Hypersensitivity**

ممكن تكون خفيفة وبعدين تتطور لـangioedema وممكن توصل ل Steven-Johnson syndrome

-sulfa allergies **When patients report previous sulfa allergies, it is paramount to acquire a description of the reaction to direct appropriate therapy.**

- **Hematopoietic disturbances:**

-hemolytic anemia in patients with G6PD deficiency **High oxidative stress that lead to the break of red blood cells**



Sulfonamides

هسا احنا عنا bilirubin في الدم بس ما بعدي ال BBB عكس ال new borne لانو free

Adverse effects

- **Kernicterus** Bilirubin-associated brain damage (kernicterus} may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the blood-brain barrier is not fully developed.

-in newborns

-sulfa displace protein-bound bilirubin in plasma

- **Drug-drug interaction**

-increase anticoagulant effect of warfarin

- **Contraindications**

-newborn, infants, breastfeeding women

-with methenamine

Trimethoprim

Trimethoprim

(Sulfonamides) بشتغل على الخطوة اللي بعدها من ←

Inhibition of this enzyme prevents the formation of the metabolically active form of folic acid, tetrahydrofolic acid, and thus, interferes with normal bacterial cell functions

Mechanism of action

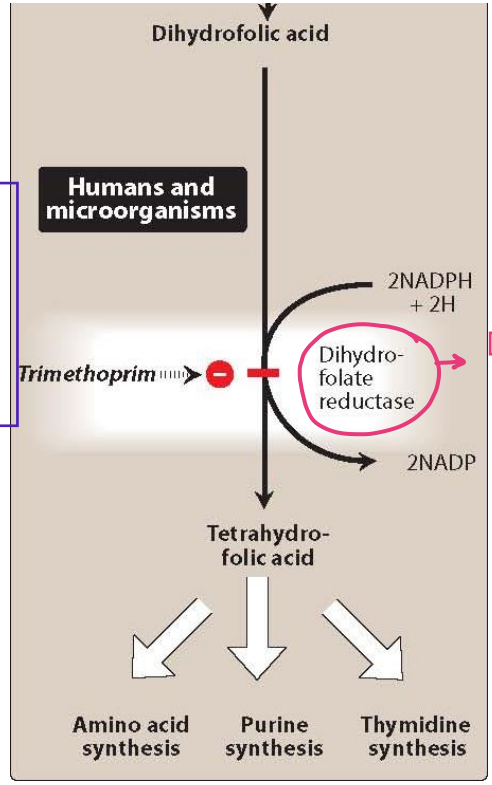
- Dihydrofolate is reduced to tetrahydrofolate (active form of folate) by dihydrofolate reductase
- Trimethoprim inhibits dihydrofolate reductase
- Decreases purine and pyrimidine synthesis
- Bacterial vs mammalian selectivity
- Mostly combined with sulfa drugs

More selectivity ←

* Less selectivity

Trimethoprim binds to bacterial dihydrofolate reductase more readily than it does to human dihydrofolate reductase

يعني ممكن يكون selective اله toxicity of the drug



عنا ← عند البكتريا

Similar but not identical

لها اكيد بتختلف في فرق بـ الـ structure

سمع نحكي عنها تصنع وقال الدكتور حتى نعرفها

تتذكرو القاعدة الي كنا نحكي عنها انو احنا يفضل استخدام نوع واحد من ال antibiotics,بس حكينا انو في بعض السيناريو انو نستخدم combination زي في وقت ال multi resistant drugs وهكذا useful

Trimethoprim

Antibacterial spectrum

- Similar to sulfa drugs e.g., sulfamethoxazole
- More potent as a single agent → more potent than the sulfonamides
- Can be used alone. For what? … but not very often…

Trimethoprim may be used alone in the treatment of urinary tract infections (UTIs) and in the treatment of bacterial prostatitis

Mechanisms of resistance

نفس ال sulfo بس ال Target غير

- Altered dihydrofolate reductase

It has a lower affinity for trimethoprim so it will Lose its function to target its target

- Efflux pumps **decrease permeability**

بعمل inhibition ل step مشتركة في بكتيريا وفينا عكس ال sulfanilamide كان ال adverse الو على ال pharmakinatic و بأثر على البكتيريا جستت

Trimethoprim

Adverse effects

In the mammalian cells of humans

- can produce the effects of folic acid deficiency.

-megaloblastic anemia — The bone marrow will not be able to produce functional red blood cells and there will be large RBCs and decrease in the number of these cells

-leukopenia — Decrease in leukocytes in the blood

-granulocytopenia, — Decrease of peripheral blood granulocytes below lower limit of normal range

***Reversed by administration of folinic acid, which does not enter bacteria.

- Hyperkalemia

especially at higher doses and when administered with other medication that causes hyperkalemia

ممكن تسبب cardiac او cardiac toxicity arrhythmia

* اكثر مكان بحتاج فيه pyrimidine و purine

function: تعويض النقص في folic acid

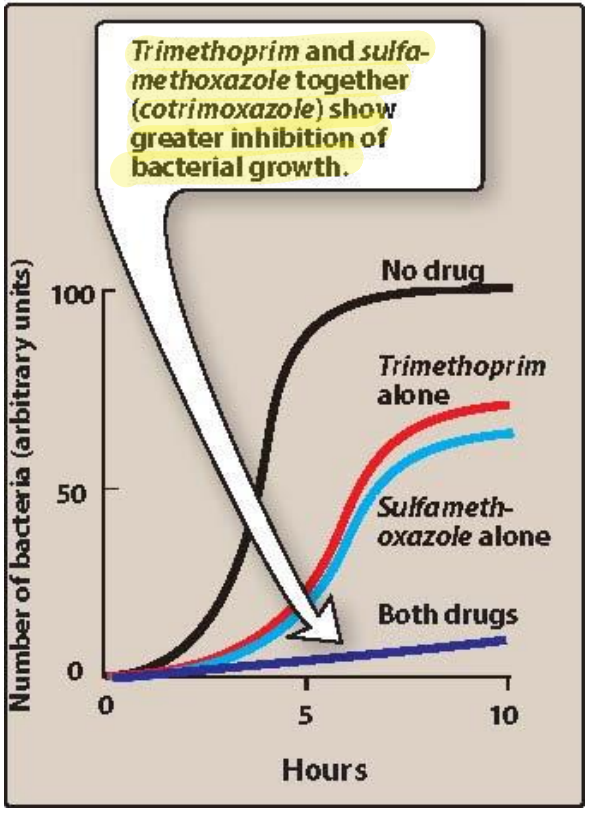
* اعطيت هاد ال antibiotic وقتل البكتريا بس ال effect اجتت لل bone marrow وهاد عند المريض (Megaloblastic anemia) كيف احلها؟ عن طريق اعطيه folic acid حا بأثر على شغل ال antibiotic

Trimethoprim/Sulfamethoxazole = (Cotrimoxazole)

The combination shows greater antimicrobial activity than equivalent quantities of either drug used alone and because they work on the same pathway

- The combination has a synergistic effect
- inhibition of two sequential steps in the synthesis of tetrahydrofolic acid.

Sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors, and trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate



Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

Antibacterial spectrum

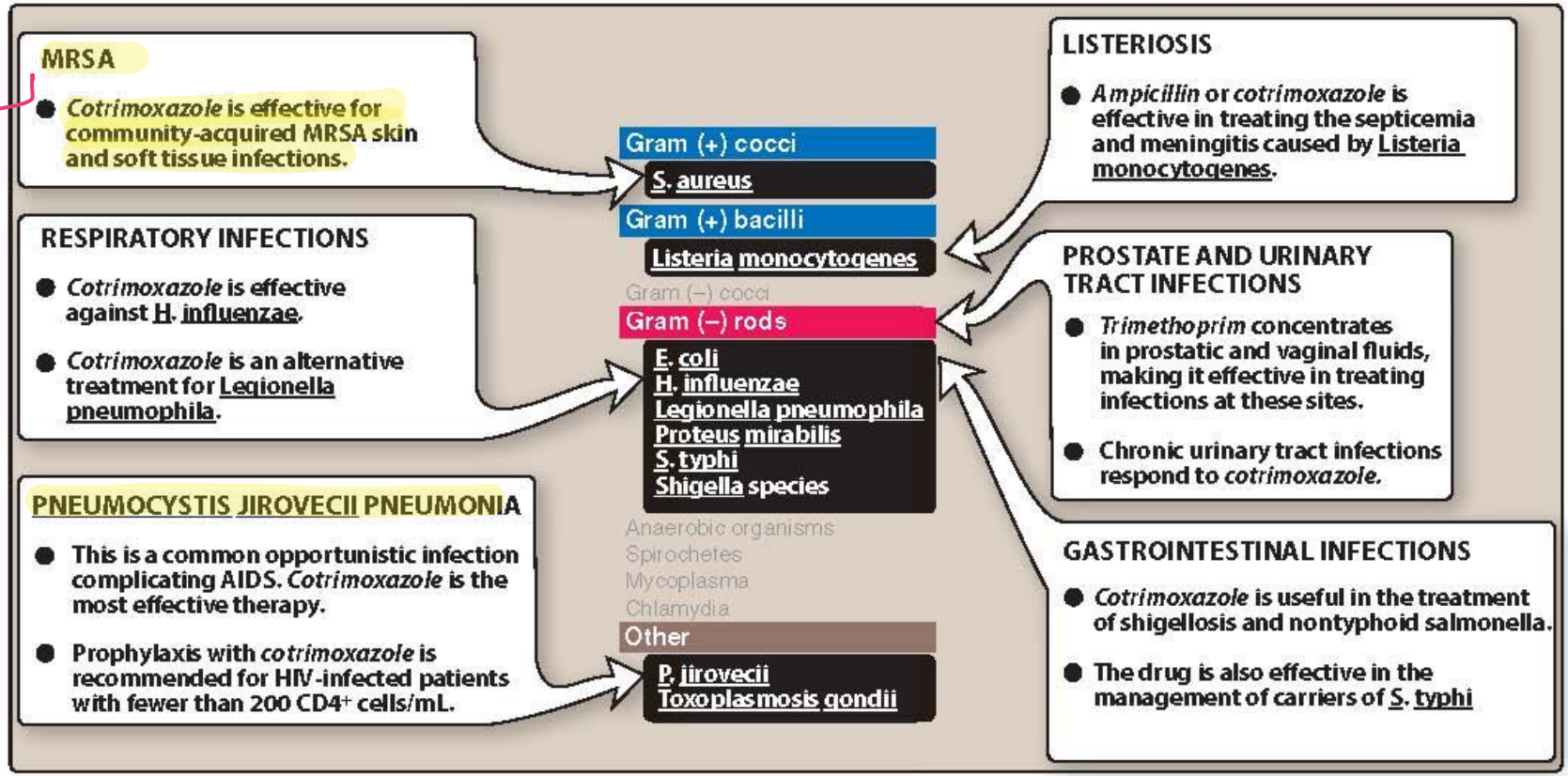
Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone

- Effective in treating UTIs and RTIs
- Effective against *Pneumocystis jirovecii* pneumonia
- Skin and soft tissue MRSA infections
- Drug of choice for infections caused by Nocardia spp.

Opportunitic

AIDS حويفين عنزو

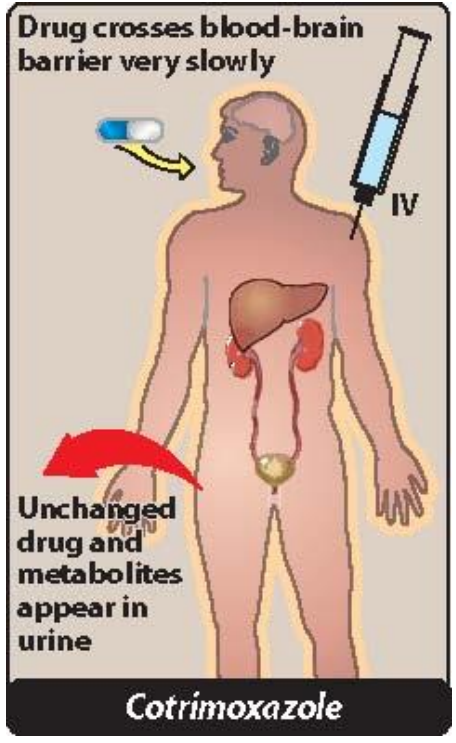
Trimethoprim/Sulfamethoxazole (Cotrimoxazole)



Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

Pharmacokinetics

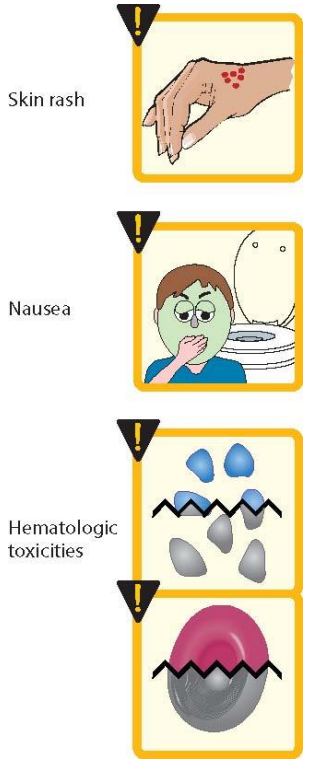
- Administered orally (IV reserved for severe cases of PCP) severe pneumonia caused by Pneumocystis jirovecii
- Crosses BBB
- Excreted in the urine



Trimethoprim/Sulfamethoxazole (Cotrimoxazole)

Adverse effects

- N/V/D
- Skin reactions
- Glossitis/stomatitis
- Hyperkalemia
- Megaloblastic anemia **trimethoprim** حكينا عنها قبل وبرضه سببها ال
- Hemolytic anemia in patients with G6PD def **a disorder in which red blood cells are destroyed faster than they can be made due to sulfa drugs**
- Drug-drug interaction with warfarin



هادمهم + زبدة الكلام

Urinary Tract Antiseptics/Antimicrobials

- UTIs are more prevalent in women and elderly
- Most common cause: *E. coli* (80% of uncomplicated UTIs)
- Second most common cause: *Staphylococcus saprophyticus*

gram (-)

Most frequently used agents:

1. **Cotrimoxazole**
2. **Nitrofurantoin**
3. **Fluoroquinolones**
4. **Methenamine**

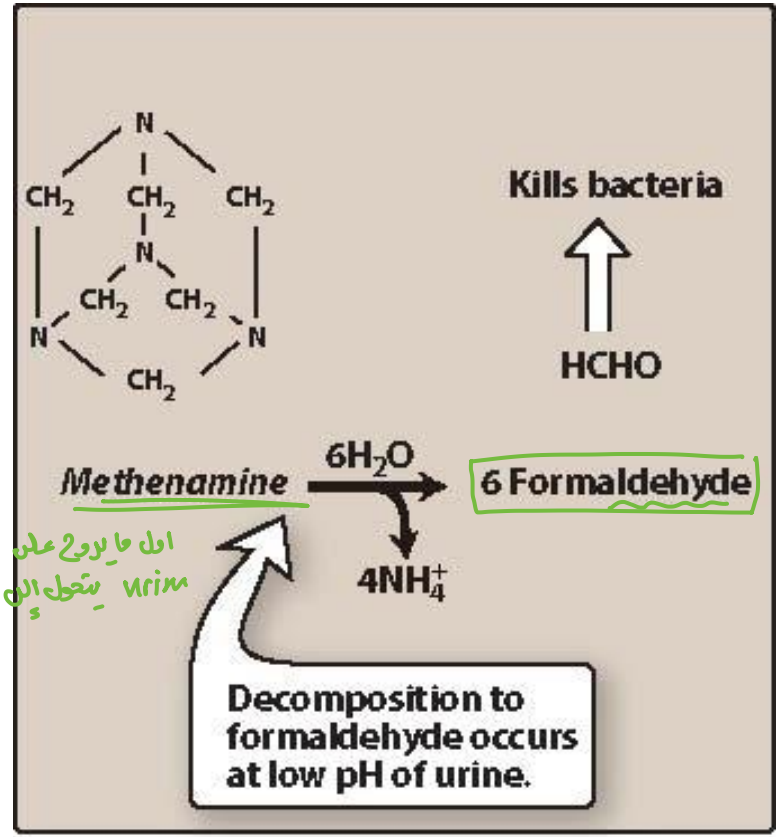
severe complecated

for simple

Methenamine

- **MOA**: decomposes at an acidic pH of 5.5 or less in the urine → produces formaldehyde → toxic to most bacteria تأثيره محدود بسبب ال acidity of urine
- **Antibacterial spectrum**: used for chronic suppressive therapy to reduce UTIs
- Some activity against Pseudomonas or Proteus spp

but urine pH must be kept acidic to achieve bactericidal activity



Nitrofurantoin

- Nitrofurantoin is now first-line for uncomplicated cystitis
- **MOA**: Major inhibitor of DNA and RNA synthesis
- Useful against *E.coli*
- Can also cause hemolytic anemia in patients with G6PD
- Should not be used in patients with renal impairment or term pregnant women

nonpregnant women are provided in Table 2, below.

Table 2. Treatment Regimens for Complicated Cystitis in Nonpregnant Women [17] (Open Table in a new window)

First-line therapy

Oral:

Patients with complicated cystitis who can tolerate oral therapy may be treated with the following options:

- Ciprofloxacin (Cipro) 500 mg PO BID for 7-14d **or**
- Ciprofloxacin extended release (Cipro XR) 1 g PO daily for 7-14d **or**
- Levofloxacin (Levaquin) 750 mg PO daily for 5d

Parenteral:

Patients who cannot tolerate oral therapy as outlined above or patients with infection that is suspected to be due to resistant organisms should be treated with parenteral therapy, as follows:

- Ciprofloxacin (Cipro) 400 mg IV q12h for 7-14d **or**

- Levofloxacin (Levaquin) 750 mg IV daily for 5d **or**
- Ampicillin 1-2 g IV q6h plus gentamicin 2 mg/kg/dose q8h for 7-14d **or**
- Piperacillin-tazobactam (Zosyn) 3.375 g IV q6h **or**
- Doripenem 500 mg (Doribax) IV q8h for 10d **or**
- Imipenem-cilastatin (Primaxin) 500 mg IV q6h for 7-14d **or**
- Meropenem (Merrem) 1 g IV q8h for 7-14d

Duration of therapy: Shorter courses (7d) are reasonable if patient improves rapidly; longer courses (10-14d) are reasonable if patient has a delayed response or is hospitalized.

Parenteral therapy can be switched to oral therapy once clinical improvement is observed.

Second-line therapy

- Cefepime (Maxipime) 2 g IV q12h for 10d **or**
- Ceftazidime (Fortaz, Tazicef) 500 mg IV or IM q8-12h for 7-14d

Duration of therapy: Shorter courses (7d) are reasonable if patient improves rapidly; longer courses (10-14d) are reasonable if patient has a delayed response or is hospitalized.

Parenteral therapy can be switched to oral therapy once clinical improvement is observed.

* قال الدكتور مهم نفرقهم وبين ال first line و second وجيبك عشان شو ؟

عشان ما نضيعهم واحنا جوا الامتحان

← هاي الصور من External Reading على التيمز

women are provided in Table 1, below.

Table 1. Treatment Regimens for Uncomplicated Cystitis in Nonpregnant Women [2] (Open Table in a new window)

First-line therapy

- Trimethoprim/sulfamethoxazole* 160 mg/800 mg (Bactrim DS, Septra DS) 1 tablet PO BID for 3d (use when bacterial resistance is < 20% and patient has no allergy) **or**
- Nitrofurantoin monohydrate/macrocrystals (Macrobid) 100 mg PO BID for 5-7d **or**
- Nitrofurantoin macrocrystals (Macrodantin) 50-100 mg PO QID for 7d **or**
- Fosfomycin (Monurol) 3 g PO as a single dose with 3-4 oz of water

Second-line therapy

- Ciprofloxacin (Cipro) 250 mg PO BID for 3d **or**
- Ciprofloxacin extended release (Cipro XR) 500 mg PO daily for 3d **or**
- Levofloxacin (Levaquin) 250 mg PO q24h for 3d **or**
- Ofloxacin 200 mg PO q12h for 3d

Alternative therapy

- Amoxicillin-clavulanate (Augmentin) 500 mg/125 mg PO BID for 3-7d **or**
- Amoxicillin-clavulanate (Augmentin) 250 mg/125 mg PO TID for 3-7d **or**
- Cefdinir 300 mg PO BID for 7d **or**
- Cefaclor 500 mg PO TID for 7d **or**
- Cefpodoxime 100 mg PO BID for 7d **or**
- Cefuroxime 250 mg PO BID for 7-10d

*Should generally be avoided in elderly patients because of the risk of affecting renal function.