

بسم الله الرحمن الرحيم

قبل ما نبليش بالشابتر باذن الله ٥ دقائق من وقتك دعاء لاهلنا في فلسطين

اللهم انصر إخواننا في المسجد الأقصى، اللهم كن لهم ولا تكن عليهم،
اللهم انتقم من أعدائهم واقذف الرعب في قلوبهم وردّ كيدهم في
نحوهم اللهم انصر المرابطين المستضعفين من أهل فلسطين.

اللهم احفظ أرواحهم وأبناءهم وردهم إلى ديارهم مردًا كريمًا آمنًا.

- نعوذ بك يا الله من هذا العجز ونحن نرى إخواننا ولا نستطيع صرفًا
ولا دفعًا ولا وصولًا اللهم إنا نشكو إليك ضعف قوتنا وقلة حيلتنا
وهواننا على الناس اللهم إنا نستودعك المسجد الأقصى مسرى رسول
الله يا من لا تضيع عنده الودائع فاحفظهم بحفظك ورعايتك.

اللهم إنهم أهلنا قد ظلموا بغير حق، وأخرجوا من ديارهم في شهرك
الكريم ومُنعوا الصلاة في مسجدك المقدس، اللهم فانتصر لهم واربط
على قلوبهم وردّهم إلى ديارهم ومسجدهم آمنين، اللهم واشدد على
أعدائهم حتى يروا العذاب الاليم.

Antifungal Drugs

Pharmacology 3

Dr. Heba Khader

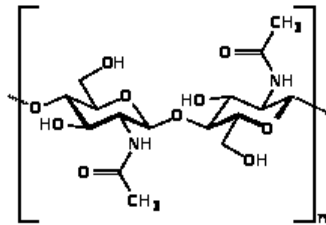
Mohammad Kh

Fungi

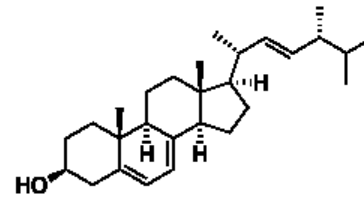
- Eukaryotic organisms

من الاشياء الي بتميزها عن ال human cell
(باللون الاخضر)

- Have rigid cell wall contain chitin (derivative of glucose) and polysaccharides
- Cell membrane composed of ergosterol



Structure of the chitin molecule



Ergosterol

ال fungi هي Eukaryotic organism صارت تشبه اكثر ال human.

فصارت اصعب اكثر انه يلاقوا selective toxicity عال fungi من غير ما يأتروا على ال human cell, لكن لا زالت الها خصائصها عن ال human cell

احنا بال ال human cell ما عنا ergosterol ...عنا cholesterol.

(human cell contain cholesterol

fungi contain ergosterol)

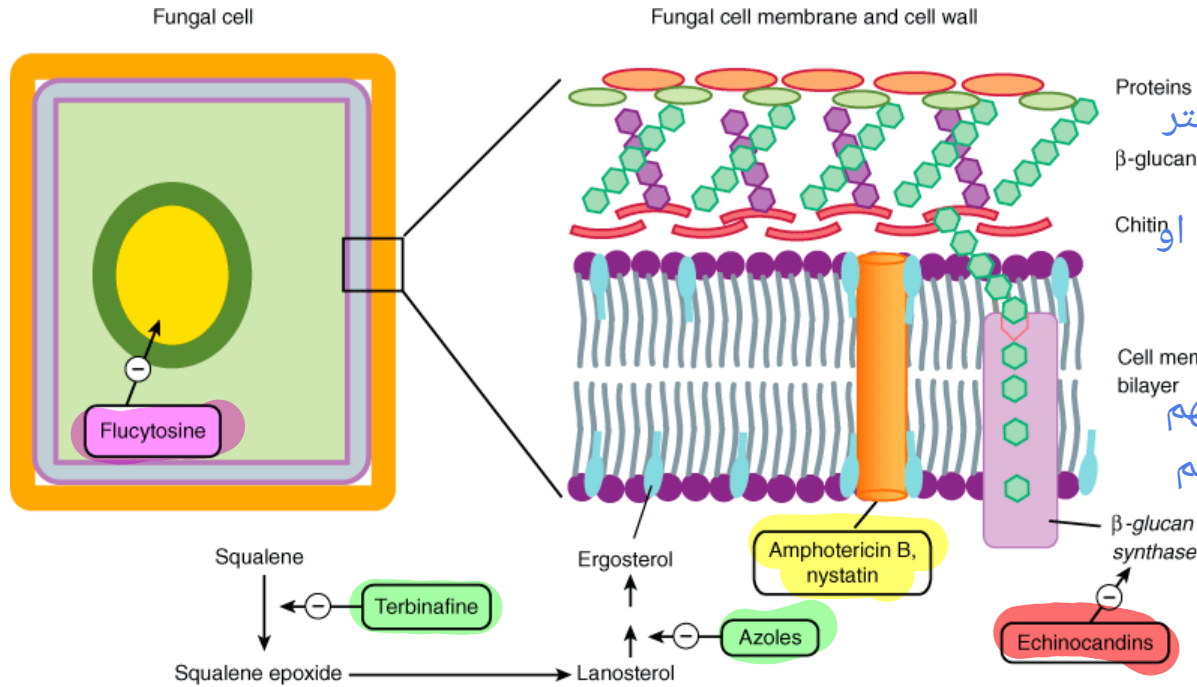
(1) شكل يوضح ال fungi بصورة اكبر ، وبورجيك ال antifungal medication كمان

Fungal cell wall and membrane

(4) الي معين عليه فالاحمر
B- بعمل inhibition بال
glucan الي هو جزء بال cell
wall بال
.fungai(echinocandins)

(5) اما الي معين عليه
بالاصفر هذول بعملوا
cell pores بال
membrane بصير في
potassium , loss
other molecules
وبعملوا disruption بال
cell membrane
integrity وبعملوا
.fungal death

قدرتهم انه يعملوا هيكل
بعتد على وجود ال
ergosterol بربطوا فيه
وبعملوا هاض الحكي كله.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: <http://www.accessmedicine.com>
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(6) الي معين عليه فالزهري بعملولي
inhibition ال nucleic acid synthesis
بصير جوا الخلية، لما نوصله بنحكي من وين
ال selective toxicity تاعته.

(3) الي معين عليهم بالاخضر هم group of drugs الوظيفة تاعتهم هي انهم
يمنعوا ال synthesis ال ergosterol والي هم (Azole, Terbinafine)، وبما
انه هاض اشئ بال fungi هاض بقلل ال toxicity عال human
cell، وكل واحد طبعا له طريقته الخاصة بس الهدف نفسه

ال fungal infections بسموها mycoses , مجرد ما انتها اسم المرض
ب mycoses معناها انه المسبب fungal.

- Infectious diseases caused by fungi called **mycoses** common
- Many common mycotic infection are superficial and only involve the skin, but fungi may also penetrate the skin causing subcutaneous, cutaneous, and systemic infections



Superficial



Subcutaneous
Chromoblastomycosis



Cutaneous

Common fungal infections

قدم رياضي ، هي ال fungal بتحب
الاماكن الي بصير فيها عرق بكميات
كبيرة

- Athlete's foot

اماكن تواجدھا اما جلدة الرأس ،

- Ringworm ... الايد ، الظهر



Ringworm on the back



Ringworm on the arm



Ringworm on the scalp



- Yeast diaper rash يظهر بمنطقة الحفاضة
فالطفل (infant) وبعملي

احمرار

- Candidiasis

- in the mouth or throat is called “thrush” or oropharyngeal candidiasis.
- in the vagina is commonly referred to as a “yeast infection.” It occurs when there is overgrowth of the normal yeast in the vagina.
- Invasive candidiasis occurs when *Candida* species enter the bloodstream and spread throughout the body.

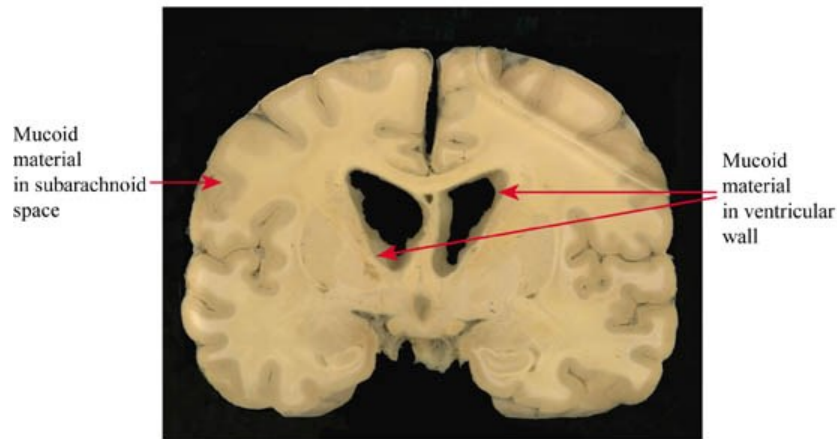


يمكن تعمل systemic
fungal infections

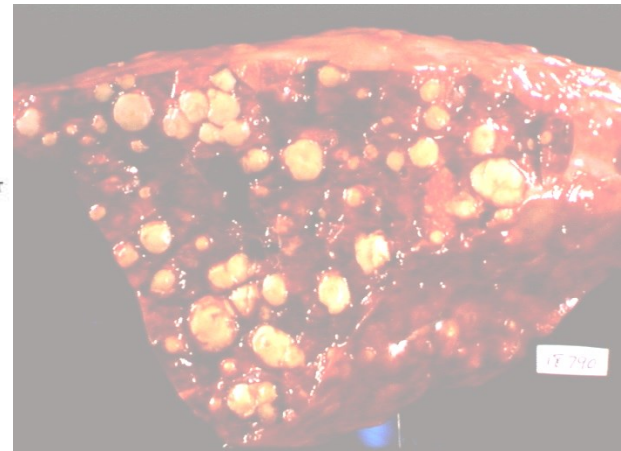
ال systemic بتصير بالناس الي عندها immunocompromised، الي هم.....

انتهازي

- Fungi is opportunistic organism which make systemic infection in immunosuppressed individuals (cancer, transplant patients, those debilitated by AIDS, tuberculosis)
امثلة عليهم
- Opportunistic fungi: cryptococcal meningitis or aspergillosis



Cryptococcal meningitis - A coronal section of the brain



Aspergillus pneumonia in lung of deer

الادوية مقسمة لقسمين

1- systemic

2-topical

Antifungal Drugs

وال systemic مقسم برضه لثنين

1-systemic infection

2- oral mucocutaneous infection

- The antifungal drugs presently available fall into the following categories:

- ✓ Systemic drugs (oral or parenteral) for systemic infections

- ✓ Amphotericin B

- ✓ Flucytosine

- ✓ Azole antifungals

- ✓ Echinocandins

- ✓ Oral systemic drugs for mucocutaneous infections

- ✓ Griseofulvin

- ✓ Terbinafine

- ✓ Topical drugs for mucocutaneous infections.

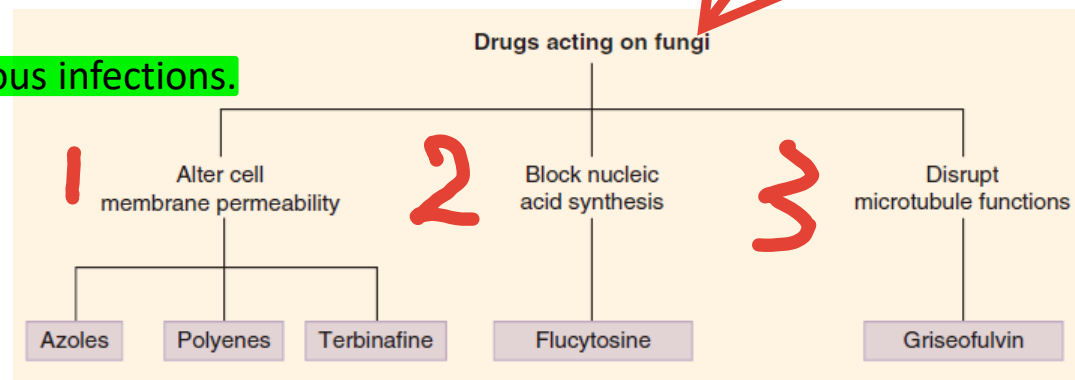
- ✓ Nystatin

- ✓ Topical azoles

- ✓ Terbinafine

ال azoles مجموعة كبيرة من ال drug
في منها systemic وفي منها topical

يمكن كمان نلاقيهم مقسمين حسب ال
mechanism of action

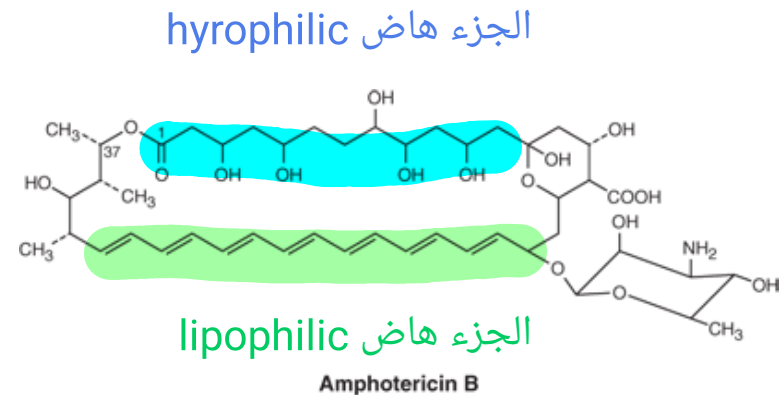


برضو ال terbinafine
في منها systemic oral
وفي منها topical

ال amphotericin B & nystatin هم polyene mechanism بس واحد systemic والثاني topical group وك

Amphotericin B

- Naturally occurring polyene macrolide antibiotic (polyene = containing many double bonds; macrolide = containing a large lactone ring of 12 or more atoms).
- For many years, amphotericin B was the only efficacious antifungal drug available for systemic use. While highly effective in many serious infections, it is also quite toxic.
- In the last several decades, the relatively nontoxic azole drugs (both oral and parenteral formulations) and the echinocandins (only available for parenteral administration) have been introduced.



يعني هو amphipathic

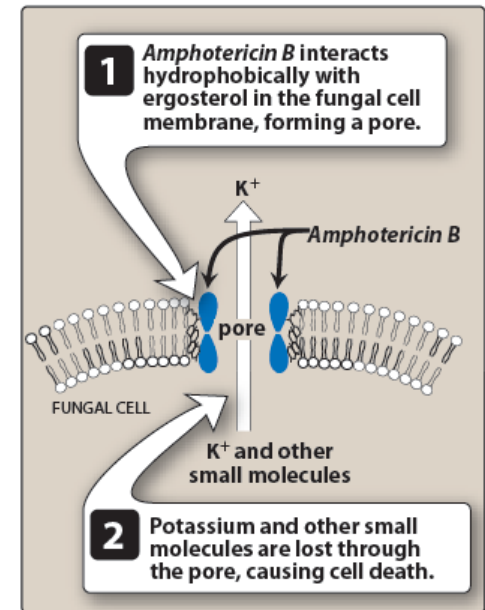
ال Amphotericin B هو polyene macrolide antibiotic عنده double bond كثير ورا بعض هو من اكثر الادوية الفعالة بس بنفس الوقت toxic فعشان هيك بنخليه وقت المريض يكون بخطر كبير او في خطر عحياته يعني

فبندله ب azole, echinocandins

Amphotericin B

ال Amphotericin B ييجي على ال fungal cell membrane
تاعها وبتصير تدور على ال ergosterol عشان ترتبط
فيه بالجزء ال lipophilic تاعه والجزء ال hydrophilic بعمل فيه ال
pore (بناءً على حكي الدكتور) هاض الاشوي راح يخرّب عندي الخلية
ويسمح لل electrolyte وخصوصا ال K^+ بانه يخرج منها وينتج عندي
موت للخلية

- **Mechanism of action:**
- The antifungal action of amphotericin B is due to its effects on the permeability and transport properties of fungal membranes.
- Polyenes are molecules with both hydrophilic and lipophilic characteristics (ie, they are amphipathic). They bind to **ergosterol**, a sterol specific to fungal cell membranes, and cause the formation of artificial pores.
- The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.
- Some binding to human membrane sterols does occur, probably accounting for the drug's prominent toxicity.



ال toxicity تاعته كلها بتيجي انه اوقات
يربط بال human membrane sterols

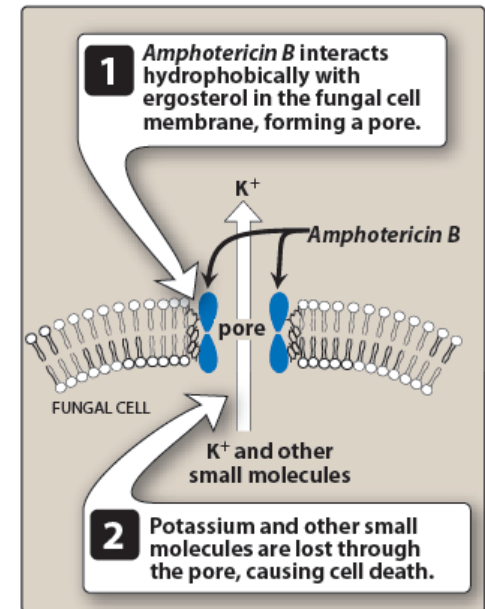
Amphotericin B

- **Resistance:**
- Resistance to amphotericin B occurs if ergosterol binding is impaired, either by:
 - decreasing the membrane concentration of ergosterol
- or
- by modifying the sterol target molecule to reduce its affinity for the drug.

ال resistance تاعته بكل بساطة احدي
الخطتين:

خطة A انه يقلل عدد ال ergosterol

خطة B انه يقلل ال ergosterol affinity للدواء



يعطيه oral اذا بدى اعالج المعدة نفسها (fungi)
(within the lumen of the tract)

Amphotericin B

- **Pharmacokinetics:** slowing the IV infusion
amphotericin B يقلل ال side effect
- Amphotericin is poorly absorbed from the gastrointestinal tract and is usually administered **intravenously** (slow intravenous infusion).
- **Oral** amphotericin B is thus effective only on fungi within the lumen of the tract and cannot be used for treatment of systemic disease.
- The drug is widely distributed in most tissues, but only 2–3% of the blood level is reached in cerebrospinal fluid, thus occasionally necessitating intrathecal therapy for certain types of fungal meningitis.
- **Elimination is mainly via hepatic metabolism**; the half-life is approximately 2 wk.
- **A small fraction of the drug is excreted in the urine**; dosage modification is necessary only in extreme renal dysfunction.

اذا ال infection هي fungal
meningitis فبدى اعطيه على شكل
Intrathecal لانه مش كثير
الامتصاص كويس فال cns

Amphotericin B

الدواء يستخدموه

initially to reduce fungal burden

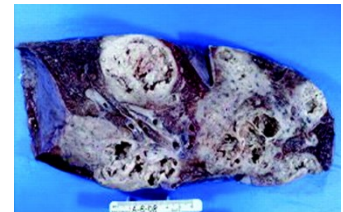
يقللوا عدد ال fungal ويعملوا control لل disease وبعدين يكملوا فدواء ثاني زي ال azole anti fungal

بعملوا هيك نظرا لل toxicity تاعت ال amphotericin b

- **Clinical uses:**

- Amphotericin B is one of the most important drugs available for the treatment of systemic mycoses and **is often used for initial induction regimens to rapidly reduce fungal burden and then replaced by one of the newer azole drugs for chronic therapy or prevention of relapse.**
- **It has the widest antifungal spectrum of any agent and remains the drug of choice, or codrug of choice, for most systemic infections caused by *Aspergillus*, *Blastomyces*, *Candida albicans*, *Cryptococcus*, *Histoplasma*, and *Mucor*.**
- Amphotericin B is usually given by **slow intravenous infusion** at a dosage of 0.5–1 mg/kg/d, but **in fungal meningitis intrathecal** administration, though dangerous, has been used.
- **Local administration of the drug**, with minimal toxicity, has been used in **treatment of mycotic corneal ulcers and keratitis.**

عملوا منه local administration لل fungal infection
(topcal applications for eye) للعين



Systemic mycosis:
large histoplasmosis
abscesses involving
the lung

Amphotericin B

symptoms



- **Adverse Effects:**

1. **Infusion-related reactions** are nearly universal and consist of **fever, chills, muscle spasms, vomiting, headache, and hypotension.**
- They can be ameliorated by **slowing the infusion rate or decreasing the daily dose.** الحل الي مخطط بالازرق
 - **Premedication** with antipyretics, antihistamines, meperidine (pethidine), or corticosteroids can be helpful.
 - **When starting therapy, many clinicians administer a test dose of 1 mg intravenously to scale the severity of the reaction. This can serve as a guide to an initial dosing regimen and premedication strategy.**
 - **Hypotension:** A shock-like fall in blood pressure accompanied by hypokalemia may occur, **requiring potassium supplementation.** Care must be exercised in patients taking *digoxin* and other drugs that can cause potassium fluctuations.

قبل ما اعمل الحكي هاض كله بدي اتأكد اذا المشكلة اساسا من ال
...Infusion-Related reaction

كيف؟ بعمل اشبي اسمه "Test dose"

adverse effects واشوف اذا صار عنده ال 1 mg intravenously
تاعونه

ولكن اذا صار عنده Hypotension من ال amphotericin b هاض
الاشبي مش كويس بالمرة لانه عبارة عن rapid fall in blood pressure
وبصاحبه hypokalemia وحله اني اعطيه potassium
supplementation, وطبعا لازم يعملوله monitoring لانه يمكن عملي
بعديها hyperkalemia فلازم انتبه للادويه الي بتنعطاله زي مثلا ال
digoxin.

Amphotericin B

2. Nephrotoxicity

- Renal damage is the most significant toxic reaction. Renal function usually returns with discontinuation of the drug, but residual damage is likely at high doses. وهاي اذا وقفو الدواء بتنحل وبترج الامور طبيعية
- او اني زي النقطة الرابعة تحت Amphotericin B decreases the glomerular filtration rate and causes renal tubular acidosis with magnesium and potassium wasting. ال renal tubular acidosis
- Anemia may result from decreases in the renal formation of erythropoietin. يرتبط بال cholesterol
- It is common practice to administer normal saline infusions with the daily doses of amphotericin B to reduce renal damage. تاع الكلية
- Dose reduction (with lowered toxicity) is possible in some infections when amphotericin B is used with flucytosine. الحل اني اقلل ال dose بالحالتين

3. Neurotoxicity ال Neurotoxicity بخافوا منها بس اذا انعطى الدواء Intrathecal يمكن يعمل seizure and neurologic damage

- Intrathecal administration of amphotericin B may cause seizures and neurologic damage.

Lipid Formulation of Amphotericin B

Therapy with amphotericin B is often limited by toxicity, especially drug-induced renal impairment. This has led to the development of lipid drug formulations on the assumption that lipid-packaged drug binds to the mammalian membrane less readily, permitting the use of effective doses of the drug with lower toxicity. Liposomal amphotericin preparations package the active drug in lipid delivery vehicles, in contrast to the colloidal suspensions, which were previously the only available forms. Amphotericin binds to the lipids in these vehicles with an affinity between that for fungal ergosterol and that for human cholesterol. The lipid vehicle then serves as an amphotericin reservoir, reducing nonspecific binding to human cell membranes. This preferential binding allows for a reduction of toxicity without sacrificing efficacy and permits use of larger doses. Furthermore, some fungi contain lipases that may liberate free amphotericin B directly at the site of infection.

Three such formulations are now available and have differing pharmacologic properties as summarized in Table 48–1. Although clinical trials have demonstrated different renal and infusion-related toxicities for these preparations compared with regular amphotericin B, there are no trials comparing the different formulations with each other. Limited studies have suggested at best a moderate improvement in the clinical efficacy of the lipid formulations compared with conventional amphotericin B. Because the lipid preparations are much more expensive, their use is usually restricted to patients intolerant to, or not responding to, conventional amphotericin treatment.

TABLE 48–1 Properties of conventional amphotericin B and some lipid formulations.¹

Drug	Physical Form	Dosing (mg/kg/d)	C _{max}	Clearance	Nephrotoxicity	Infusional Toxicity	Daily Cost (\$)
Conventional formulation							
Fungizone	Micelles	1	—	—	—	—	24
Lipid formulations							
AmBisome	Spheres	3–5	↑	↓	↓	↓	1300
Amphotec	Disks	5	↓	↑	↓	↑(?)	660
Abelcet	Ribbons	5	↓	↑	↓	↓(?)	570

¹Changes in C_{max} (peak plasma concentration), clearance, nephrotoxicity, and infusional toxicity are relative to conventional amphotericin B.

السلامة هذول وما فيهن انه بحكولك انه amphotericin b عبارة عن شخص غدار وخاين ، عملوا فكرة انه يربط ال amphotericin b ب lipid ويدخلوه للجسم فالدوا وهو ماشي علاقته حلوة مع ال lipid هاض ومرتبطين ومن احلى ما يكون لحد ما يشوف ال ergosterol و حس انه احلى وافضل 😍 من ال lipid الي معه فحس انه ال affinity تجاهه كثير عالية فترك هاض ال lipid وراح ارتبط فيه ، شاف قدامه طبعا شوية cholesterol بس عادي يعني شافه نفسه نفس ال lipid وقلق شو بدي فيه؟ ما ال ergosterol احسن وافضلوبس 😊

السلامة الثانية

بورجوك انه بهاض الحل قدره يعطوا الدوا بهالشكل ب dose اعلى و toxicity اخف المشكلة الي فيه بس انه سعره كثير عالي "كثير" ومثال عليه (sphere,disks,ribbons)