UNIVERSITAS MUHAMMADIYAH JAKARTA
FAKULTAS KEDOKTERAN DAN KESEHATAN

SURAT TUGAS
Nomor : 42A/F.7-UMJ/IX/2022

Yang bertanda tangan di bawah ini :

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Untuk **mengembangkan bahan kuliah Farmakologi pada Sistem Kedokteran Tropis**

Demikian surat tugas ini diberikan kepada yang bersangkutan untuk dilaksanakan sebagai amanah.

Jakarta, 10 September 2022
Dekan Fakultas Kedokteran dan Kesehatan UMJ

Dr. dr. Muhammad Fachri, Sp.P, FAPSR, FISR
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Tembusan :
1. Wadek I, II
2. Bag Keuangan
3. Arsip

KEMOTERAPI MALARIA

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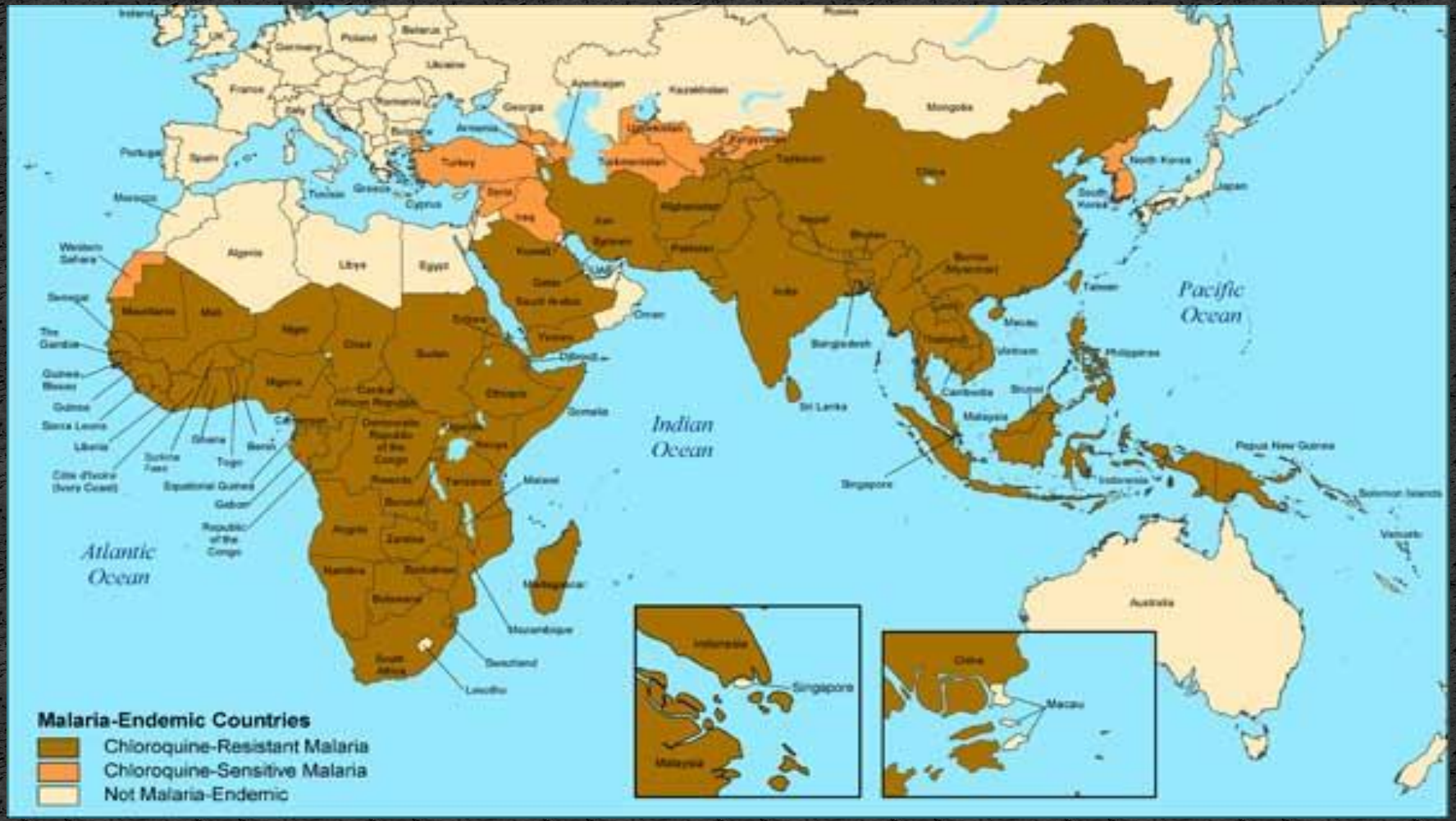
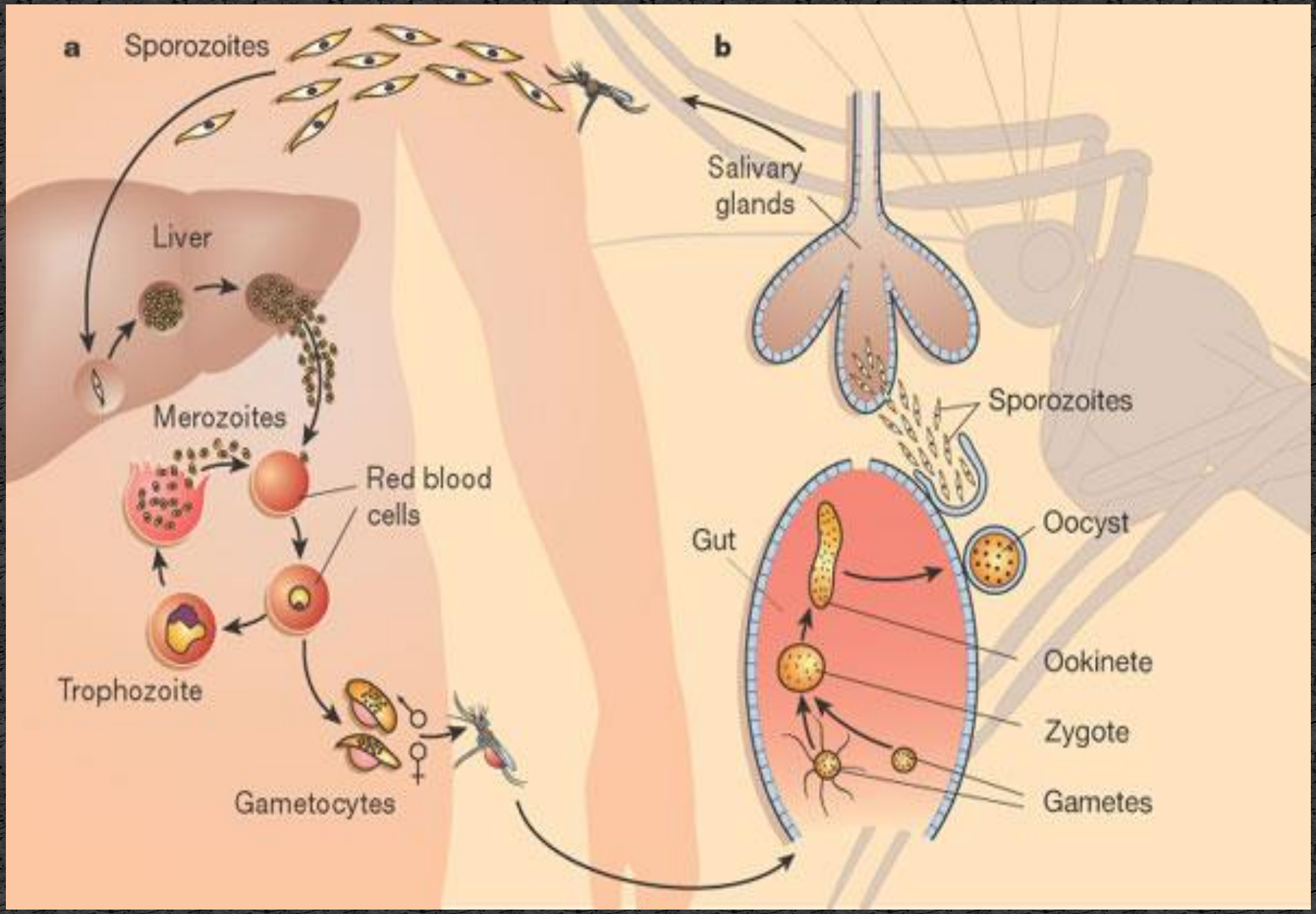
Pendahuluan

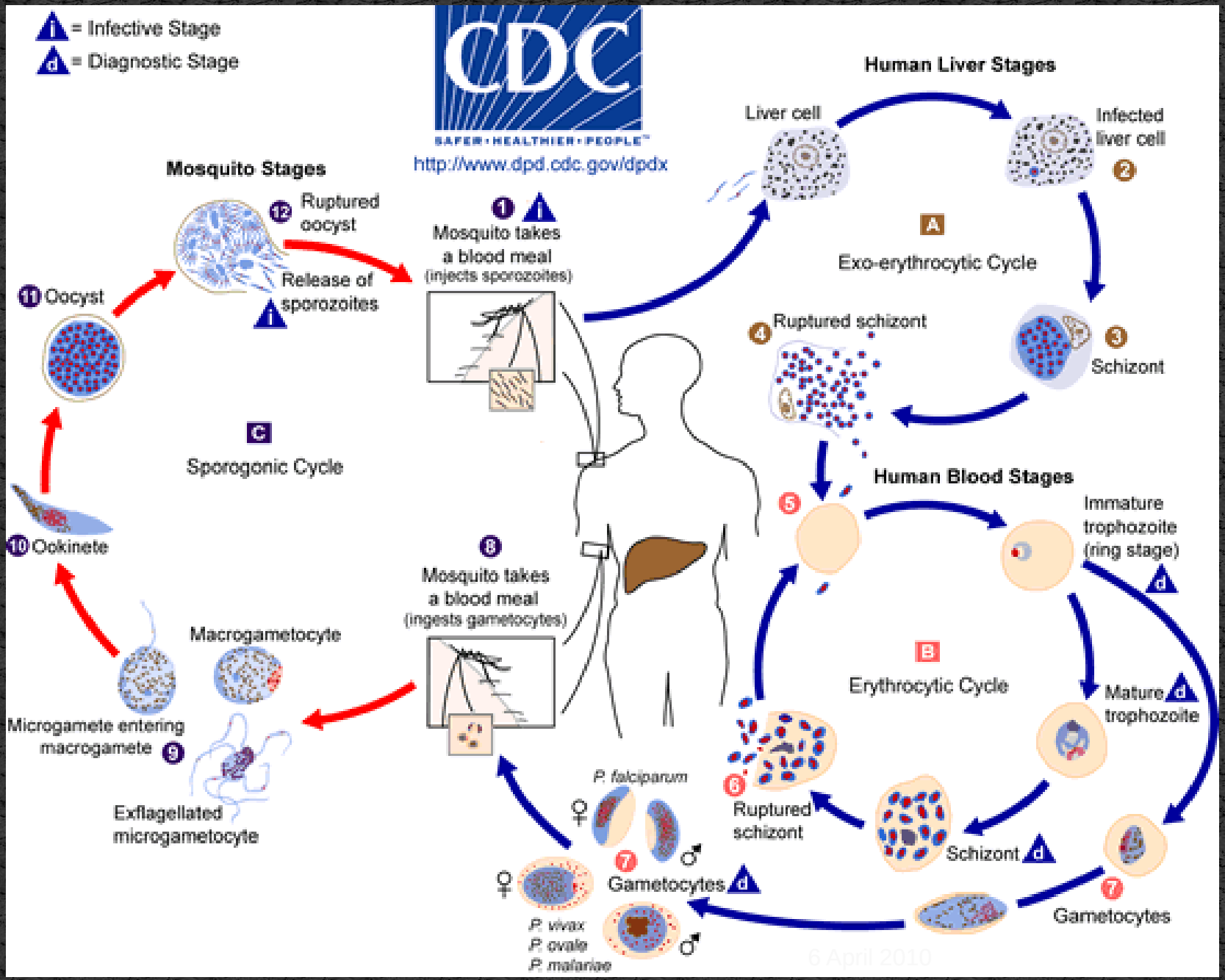
- Malaria terutama yg disebabkan oleh *Plasmodium falciparum* merupakan infeksi parasit pd manusia yg paling merusak.
- ~ 500 juta orang mengidap malaria, sekitar 2 juta mati setiap tahun.
- Prevalensinya meningkat → masalah kesehatan & ekonomi dan resiko serius thd pengunjung dari daerah nonendemik
- Kegagalan eradikasi: Resistensi insektisida (1950) dan resistensi obat (1960)

Malaria-endemic countries in the Eastern Hemisphere



Malaria-endemic countries in the Western Hemisphere.


a
Sporozoites
Liver
Merozoites
Red blood cells
Trophozoite
Gametocytes
b
Salivary glands
Sporozoites
Oocyst
Gut
Ookinete
Zygote
Gametes


= Infective Stage
= Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™
http://www.dpd.cdc.gov/dpdx
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
3
Schizont
4
Ruptured schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
d
Mature trophozoite
B
Erythrocytic Cycle
6
Ruptured schizont
Schizont
d
7
Gametocytes
Gametocytes
d
P. falciparum
P. vivax
P. ovale
P. malariae
8
Mosquito takes a blood meal (ingests gametocytes)
Mosquito Stages
1
Mosquito takes a blood meal (injects sporozoites)
12
Ruptured oocyst
Release of sporozoites
11
Oocyst
10
Ookinete
C
Sporogonic Cycle
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte

Biologi Infeksi Malaria

- Sporozoid dari ludah nyamuk masuk kedalam sirkulasi setelah gigitan, menuju ke sel hati, berubah, berkembang biak menjadi schizont, tanpa ada gejala.
- Sel hati pecah, mengeluarkan ribuan merozoid, menyerang eritrosit. Begitu pecah tak ada P falcifarum dan P malariae yang tertinggal di hati, tetapi P vivax dan P ovale menetap dan menyerang eritrosit berulang kali.
- Di dalam eritrosit parasit berkembang aseksual menjadi tropozoid, schizont, dan pecah mengeluarkan merozoid, menyerang eritrosit lain.
- Pecahnya eritrosit disertai gejala demam dan menggigil yang timbul periodik.

Klasifikasi Obat Antimalaria

- Didasarkan pada *life-cycle* parasit dalam tubuh manusia.
- Tak ada obat yang membunuh sporozoit. Hanya mencegah timbulnya gejala akibat parasit fase eritrosit aseksual.
- Tak satupun obat yang sekaligus efektif terhadap parasit pada fase hati dan fase eritrosit, sehingga penyembuhan sempurna memerlukan kombinasi obat.

Klasifikasi Obat Antimalaria.

	Primer	Hipnozoid	Aseksual	Gametosit
Kelas I				
Chloroquin	-	-	+	(±)
Mefloquin	-	-	+	-
Kinin/Kinidin	-	-	+	(±)
Fansidar	-	±	+	-
Tetracycline	-	-	±	-
Kelas II				
Atovaquone-Proguanil (Malarone)	-	(+)	+	-
Kelas III				
Primaquin	-	+	-	+

Klasifikasi Obat Antimalaria

- **Kelas I**
  - Target: fase eritrosit aseksual.
  - Tak bermanfaat untuk parasit hati fase primer, fase laten, atau P falciparum (gametosit).
  - untuk profilaksis: diminum beberapa minggu setelah terpapar, sampai selesai fase hati dan masuk ke dalam fase eritrosit
- **Kelas II**
  - Target: fase hati primer P falciparum dan fase aseksual eritrositer semua plasmodium.
- **Kelas III (primaquin)**
  - Target: fase hati dan gametosit.
  - Khusus membasmi hypnozoit P vivax dan P malariae pada infeksi berulang.

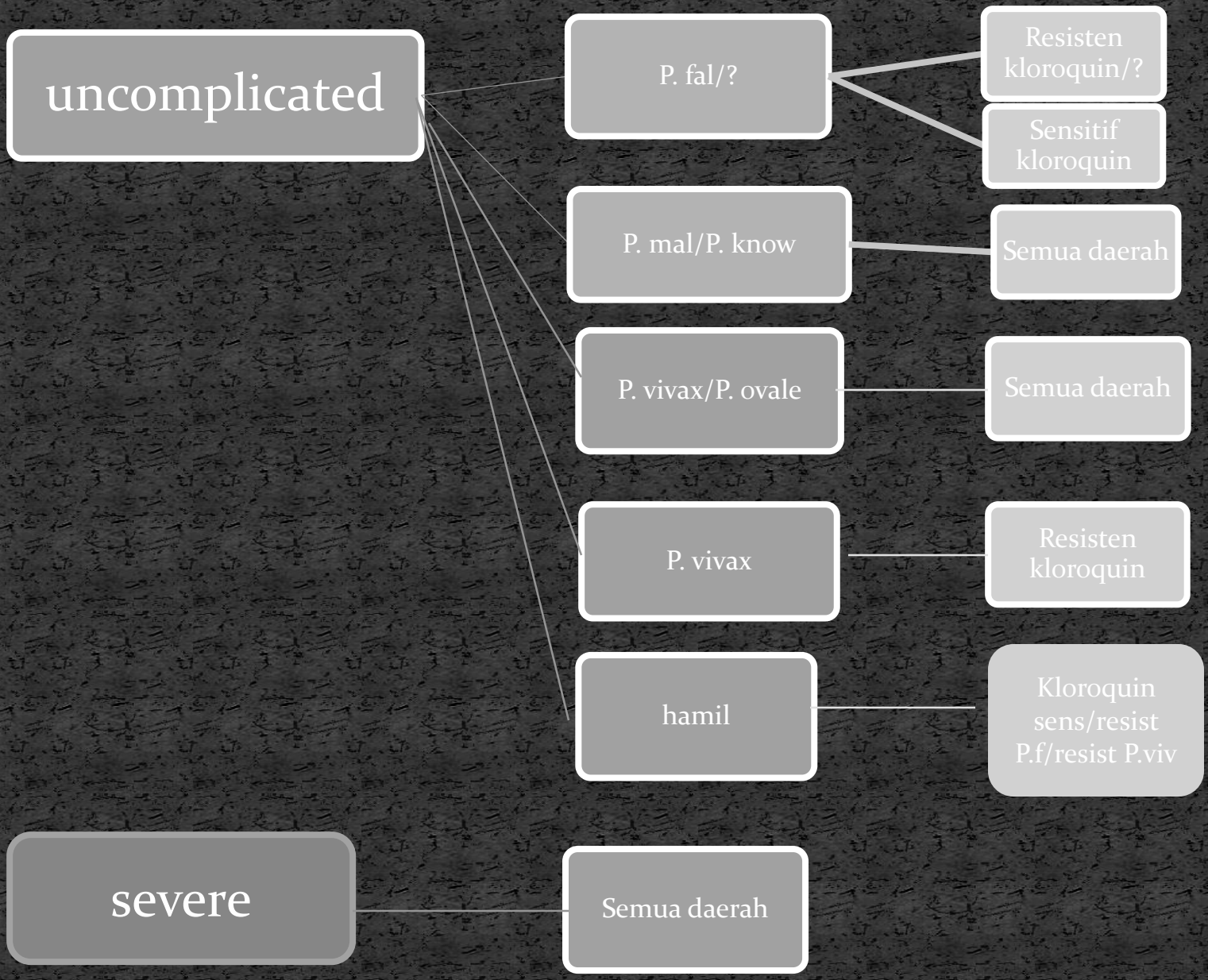
Kemoprofilaksis malaria

- **Profilaksis plasmodium sensitif kloroquin**
  - Kloroquin fosfat (ARALEN)
    500 mg/mgg:1-2 mgg sblm s/d 4 mgg stlh
- **Profilaksis P. falciparum atau P.vivax resisten klorokuin**
  - Atovaquone 250 mg-proguanil 100 mg (MALARONE)
    1 tab/hr: 1-2 hr sblm s/d 7 hr stlh
  - Mefloquine 250 mg (LARIAM)
    1 tab/mgg: 1-2 mgg sblm s/d 4 mgg stlh
  - Doxycycline 100 mg(VIBRAMYCIN)
    1 tab/hr: 1 hr sblm s/d 4 mgg stlh
  - Primaquin
    30 mg/hr: 1-2 hr sblm s/d 7 hr stlh

Treatment: General Approach

- Terapi hrs menunggu hsl lab
- *Presumtive treatment* (tanpa hsl lab) pada:
  - Dugaan klinis yang kuat
  - Penyakit yg parah
  - Tidak bisa dilakukan pem lab
- Panduan terapi
  - Spesies plasmodium
    - P. falciparum & P. knowlesi (caution !!!)
    - P. vivax & P. ovale (hipnozoit !!!)
    - P. falciparum & P. vivax (beda pola resistensi obat)
  - Keadaan klinis pasien
  - Pilihan obat (resisten-sensitif bdsrkn lab/daerah)

Alur terapi


uncomplicated
P. fal/?
Resisten kloroquin/?
Sensitif kloroquin
P. mal/P. know
Semua daerah
P. vivax/P. ovale
Semua daerah
P. vivax
Resisten kloroquin
hamil
Kloroquin sens/resist P.f/resist P.viv
severe
Semua daerah

Pengobatan Malaria tanpa komplikasi

- **P falcifarum & P malariae sensitif chloroquine**: chloroquine fosfat 1 gr (2 tab) segera, kemudian 500 mg pd jam ke-6, 24, dan 48. Dosis total 2500 mg
- **P vivax & P ovale sensitif kloroquin**

  kloroquin (sda), stlh srgn akut (hari ke-4) berikan primaquine 30 mg basa selama 14 hari.
- **P falcifarum resisten chloroquine**:
  1. Atovaquone-proguanil (Malarone): 1 ddx4 tab (3 hr)
  2. Artemether-lumefantrine (Coartem): 2 ddx1 tab (3hr)
  3. Quinin sulfat (3x650 mg,3-7 hari) PLUS: doxycycline 2x100 mg ATAU Tetracycline 4x250mg ATAU Clindamycin base 20 mg/kg/hr div in 3 dose slm 7 hr
  4. Mefloquine base 750 mg → 6-12 jam: 500 mg
- **P vivax resisten chloroquine**

  Sda (1,3,4) + Primaquin sda

- Pengobatan malaria berat
  - Loading dose
    - Quinidine glukonat (garam) IV 10 mg/kg (1-2 jam) → 0,02 mg/kg/mnt (min 24 jam)
  - Maintenance dose:
    - Oral quinin + doxycycline/tetracyclin/clindamycin
- Pengobatan malaria pd wanita hml
  - Sensitif kloroquin: kloroquin sda
  - P. fal resisten kloroquin: quinin sulfat+ clindamycin
  - P. vivax resisten kloroquin: quinin sulfat

Chloroquine

- Abs GIT, IM, SC. Vd >100 L/kgBB, redistribusi lambat. Oral: kdr pnck 3-5 jam; $t_{1/2}$ terminal 1-2 bulan.
- Antimalaria: fs eritrosit aseksual (semua), gametosit (kec P. fal)
- ES: retinopati, ototoksik, jantung (↓ TD, aritmia, QRS >, gel T abn), saraf (kejang, koma), urtikaria, dermatitis, hemolisis pd defisiensi G6PD, agranulositosis,
- KI: epilepsi, myasthenia gravis, psoriasis, penyakit retina
- Perhatian: gangguan hati, GIT, saraf
- **Jgn digunakan bersama mefloquin → ↑ kejang**
- Absorpsi dihambat oleh Mg, Ca, dan kaolin, aman utk wanita hamil dan anak.

Quinine dan Quinidine

- *Gametocidal* thd P vivax dan P ovale, tidak thd P falcifarum. Schizonticide thd keempat plasmodium
- Obat lini pertama malaria falcifarum berat, iv (SC -)
- Terapi lini pertama malaria falcifarum tanpa komplikasi, peroral. Kombinasi doxycycline ↑ kbhsln terapi.
- Quinidine adalah dextroisomir quinin, aktifitas antimalaria sama. T1/2 quinidine lebih pendek dari t1/2 quinine, karena ikatan protein rendah.
- ES: cinchonism, hipoglikemia, hipotensi, hstv, QT memanjang, blok AV, VT, VF
- KI: tinitus, neuritis optik, hipersensitifitas, hemolisis pada def. G6PD,.
- Interaksi: ↑warfarin dan digoxin. Abs ↓ dg antasida Al

Mefloquine

- Tidak dianjurkan di Asia Tenggara krn resisten
- Fase eritrosit aseksual semua Plasmodium spp
- Terapi P falcifarum resisten chloroquine dan plasmodium lain. Profilaksis P falcifarum resisten chloroquine.
- Hanya oral, ikatan protein tinggi, $t_{1/2}$: 20 hari, diberikan 1x/minggu.
- Resistensi silang dengan quinidine.
- ES: saluran cerna, darah, hati, gejala neuro-psikiatrik.
- KI: epilepsi, penyakit jiwa, aritmia.
- Aman utk wanita hamil (stlh 3 bln-WHO) dan anak.
- Tak digunakan bersama quinine/quinidine, halofantrine.

Primaquine

- Aktif thd fase hati semua plasmodium, satu2-nya obat utk hypnozoid *dormant* P ovale dan P vivax, *gametocidal* thd semua plasmodium.
- Hanya oral, abs baik, Tmax;1-2 jam, $t_{1/2}$: 3-8 jam, distribusi luas.
- Indikasi: 1) malaria akut ovale dan vivax, mulai dengan chloroquine, lanjutkan dengan primaquine 14 hari; 2) profilaksis terminal vivax dan ovale; 3) gametocid thd P falcifarum, memutus transmisi.
- ES: sal.cerna, darah, aritmia, hemolisis pd def. C6PD.
- KI: riwayat granulositopenia, RA, SLE methemoglobinemia, def. G6PD, wanita hamil

Pyrimethamine dan Proguanil.

- Hambat sintesis asam folat, kombinasi dgn obat lain lebih efektif. Fansidar kombinasi 25 mg pyrimethamine dan 500 mg sulfadoxine; maloprim kombinasi pyrimethamine dan dapson. Malarone kombinasi proguanil 100 mg dan atovaquone 250 mg.
- Absorpsi lambat, $t_{1/2}$ proguanil 16 jam dan pyrimethamine 3.5 hari.
- Kerja lambat thd fase eritrosit semua plasmodium, aktif sedikit thd fase hati. Tak aktif thd fase gametocid dan fase hati P vivax dan P ovale.
- Indikasi: 1) chloroquine 500 mg/minggu + proguanil 200 mg/hari utk profilaksis P falcifarum; 2) fansidar utk P falcifarum resisten chloroquine; 3) terapi *presumptive* malaria falcifarum; 4) terapi lini pertama toxoplasmosis, kombinasi dengan SD.

Halofantrine dan Lumefantrine

- Hanya efektif thd fase eritrosit semua plasmodium.
- Absorpsi tak teratur, Tmax: 16 jam, $t_{1/2}$: 4 hari, ekskresi feses.
- Efektif thd P falcifarum resisten chloroquine, resistensi silang dengan mefloquine.
- ES: sal cerna, hipersensitifitas, PR dan QT memanjang.
- KI: gangguan konduksi jantung.

MALARONE

- Adalah kombinasi tetap atovaquone 250 mg dgn proguanil 100 mg.
- Efektif utk pencegahan dan pengobatan malaria falciparum. Utk profilaksis diminum 1 tablet tiap hari selama di daerah endemik. Lama pengobatan lebih pendek dari pengobatan dgn mefloquin dan doxicyclin.
- ES: ringan (nyeri abdomen, nause, muntah, diarrhea).

Artemisinin dan Turunan

- Artemisinin (qinghaosu) adalah antipyretik di China sejak 2000 tahun yl.
- Artemisinin tak larut air, artesunat larut air, arthemeter larut lemak.
- Absorbsi cepat, Tmax:1-2 jam, $t_{1/2}$:1-3 jam, dihydroartemisin metabolit aktif.
- Schizonticide fase eritrosit thd semua plasmodium, tak ada efek thd fase hepar.
- I: P falcifarum *multi-drug resistant*, mudah kambuh dan tak berguna utk profilaksis krn $t_{1/2}$ pendek.
- ES: saluran cerna. KI: wanita hamil.

ANTELMINTIK

Dr. Rina Nurbani, M.Biomed

Soil Transmitted Diseases

- widespread, greatest prev in tropical, developing countries
- 2002: diperkirakan 1,5 M (Al), 1,3 M (hookworm), 1,1 M (Tt)
- Penyebab anemia, pertumbuhan terhambat, perkembangan intelektual terganggu, gangguan fungsi kognitif.
- Terutama menyerang anak 5-14 tahun.
- Pembrantasan oleh pemerintah dan WHO, dgn prinsip: berikan antelmintik spektrum lebar pada anak sekolah SD secara periodik. Dosis tunggal albendazole/mebendazole turunkan beban kecacingan, naikkan Hb, pacu pertumbuhan badan, tingkatkan prestasi , kurangi ketakhadiran.

Kemoterapi Nematoda

Penyakit	Obat Terpilih
Ascaris lumbricoides	→ Mebendazole/pyrantel/ pamoate/piperazine
Trichuris trichiura	→ Mebendazole/albendazole
Necator americanus/ Ancylostoma duodenale	→ Pyrantel p/mebend/albendazol
Strongyloides stercoralis	→ Ivermectin
Enterobius vermicularis	→ Mebendazole/pyrantel pamoate
Trichinella spiralis	→ Mebendazole +corticosteroid
Trichostrongylus sp	→ Pyrantel pamoate/mebendazole
Cutaneous larva migrans	→ Albendazole/ivermectin
Visceral larva migrans	→ Albendazole
Wuchereria bancrofti	→ Dietylcarbamazine
Onchocerca volvulus	→ Ivermectin
Dracunculus medinensis	→ Metronidazole

Kemoterapi Trematoda

Schistosoma hematobium (Bilharziasis)	Praziquantel
Schistosoma mansoni	Praziquantel
Schistosoma japonicum	Praziquantel
Clonorchis sinensis (liver fluke)	Praziquantel
Paragonimus westermani (lung fluke)	Praziquantel
Fasciola hepatica (sheep liver fluke)	Bithionol
Fasciolopsis buski (large intestinal fluke)	Praziquantel/niclosamide
Heterphyes heterophyes	Praziquantel/niclosamide

Kemoterapi Cestoda

Taenia saginata (beef tapeworm)	Praziquantel/niclosamide
Diphyllobothrium latum (fish tapeworm)	Praziquantel/niclosamide
Taenia solium (pork tapeworm)	Praziquantel/niclosamide
Cysticercosis (larva pork tapeworm)	Albendazole
Hymenolepsi nana (dwarf tapeworm)	Praziquantel
Echinococcus granulosus (hydatid disease)	Albendazole

Albendazole

- hambat sintesis *microtubule* cacing → hambat penggunaan glukosa
- Efek *larvicidal* thd hydatid disease, cycticercosis, ascariasis, ancylostomiasis, necator. Efek *ovicidal* thd ascariasis, ancylostomiasis, trichiuriasis.
- Berikan waktu perut kosong utk infeksi intestinal, dan setelah makan uth infeksi sistemik
- I: 1) ascariasis, trichiuriasis, ancylostomiasis, strongiloides, enterobiusis (matikan cacing, turunkan jumlah telor); 2) obat terpilih utk hydatid; 3) neurocycticercosis, cutaneous larva migrans. 4) filariasis (+ivermectin)/DEC)
- Dosis Hidatid & sistiserkosis: > 60 kg: 400 mg 2x/hr bersama makan. < 60 kg: 15 mg/kg/hr dibagi 2 dosis
- ES: pancytopenia, gangguan fungsi hati penggunaan jangka lama.
- KI: hipersensitifitas, cirrhosis hepatis.

Diethylcarbamazine

- Lumpuhkan microfilaria, terlepas dari jaringan, dihancurkan oleh mekanisme pertahanan tubuh; minum sesudah makan supaya cepat diserap.
- Dosis: 2mg/kgBB; 3x/hr stlh mkn 2-3 minggu
- I: 1) Terpilih utk W bancrofti, B malayi, B timoriensis, dan loa-loa. Microfilaria cepat terbunuh, cacing dewasa lebih lambat. 2) Profilaksis di daerah endemik.
- ES: Reaksi alergenik protein cacing mati menyertai pengobatan. Berikan kortikosteroid sebelum pengobatan , tambahkan antihistamin bila reaksi alergenik timbul. ES lain: anoreksia, nausea, muntah, vertigo, sakit kepala.

Ivermectin

- Terpilih utk strongyloidiasis, onchocerciasis, microfilaricidal thd onchocerciasis.Tak bunuh cacing dewasa, tapi hambat penglepasan microfilaria. Pemberian berulang tekan produksi microfilaria.

- Diserap peroral, C_{max} 4-5 jam, Ikatan protein 93%, Vd = 50 l/kgBW, $t_{1/2}$: 56 jam, efflux dari SSP oleh p-glycoprotein.
- Potensiasi sinap GABA cacing → paralisis
- I: 1) mass treatment kontrol onchocerciasis dan turunkan penularan; 2) terapi *suppressive* strongyloidiasis, diminum 1x/bulan; 3) efektif thd scabies, cutaneous larva migrans.
- KI: hamil. Jgn diberikandg barbiturat, benzodiazepin
- ES: saluran cerna, vertigo, hipersensitifitas, alergi protein cacing, depresi SSP, ataxia

Mebendazole

- Absorpsi <10%, ikatan protein >90%, t1/2: 2-6 jam.
- Hambat sintesis microtubule; spektrum lebar,matikan telor ascaris, trichiuria, ancylostoma.
- I: ascariasis, trichiuriasis, ancylostomiasis.
- ES: saluran cerna, hipersensitifitas.
- KI: kehamilan.
- Interaksi dengan carbamazepine dan cimetidine.

Niclosamide

- Absorpsi sedikit sekali; obat dikunyah dulu, sebelum ditelan.
- Membunuh cacing dewasa.
- I: obat lini kedua T saginata, T solium, diphyllobothrium latum; obat pengganti untuk F buski, H heterophyes.
- ES: saluran cerna.
- KI: kehamilan dan anak < 2 thn

Piperazine

- Hanya utk ascariasis.
- Mudah diserap, t_{max}:2-4 jam, tak dimetabolisir, ekskresi selesai dalam 24 jam.
- Melumpuhkan otot cacing dengan hambat ACH di *myoneural junction* → paralisis →cacing mudah dikeluarkan oleh peristaltik usus
- Dosis: (slm 2 hari) Dws 3,5g 1x/hr; anak 75 mg/kgBB 1x/hr
- ES: saluran cerna, pusing dan sakit kepala.
- KI: kehamilan, ganguan fungsi ginjal dan hati, epilepsi dan penyakit saraf kronik.

Praziquantel

- Efektif utk semua schistosoma, trematoda lain, dan cestoda.
- Efektif dan aman dalam dosis tunggal, berguna utk pengobatan masal.
- Bioavailabilitas 80%, pentreasi ke CSF, t1/2: 0.8-1.5 jam, ikatan protein 80%, ekskresi melalui ginjal dan cairan empedu. Interaksi dengan carbamazepine dan cimetidine.
- Melumpuhkan otot cacing dan mematikan, peristaltik mendorong cacing keluar.
- I: terpilih utk semua schistosomiasis, P westermani, F buski, H heterophyes, dan T solium & saginata

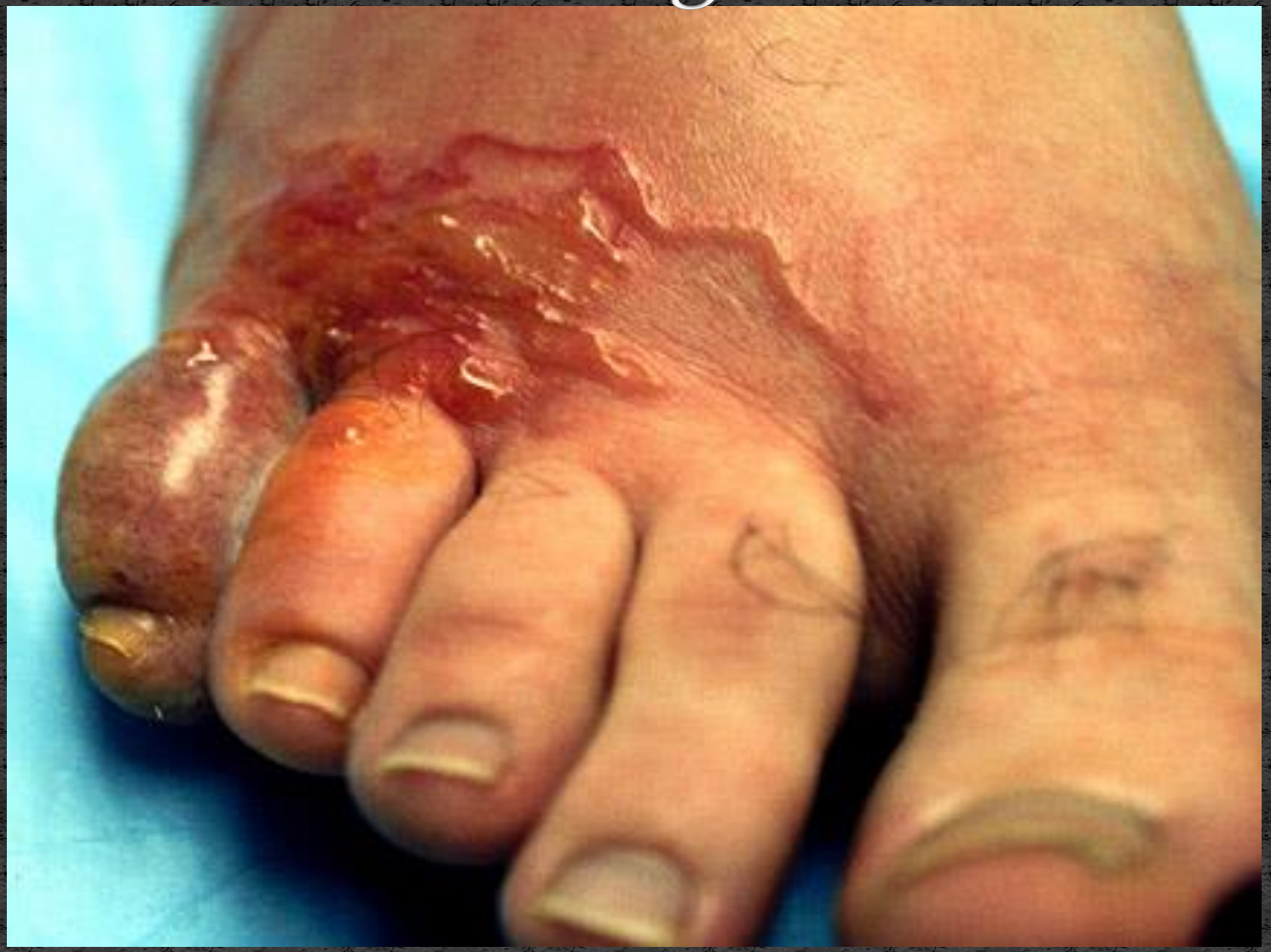
Pyrantel pamoate.

- Spektrum lebar: sangat efektif utk enterobiosis, ascariasis, trichostrongyloidiasis; aktif thd ancylostomiasis; tak aktif thd trichiuriasis dan strongyloidiasis.
- Absorpsi jelek, hanya efektif utk cacing saluran cerna.
- Hambat kolinesterase→ ↑ACH →cacing spastis dan terdorong keluar.
- Dosis tunggal 10 mg/kgBB
- ES: saluran cerna, lemas, ngantuk, gangguan fungsi hepar.
- Jangan diberikan bersama piperazin

Thiabendazole

- Pengganti ivermectin utk strongyloidiasis dan cutaneous larva migrans.
- Absorpsi cepat, t_{max}: 1-2 jam, $t_{1/2}$: 1-2 jam, metabolisme di hati.
- Lebih toksik dari albendazole, mebendazole, dan ivermectin.
- SE: saluran cerna, pusing, gagal hati *irreversible*, sindroma Steven-Johnson fatal.
- KI: kehamilan, anak, penyakit hati dan ginjal.

Cutaneous larva migrans



ANTIFUNGAL AGENTS

dr. Rina Nurbani, M.Biomed, Sp.Ak

Standar Kompetensi Dokter Indonesia

Tingkat kemampuan yang harus dicapai:

Tingkat Kemampuan 1: mengenali dan menjelaskan

Lulusan dokter mampu mengenali dan menjelaskan gambaran klinik penyakit, dan mengetahui cara yang paling tepat untuk mendapatkan informasi lebih lanjut mengenai penyakit tersebut, selanjutnya menentukan rujukan yang paling tepat bagi pasien. Lulusan dokter juga mampu menindaklanjuti sesudah kembali dari rujukan.

Tingkat Kemampuan 2: mendiagnosis dan merujuk

Lulusan dokter mampu membuat diagnosis klinik terhadap penyakit tersebut dan menentukan rujukan yang paling tepat bagi penanganan pasien selanjutnya. Lulusan dokter juga mampu menindaklanjuti sesudah kembali dari rujukan.

Tingkat Kemampuan 3: mendiagnosis, melakukan penatalaksanaan awal, dan merujuk

3A. Bukan gawat darurat

Lulusan dokter mampu memb
pendahuluan pada keadaan
mampu menentukan rujukan
selanjutnya. Lulusan dokter juga
rujukan.

3B. Gawat darurat

Lulusan dokter mampu membuat diagnosis klinik dan memberikan terapi pendahuluan pada keadaan gawat darurat demi menyelamatkan nyawa atau mencegah keparahan dan/atau kecacatan pada pasien. Lulusan dokter mampu menentukan rujukan yang paling tepat bagi penanganan pasien selanjutnya. Lulusan dokter juga mampu menindaklanjuti sesudah kembali dari rujukan.

Tingkat Kemampuan 4: mendiagnosis, melakukan penatalaksanaan secara mandiri dan tuntas

Lulusan dokter mampu membuat diagnosis klinik dan melakukan penatalaksanaan penyakit tersebut secara mandiri dan tuntas.

4A. Kompetensi yang dicapai pada saat lulus dokter

4B. Profisiensi (kemahiran) yang dicapai setelah selesai internsip dan/atau Pendidikan Kedokteran Berkelanjutan (PKB)

el kompetensi tertinggi adalah **4A**

Infeksi Jamur		
18	Tinea kapitis	4A
19	Tinea *barbe*	4A
20	Tinea fasialis	4A
21	Tinea korporis	4A
22	Tinea manus	4A
23	Tinea unguium	4A
24	Tinea kruris	4A
25	Tinea pedis	4A
26	Pitiriasis vesikolor	4A
27	Kandidosis mukokutan ringan	4A

Kingdom Fungi and Its Impact on Humans

- The incidence of life-threatening fungal infections has increased in immunocompromised patient populations:
  - Patient receiving hematologic or solid-organ transplantation
  - Cancer chemotherapy
  - Immunosuppressive medications
  - HIV/AIDS
- Amphotericin B remains the gold standard of systemic antifungal pharmacotherapy, but alternative therapies have emerged
- Type of antifungal infections:
  - Invasive
  - Mucosal
  - Superficial

Kingdom Fungi and Its Impact on Humans

- The antifungals in common clinical use act mainly at sites involving the cell wall and cell membrane (Fig. 61-1)

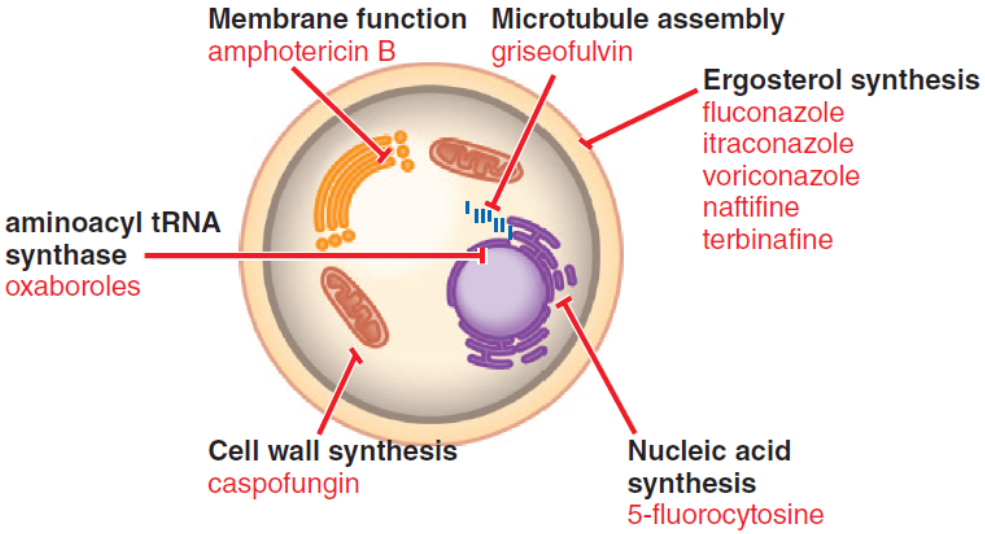


Figure 61–1 *Sites of action of antifungal agents.* Many antifungal agents act at sites involving cell wall and cell membrane function. Amphotericin B and other polyenes (e.g., nystatin) bind to ergosterol in fungal cell membranes and increase membrane permeability. The imidazoles and triazoles (itraconazole, etc.) inhibit 14-α-sterol demethylase, prevent ergosterol synthesis, and lead to the accumulation of toxic 14-α-methylsterols. The allylamines (e.g., naftifine and terbinafine) inhibit squalene epoxidase and prevent ergosterol synthesis. The echinocandins (e.g., caspofungin) inhibit the formation of glucans in the fungal cell wall. Metabolites of 5-fluorocytosine can disrupt fungal RNA and DNA synthesis. Griseofulvin inhibits microtubule assembly, thereby blocking fungal mitosis. Oxaboroles inhibit fungal aminoacyly tRNA synthase, thereby inhibiting fungal protein synthesis.

TABLE 61–1 ■ PHARMACOTHERAPY OF MYCOSES

DEEP MYCOSES	DRUGS
Invasive aspergillosis	
Immunosuppressed	Voriconazole, isavuconazole, amphotericin B
Nonimmunosuppressed	Voriconazole, isavuconazole, amphotericin B, itraconazole
Blastomycosis	
Rapidly progressive or CNS	Amphotericin B
Indolent and non-CNS	Itraconazole
Candidiasis	
Deeply invasive	Amphotericin B, fluconazole, voriconazole, caspofungin, micafungin, anidulafungin
Coccidioidomycosis	
Rapidly progressing	Amphotericin B
Indolent	Itraconazole, fluconazole
Meningeal	Fluconazole, intrathecal amphotericin B
Cryptococcosis	
Non-AIDS and initial AIDS	Amphotericin B, flucytosine
Maintenance AIDS	Fluconazole
Histoplasmosis	
Chronic pulmonary	Itraconazole
Disseminated	
Rapidly progressing or CNS	Amphotericin B
Indolent non-CNS	Itraconazole
Maintenance AIDS	Itraconazole
Mucormycosis	Amphotericin B, isavuconazole
Pseudallescheriasis	Voriconazole, itraconazole
Sporotrichosis	
Cutaneous	Itraconazole
Extracutaneous	Amphotericin B, itraconazole
Prophylaxis in the immunocompromised host	Fluconazole Posaconazole Micafungin
Empirical therapy in the immunocompromised host (*category not recognized by FDA*)	Amphotericin B Caspofungin Fluconazole
Microsporidia Infection	Albendazole Fumagillin
Pneumocystis jiroveci pneumonia	Trimethoprim-sulfamethoxazole Pentamidine

SUPERFICIAL MYCOSES	DRUGS (*Administration mode*)
Candidiasis	
Vulvovaginal	*Topical* Butoconazole, clotrimazole, miconazole, nystatin, terconazole, tioconazole
	Oral Fluconazole
Oropharyngeal	*Topical* Clotrimazole, nystatin
	Oral (systemic) Fluconazole, itraconazole Posaconazole
Cutaneous	*Topical* Amphotericin B, clotrimazole, ciclopirox, econazole, ketoconazole, miconazole, nystatin
Ringworm	*Topical* Butenafine, ciclopirox, clotrimazole, econazole, haloprogin, luliconazole, ketoconazole, miconazole, naftifine, oxiconazole, sertaconazole, sulconazole, terbinafine, tolnaftate, undecylenate
	Systemic Griseofulvin, itraconazole, terbinafine
Onychomycosis	*Systemic* Griseofulvin, itraconazole, terbinafine
	Topical Efinaconazole

Sytemic … or Deeply Invasive

I. Amphotericin B

- ***Chemistry***
  - An amphip…
  - Poor aquec…
  - Broadest sp…
- ***Mechanism of…***
  - AMB binds t… e permeability → leakage of … gal cell death
- ***ADME***
  - Gastrointest…
  - IV delivery i…
  - > 90% boun…
  - Azotemia, li… plasma concentrate
  - << AMB per…
  - [AMB] in flui… r → 2/3 of [plasma]

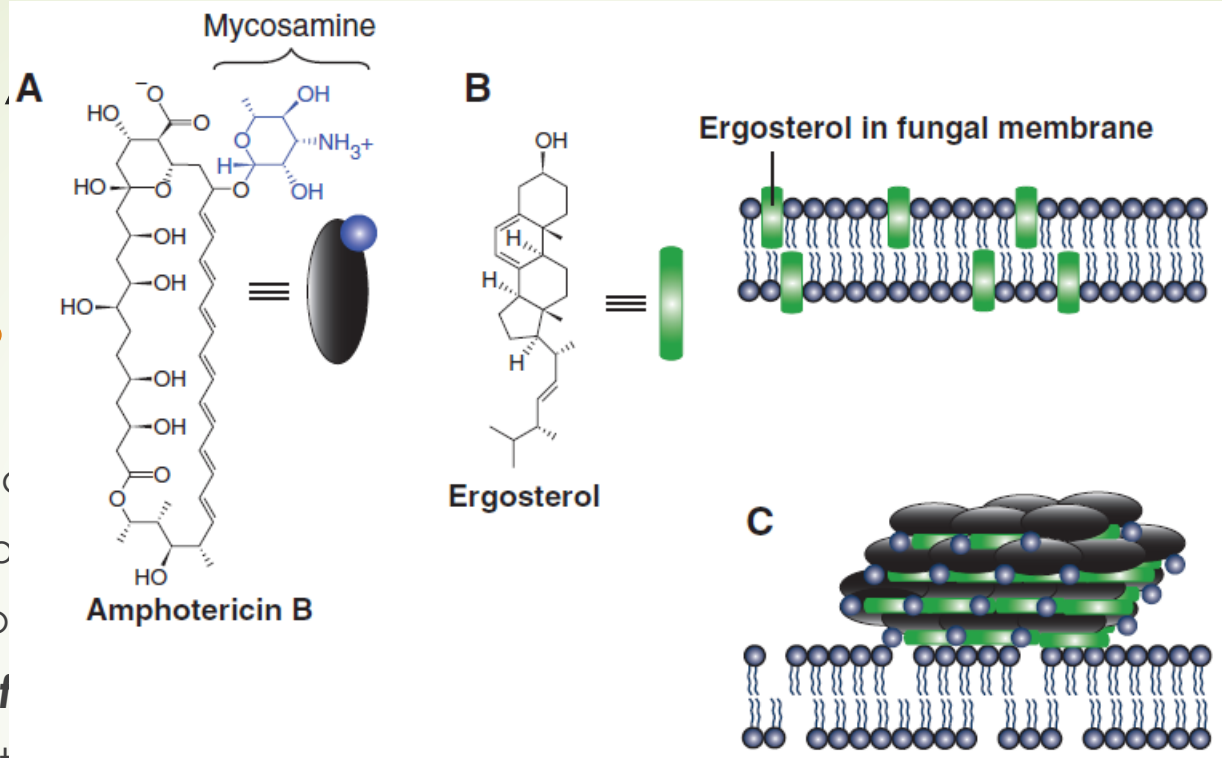


Figure 61–2 *Mechanism of action of amphotericin B.* The antifungal activity of amphotericin B depends on its capacity to bind ergosterol in the fungal cell membrane. **A.** Amphotericin is an amphipathic molecule with a mycosamine moiety (shown in blue) at one end of a 14-carbon hydrophobic chain. X-ray crystallography shows the molecule to be rigid and rod shaped, with the hydrophilic hydroxyl groups of the macrolide ring forming an opposing face to the lipophilic polyenic portion. **B.** Ergosterol, here depicted as a green rod, decorates both bilayers of the fungal membrane. **C.** Amphotericin B appears to form aggregates that sequester and effectively extract ergosterol from lipid bilayers, much like a selective sponge, disrupting membrane structure and resulting in fungal cell death.

Sytemic Antifungal Agents: Drugs for Deeply Invasive Fungal Infections

I. Amphotericin B (AMB)

- ***Antifungal Activity***
  - AMB has clinical activity against a broad spectrum of pathogenic fungi (table 61-1)
  - AMB has limited activity against the protozoa *Leishmania* spp and *Naegleria fowleri*
  - AMB has **no antibacterial activity**
- ***Therapeutic Uses***
  - AMB IV is the **treatment of choice for invasive mucormycosis**
  - AMB IV + 5-flucytosine ➔ **gold standard for induction treatment of cryptococcal meningitis**
  - AMB for patients with profound **neutropenia with fever who do not respond to broad-spectrum antibacterial agents over 5-7 days**.
- ***Adverse Effects***
  - The major acute reactions to intravenous AMB formulations are infusion-related fever and chills
  - Tachypnea, respiratory stridor, modest hypotension, azotemia, hypochromic, normocytic anemia

Sytemic Antifungal Agents: Drugs for Deeply Invasive Fungal Infections

II. Flucytosine (5-fluorocytosine)

❖ *Mechanism of Action*

- Succeptible fungi are capable of deaminating flucytosine to 5FU (5-fluorouracil)→ metabolized to 5FdUMP (inhibitor of thymidylate synthase) → **inhibiting DNA synthesis**

❖ *ADME*

- BAV >> on oral administration. Absorbed rapidly from GI tract, distributed >> in the body, minimally bound to plasma proteins
- peak Cp achieved 1-2 h. Concentration in CSF 65%-90% of Cp. It penetrate into the aqueous humor
- 80% of a given dose is excreted unchanged in the urine (clearance equivalent to creatinine)
- The t1/2 is 3-6 h in normal individuals; max 200 h in renal failure (adjust dosage)
- It is cleared by hemodialysis → give a single dose of 37,5 mg/kg after dialysis.

❖ *Terapeutic Uses*

- Orally 50-150 mg/kg/d in four divided doses

❖ *Adverse Effects*

- Depress the bone marrow → leukopenia, thrombocytopenia. Rash, nausea, vomiting, diarrhea

Systemic Antifungal Agents: Drugs for Deeply

TABLE 61–6 ■ SOME CONTRAINDICATED AZOLE DRUG COMBINATIONS

DRUG	FLUCONAZOLE	VORICONAZOLE	ITRACONAZOLE	POSACONAZOLE	ISAVUCONAZOLE
Alfuzosin		x	x	x	
Artemether	x	x			
Bepridil	x				
Clopidogrel	x				
Conivaptan	x	x	x	x	
Dabigatran			x		
Darunavir		x			
Dronedarone	x	x	x	x	
Everolimus	x	x	x	x	
Lopinavir		x			
Lumefantrine	x	x			
Mesoridazine	x				
Nilotinib	x	x	x	x	
Nisoldipine	Use with caution	x	x	x	
Quinine	x	x			
Rifapentine		x	Use with caution	Use with caution	
Ritonavir		x	Use with caution	Use with caution	Use with caution
Rivaroxaban		x	x		
Salmeterol		x	x	x	
Silodosin		x	x	x	
Simvastatin	Use with caution		x	x	
St. John's wort		x			x
Tetrabenazine	x	x			
Thioridazine	x	x			
Tolvaptan	x	x		x	
Tolvaptan	x		x		
Topotecan			x		
Ziprasidone	x	x			

INISTERED

ACONAZOLE	ISAVUCONAZOLE
–	–
	+
+	+
+	–
+	–
+	
+	+
+	

riconazole therapy.

Sytemic Antifungal Agents: Drugs for Deeply Invasive Fungal Infections

III. Imidazoles and Triazoles

3.1 Ketoconazole

- Per oral has been replaced by itraconazole except for lower cost
- Available for topical use

3.2 Itraconazole

- Triazole; it has activity against *Aspergillus* spp (imidazoles do not)
- Available: tablet, capsule, solution
- A biologically active metabolite, hydroxy-itraconazole
- Neither appears in urine or in CSF
- The *t*1/2 of itraconazole at steady state is about 30–40 h.
- Loading doses are recommended when treating deep mycoses.
- Severe liver disease will increase itraconazole Cp, but azotemia and hemodialysis have no effect
- The drug of choice for patients with indolent, nonmeningeal infections
- It is not recommended for maintenance therapy of cryptococcal meningitis in HIV-infected patients because of a high incidence of relaps

Sytemic Antifungal Agents: Drugs for Deeply Invasive Fungal Infections

3.2 Itraconazole

- Deep mycoses:
  - ✓ loading dose of 200 mg three times daily for the first 3 days. After the loading doses, two 100-mg capsules are given twice daily with food
- Onychomycosis:
  - 200 mg once daily for 12 weeks or, for infections isolated to fingernails, two monthly cycles consisting of 200 mg twice daily for 1 week followed by a 3-week period of no therapy— so-called pulse therapy
- Oropharyngeal candidiasis
  - oral solution should be taken during fasting in a dose of 100 mg (10 mL) once daily and swished vigorously in the mouth before swallowing to optimize any topical effect.
- Adverse Effects
  - Hepatotoxicity, diarrhea, abdominal cramps, anorexia, nausea, vomiting, rash, hypokalemia, hypertrigliseridemia
  - Contraindication: pregnancy or women contemplating pregnancy
- F
- f

Sytemic Antifungal Agents: Drugs for Deeply Invasive Fungal Infections

3.3 Fluconazole (triazole)

- Almost completely absorbed from the GI tract. Bav is unaltered by food or gastric acidity. Renal excretion > 90% of elimination. Diffuses into breast milk, sputum, saliva, CSF.
- Dosage interval should be increased with a decrease of creatinine clearance.
- A dose of 100-200 mg should be given after hemodialysis
- **Oropharyngeal Candidiasis** : 100-200 mg daily for 7-14 days
- **Vaginal candidiasis:** single dose 150 mg
- **Criptorcoccis with AIDS:** consolidation phase 400 mg daily in 8 weeks after induction therapy of 2 weeks IV AMB
- Tablet of 50, 100, 150 and 200 mg. Suspension 10 dan 40 mg/mL. IV solutions 2 mg/mL.
- Loading dose: twice daily maintenance dose on the first day
- Children: 12 mg/kg once daily (max 600 mg/d) without loading dose.
- Adult: up to 1200 mg daily for cryptococcal meningitis
- Adverse Effects
  - ✓ Nausea, headache, skin rash, vomiting, abdominal pain, diarrhea
- Contraindication: pregnancy

Sytemic Antifungal Agents: Drugs for Deeply Invasive Fungal Infections

IV. Echinocandins

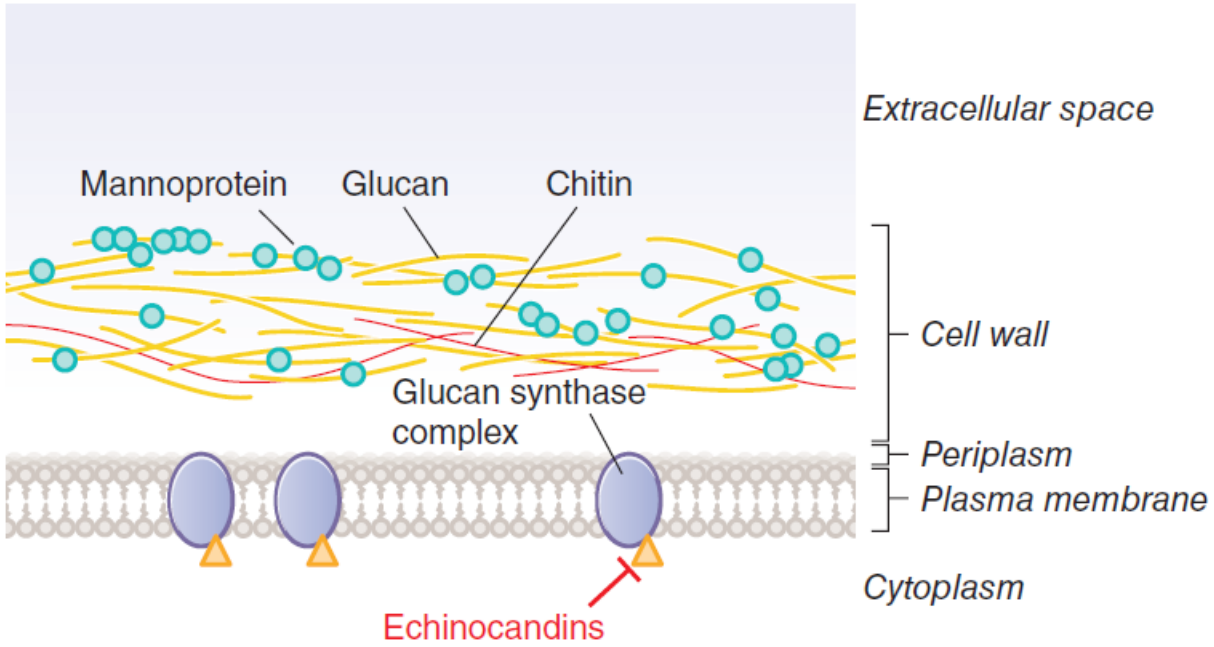


Figure 61–5 *The fungal cell wall and membrane and the action of echinocandins.* The strength of the fungal cell wall is maintained by fibrillar polysaccharides, largely β-1,3-glucan and chitin, which bind covalently to each other and to proteins. A glucan synthase complex in the plasma membrane catalyzes the synthesis of β-1,3-glucan; the glucan is extruded into the periplasm and incorporated into the cell wall. Echinocandins inhibit the activity of the glucan synthase complex, resulting in loss of the structural integrity of the cell wall. The Fks1p subunit of glucan synthase appears to be the target of echinocandins, and mutations in Fks1p cause resistance to echinocandins.

Sytemic Antifungal Agents: Drugs for Deeply Invasive Fungal Infections

V. Other Systemic Antifungal Agents

5.1 Griseofulvin

- Orally administered
- Griseofulvin inhibits microtubule function and thereby disrupts assembly of the mitotic spindle, which disrupts fungal cell division
- Taken with a fatty meal improve absorption. Plasma *t*1/2 of about 1 day. Excreted in urine
- Barbiturate decrease griseofulvin absorption from the GI tract
- *M*ycotic disease of the skin, hair, and nails due to *Microsporum, Trichophyton,* or *Epidermophyton* responds to griseofulvin therapy
- For tinea capitis in children, griseofulvin remains the drug of choice for efficacy, safety, and availability as an oral suspension
- Treatment must be continued until infected tissue is replaced by normal hair, skin, or nails, which requires 1 month for scalp and hair ringworm, 6–9 months for fingernails, and at least a year for toenails
- Itraconazole or terbinafine is much more effective for onychomycosis
- Adverse effects: incidence <<. Hepatotoxicity, leukopenia, neutropenia, albuminuria, urticarial, licen planus, erythema
- Increases the rate of metabolism of warfarin → adjust dose of warfarin

Sytemic Antifungal Agents: Drugs for Deeply Invasive Fungal Infections

V. Other Systemic Antifungal Agents

5.2 Terbinafine

- It inhibits fungal squalene epoxidase and thereby reduces ergosterol biosynthesis
- Terbinafine is well absorbed, but bioavailability is about 40% due to first-pass metabolism in the liver.
- The drug accumulates in skin, nails, and fat.
- The initial *t*1/2 is about 12 h but extends to 200–400 h at steady state.
- Terbinafine is not recommended in patients with marked azotemia or hepatic failure.
- Rifampin decreases and cimetidine increases plasma terbinafine concentrations
- 250-mg tablet daily for adults, is somewhat more effective than itraconazole for nail onychomycosis.
- Duration of treatment ranges between 6 and 12 weeks
- also effective for the treatment of tinea capitis and has been used for the off-label treatment of ringworm elsewhere on the body
- Aderse effects. Low (GI distress, headache, rash); very rarely (hepatotocicity, neutropenia, SJS, TEN)
- Countraindicated : pregnancy

Topical Antifungal Agents

- treatment of many superficial fungal infections, such as those confined to the stratum corneum, squamous mucosa, or cornea
- Indication: dermatophytosis (ringworm), candidiasis, tinea versicolor, piedra, tinea nigra, and fungal keratitis
- formulations for cutaneous application: creams or solutions.
- Ointments are inconvenient and can be too occlusive to the skin, particularly if the affected area is a macerated, fissured, or intertriginous lesion.
- Antifungal powders, whether applied by shake containers or aerosols, are useful only for lesions of the feet, groin, and similar intertriginous areas.
- topical administration is not successful for mycoses of the nails (onychomycosis) and hair (tinea capitis) and should not be used for the treatment of subcutaneous mycoses, such as sporotrichosis and chromoblastomycosis.
- penetration of topical drugs into hyperkeratotic lesions often is poor. Removal of thick, infected keratin is sometimes a useful adjunct to therapy.

Topical Antifungal Agents

I. Topical Imidazoles and Triazoles

- Indications for topical use: ringworm, tinea versicolor, and mucocutaneous candidiasis

❖ *Modes of Administration*

- Cutaneous Application
  - ✓ for tinea corporis, tinea pedis, tinea cruris, tinea versicolor, and cutaneous candidiasis applied twice a day for 3–6 weeks.
  - ✓ The cutaneous formulations are not suitable for oral, vaginal, or ocular use
- Vaginal Application
  - ✓ Vaginal creams, suppositories, and tablets for vaginal candidiasis: once a day for 1–7 days, preferably at bedtime to facilitate retention. None is useful in trichomoniasis.
  - ✓ vaginal formulations: clotrimazole tablets, miconazole suppositories, and terconazole cream—come in both low- and high-dose preparations. 3%–10% of the vaginal dose is absorbed
  - ✓ side effect is vaginal burning or itching. A male sexual partner may experience mild penile irritation.
- Oral Use
  - ✓ 10 mg oral troche of clotrimazole as topical therapy for oropharyngeal candidiasis.
  - ✓ Antifungal activity is due entirely to the local concentration of the drug; there is no systemic effect.

Topical Antifungal Agents

II. Individual Agents

2.1 Clotrimazole

- Absorption of clotrimazole: intact skini < 0.5%; vagina 3%–10%. Fungicidal concentrations remain in the vagina for as long as 3 days after application of the drug
- Adult oral dose 200 mg/d
- Adverse effects. Skin irritation, stinging sensations, erythema, edema, vesication, desquamation, pruritus, or urticaria. Vagina: 1.6% mild burning sensation. In rare instances, lower abdominal cramps, a slight increase in urinary frequency, or skin rash. a patient's sexual partner may experience penile or urethral irritation. Oral clotrimazole troches cause GI irritation in about 5% of patients.
- 1% cream, lotion, powder, aerosol solution, and solution; 1% or 2% vaginal cream; vaginal tablets of 100, 200, or 500 mg; and 10-mg troches.
- Skin (twice a day); vagina (100-mg tablet once a day at bedtime for 7 days, one 200-mg tablet daily for 3 days, one 500-mg tablet only once, or 5 g of cream once a day for 3 days (2% cream) or 7 days (1% cream). Oropharyngeal candidiasis (troches are to be dissolved slowly in the mouth five times a day for 14 days)
- Topical clotrimazole cures dermatophyte infections in 60%–100% of cases. The cure rates in cutaneous candidiasis are 80%–100%. In vulvovaginal candidiasis, the cure rate is usually greater than 80% when the 7-day regimen is used. A 3-day regimen of 200 mg once a day appears to be similarly effective, as does single-dose treatment (500 mg).
- Recurrences are common after all regimens. The cure rate with oral troches for oral and pharyngeal candidiasis may be as high as 100% in the immunocompetent host.

Topical Antifungal Agents

II. Individual Agents

2.2 Miconazole

- Miconazole readily penetrates the stratum corneum of the skin and persists for more than 4 days after application. Adverse effects. Topical vagina: burning, itching, or irritation (7%), pelvic cramps (0.2%), headache, hives, or skin rash. Irritation, burning, and maceration are rare after cutaneous application. Miconazole is considered safe for use during pregnancy, although some experts advocate avoiding vaginal use during the first trimester
- Miconazole nitrate 2% cream, ointment, lotion, powder, gel, aerosol powder, and aerosol solution. To avoid maceration, only the lotion should be applied to intertriginous areas. Miconazole is available as a 2% and 4% vaginal cream and as 100-, 200-, or 1200-mg vaginal suppositories to be applied high in the vagina at bedtime for 7, 3, or 1 days, respectively.
- tinea pedis, tinea cruris, and tinea versicolor, the cure rate exceeds 90%. Vulvovaginal candidiasis cure rate at the end of 1 month is about 80%–95%. Pruritus sometimes is relieved after a single application. Some vaginal infections caused by *C. glabrata* also respond to this drug

2.3 Ketoconazole (imidazole)

- ketoconazole 0.5% cream, foam, gel, and shampoo for common skin dermatophyte infections, for tinea versicolor, and for seborrheic dermatitis.

Topical Antifungal Agents

III. Structurally Diverse Antifungal Agents

3.1 Haloprogin

- fungicidal to various species of *Epidermophyton, Pityrosporum, Microsporum, Trichophyton,* and *Candida.* During treatment with this drug, irritation, pruritus, burning sensations, vesiculation, increased maceration, and "sensitization" (or exacerbation of the lesion) occasionally occur, especially on the foot if occlusive footgear is worn
- Haloprogin cream or solution twice a day for 2–4 weeks. Its principal use is against tinea pedis, cure rate is about 80%. It also is used against tinea cruris, tinea corporis, tinea manuum, and tinea versicolor. Haloprogin is no longer available in the U.S.

3.2 Tolnaftate

- effective for most cutaneous mycoses caused by *T. rubrum, T. mentagrophytes, Trichophyton tonsurans, E. floccosum, M. canis, M. audouinii, Microsporum gypseum,* and *M. furfur,* but it is **ineffective against *Candida***.
- Tinea pedis, the cure rate is about 80%, compared with about 95% for miconazole.
- Tolnaftate 1% concentration as a cream, gel, powder, aerosol powder, topical solution, or a topical aerosol liquid. The preparations are applied locally twice a day. Pruritus is usually relieved in 24–72 h. Involution of interdigital lesions caused by susceptible fungi is very often complete in 7–21 days. Toxic or allergic reactions to tolnaftate have not been reported

Topical Antifungal Agents

III. Structurally Diverse Antifungal Agents

3.3 Terbinafine

- targets ergosterol biosynthesis. Terbinafine 1% cream or spray, applied twice daily, is effective in tinea corporis, tinea cruris, and tinea pedis. **Terbinafine is less active against *Candida* species and *Malassezia furf*ur,** but the cream also can be used in cutaneous candidiasis and tinea versicolor.

3.4 Nystatin

- structurally similar to amphotericin B and acts through the same mechanism of action.
- The drug is not absorbed from the GI tract, skin, or vagina.
- Nystatin is useful only for candidiasis and is supplied in preparations intended for cutaneous, vaginal, or oral administration
- **Infections of the nails and hyperkeratinized or crusted skin lesions do not respond**.
- Powders are preferred for moist lesions such as diaper rash and are applied two to three times daily. Creams or ointments are used twice daily. Combinations of nystatin with antibacterial agents or corticosteroids also are available.
- Allergic reaction are uncommon. Imidazoles or triazoles are more effective than nystatin for vaginal candidiasis.
- **Nystatin suspension effective for oral candidiasis of the immunocompetent host, neonates and infants for oral thrush.**

III. Struc

3.5 Be

- %) is known as
- l is used mainly in the

Drug Facts

Drugs

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Imidazoles and Triazoles: Inhibit ergosterol biosynthesis		
Fluconazole	• Invasive candidiasis • Cryptococcosis • Coccidioidomycosis • Prophylaxis and empirical therapy in immunocompromised host	• Plasma concentrations are essentially the same whether the drug is given orally or intravenously. • Concentrations in CSF = 50%–90% of C_p • Inhibitor of CYP3A4 and CYP2C9 • Contraindicated during pregnancy
Voriconazole	• Invasive aspergillosis • Invasive candidiasis • Pseudallescheriasis	• Oral bioavailability is 96%. • Monitor C_p; serum levels of 1 to 5 mg/L maximize efficacy and minimize toxicity • Metabolized by and inhibits CYPs (2C19 > 2C9 > 3A4) • Can prolong the QTc interval • Transient visual or auditory hallucinations are frequent after the first dose. • Contraindicated in pregnancy
Posaconazole	• Oropharyngeal candidiasis • Prophylaxis in the immunocompromised host against aspergillosis and candidiasis	• Oral bioavailability enhanced by food • Drugs that ↓ gastric acid ↓ posaconazole exposure • Inhibits CYP3A4 • Can prolong the QTc interval • Adverse effects: headache and GI disorders
Isavuconazole (isavuconazonium prodrug)	• Invasive aspergillosis • Mucormycosis	• Oral bioavailability is 98%. • Substrate of and inhibitor of CYP3A4 • Does not appear to prolong QTc
Echinocandins: Inhibit 1,3-β -D-glucan synthesis in the fungal cell wall		
Caspofungin	• Invasive candidiasis • Empirical therapy in the immunocompromised host	• ↓ Dose in moderate hepatic impairment
Micafungin	• Invasive candidiasis • Prophylaxis in the immunocompromised host	• Reduction of micafungin dose in moderate hepatic failure is not required.
Anidulafungin	• Invasive candidiasis	• No dose adjustment is needed for hepatic or renal failure.
Griseofulvin: Inhibits microtubule function, disrupts assembly of the mitotic spindle		
Griseofulvin	• Ringworm • Onychomycosis	• Absorption is reduced by barbiturates • Induces hepatic CYPs
Allylamines: Inhibit fungal squalene epoxidase and reduce ergosterol biosynthesis		
Terbinafine	• Ringworm • Onychomycosis	• Bioavailability is ~ 40% due to first-pass metabolism in the liver. • The drug accumulates in skin, nails, and fat. • The initial $t_{1/2}$ is ~ 12 h but extends to 200–400 h at steady state.
Agents Active Against Microsporidia and *Pneumocystis*		
Albendazole	• Microsporidia infection	• Anthelmintic • Inhibitor of α-tubulin polymerization
Fumagillin	• Microsporidia infection	• Used in immunocompromised individuals with intestinal microsporidiosis due to *Enterocytozoon bieneusi* unresponsive to albendazole • Not approved for human use in the U.S.
Trimethoprim-sulfamethoxazole	• *Pneumocystis jiroveci* pneumonia	• See Chapter 56
Pentamidine	• *Pneumocystis jiroveci* pneumonia	• Prophylaxis use to prevent PJP in at-risk individuals who cannot tolerate trimethoprim-sulfamethoxazole
Topical Antifungal Agents		
Imidazoles and Triazoles Clotrimazole, miconazole, ketoconazole, etc.	• Dermatophytosis (ringworm), candidiasis, tinea versicolor, piedra, tinea nigra, and fungal keratitis	• Available for cutaneous application as creams or solutions • Some are available as vaginal creams or suppositories or as oral troches
Tavaborole	Toenail onychomycosis due to *T. rubrum* or *T. mentagrophytes*	• Apply daily for 48 weeks

Polyenes: Interac

Amphotericin B deoxy (C-AMB)

mia, renal tubular

fever and chills

lder children and adults

Amphotericin B colloi dispersion (ABCD) (no in the U.S.)

toxic than C-AMB.

st with L-AMB.

Liposomal amphoteri (L-AMB)

Amphotericin B lipid c (ABLC)

Pyrimidines: Disr

Flucytosine

lness as single-agent

and thrombocytopenia

Imidazoles and T

Ketoconazole

Itraconazole

becoming pregnant