Antifungal drugs - antimycotics

(basic principles, main categories and adverse events)

Regina Demlova, MD, Ph.D.

Fungal Infection in Humans = Mycosis

- Major Types of Mycoses
  - Superficial
  - Systemic
  - Opportunistic
- Symptoms vary from cosmetic to life threatening

Superficial mycoses

- ✓ Dermatophytosis (tinea)

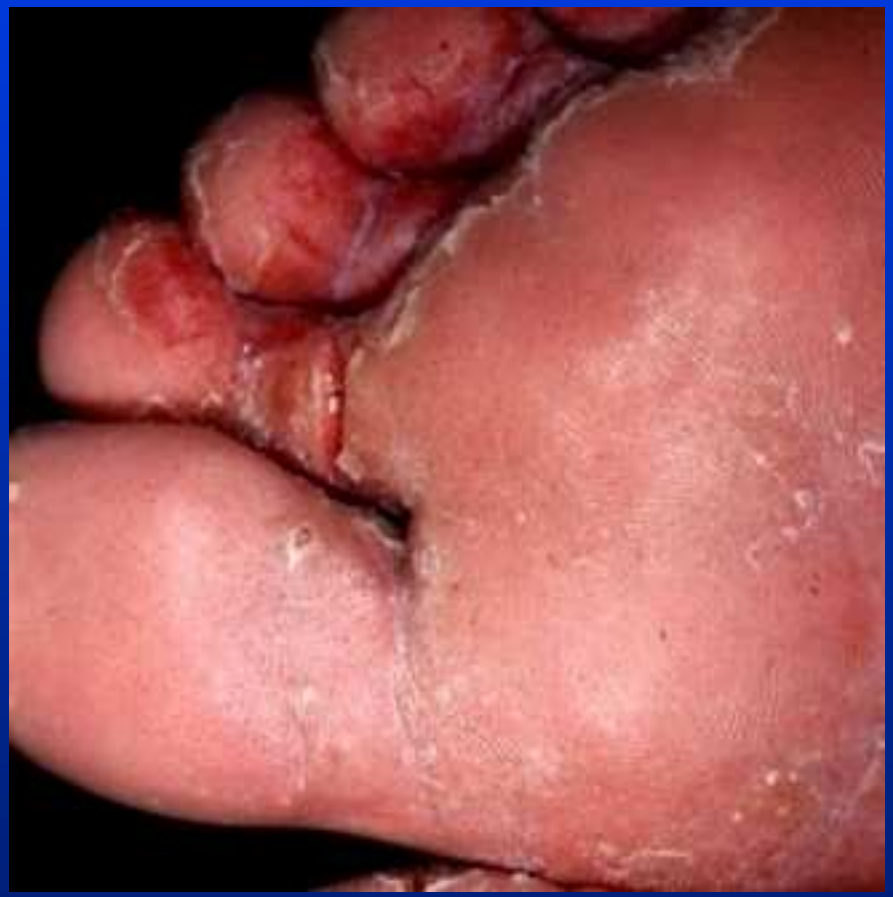
  trychophyton

  epidermophytom

  microsporum

- ✓ Superficial candidiasis

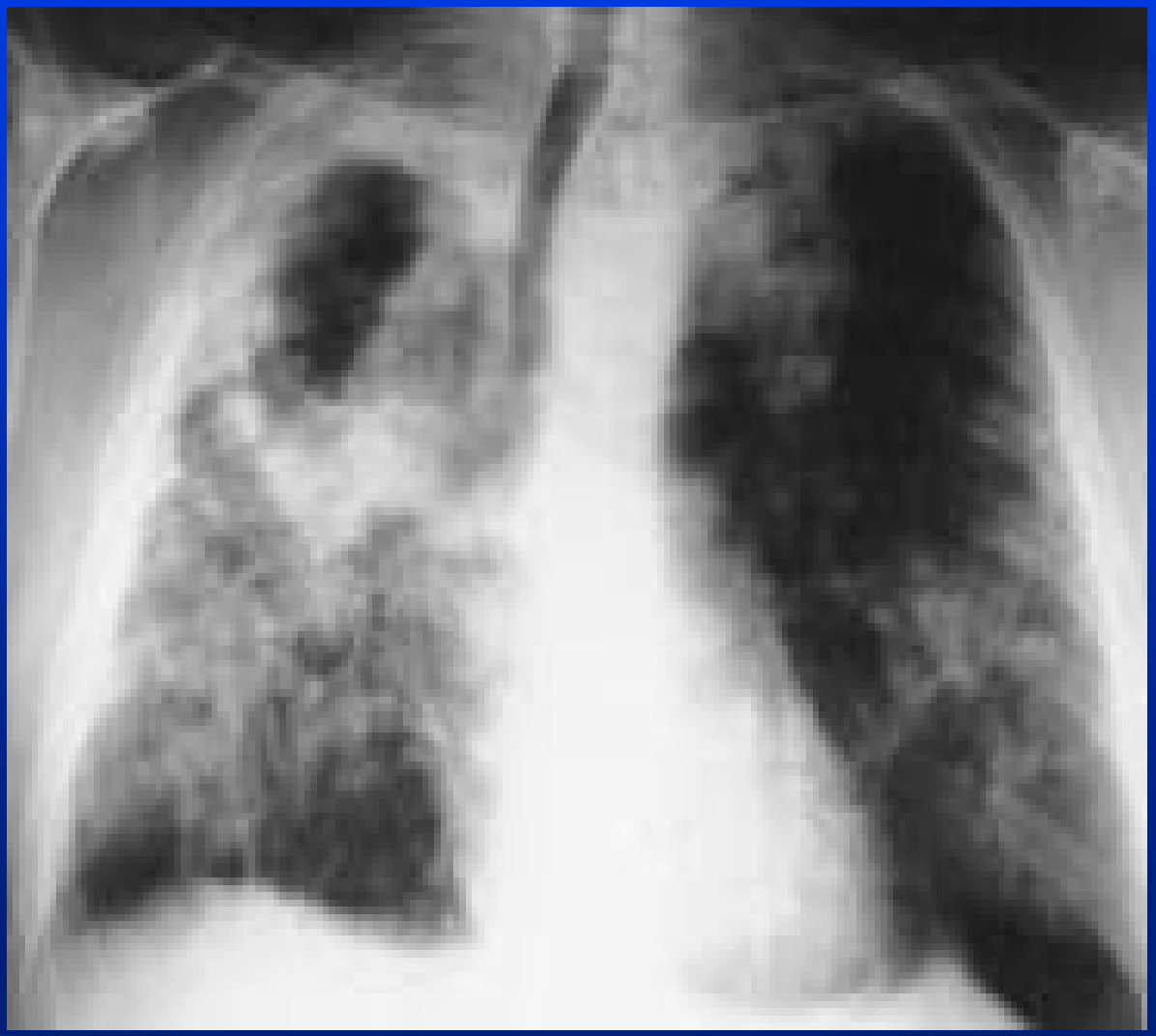
Tinea pedis



Systemic mycoses

- ✓ Pulmonary aspergillosis
- ✓ Cryptococcal meningitis and endocarditis
- ✓ Cerebral mukomycosis
- ✓ Systemic candidiasis

Pulmonary aspergillosis



Main categories

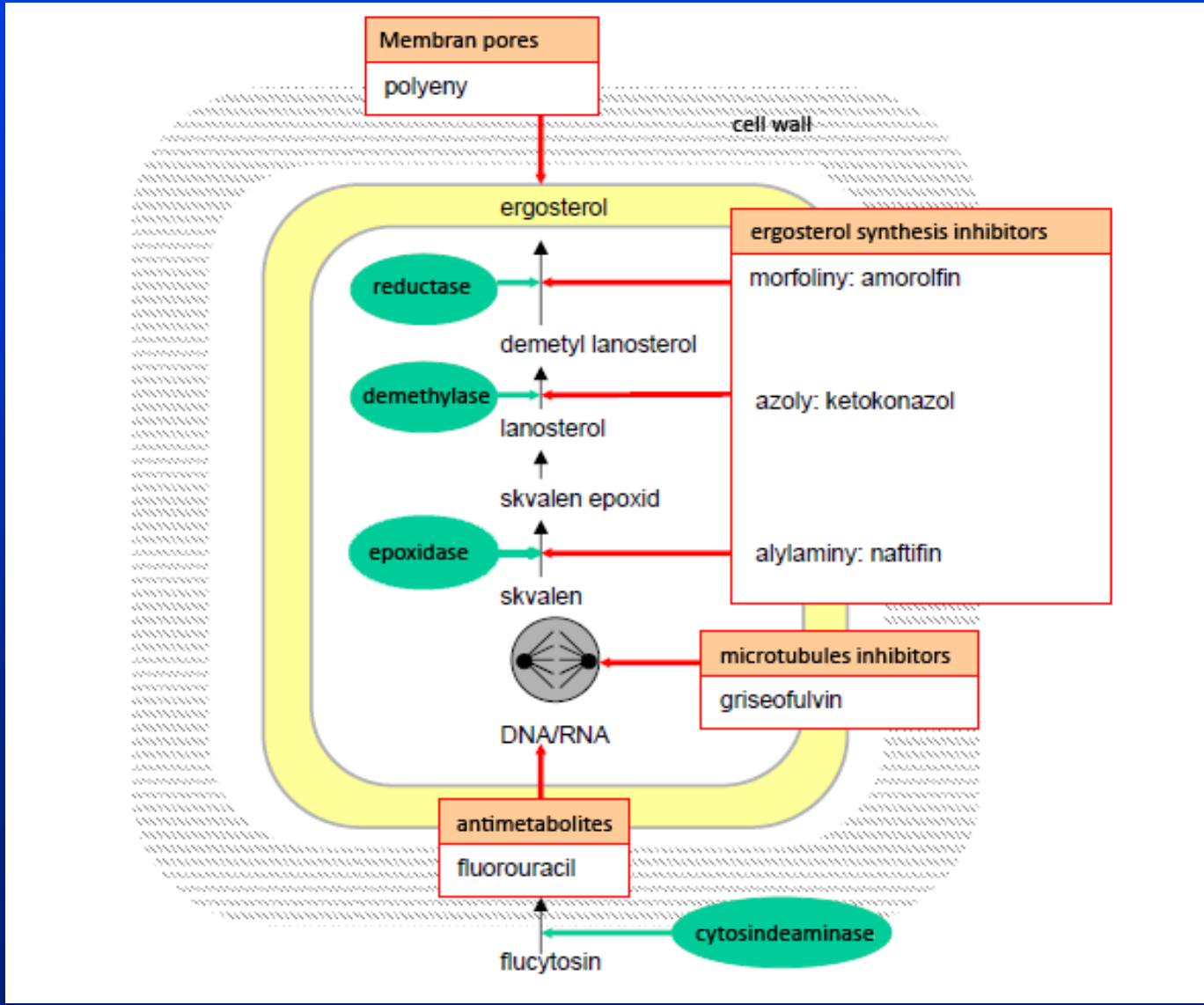
A. Polyene antimycotics

B. Azole-based antimycotics

C. Allylamines

D. Others (pyrimidines, griseofulvin)

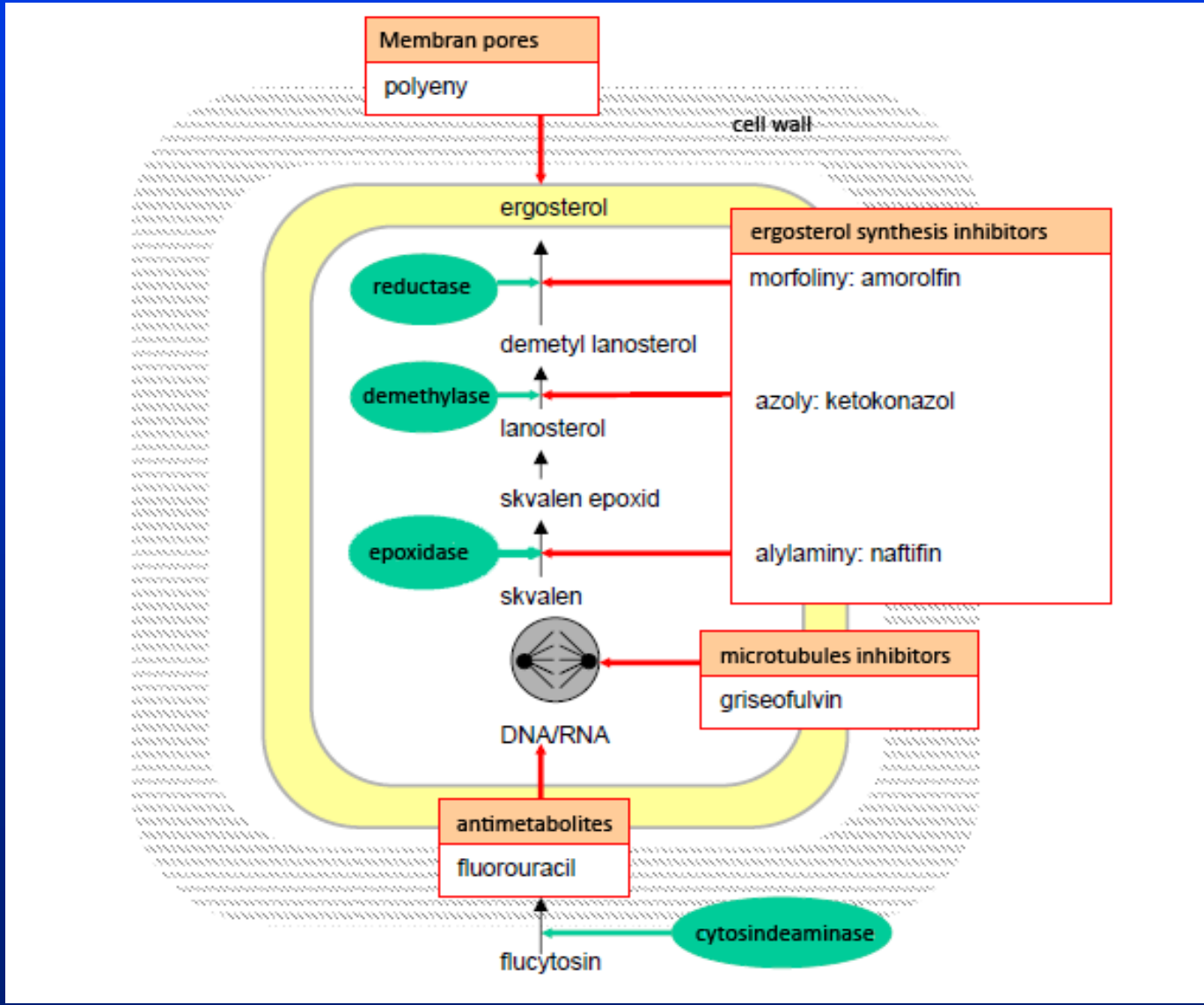
Physiology – fungal cell



A. polyenes : mechanism of action

- ✓ the interaction of the antifungal with membrane sterol results in the production of aqueous pores
- ✓ this configuration gives rise to a pore
- ✓ leading to altered permeability, leakage of vital cytoplasmic components, and death of the organism

Polyenes


Membran pores
polyeny
cell wall
ergosterol
ergosterol synthesis inhibitors
morfoliny: amorolfin
reductase
demetyl lanosterol
demethylase
azoly: ketokonazol
lanosterol
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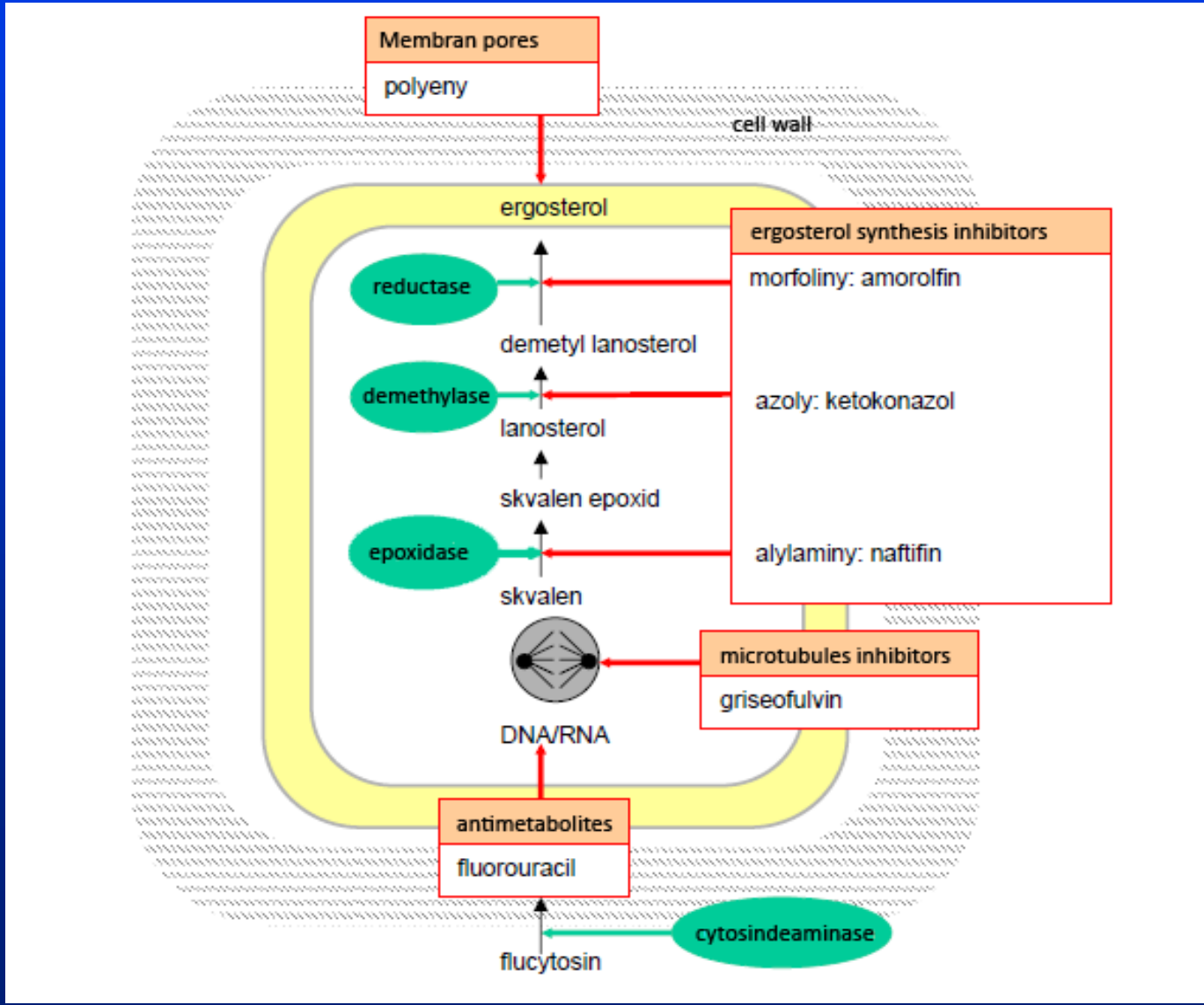
Polyenes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Polyenes

- ✓ Systemic (i.v. administration)

  amphotericin B

- ✓ Local (topical)

  nystatin (MACMIROR)

  natamycin (PIMAFUCORT)

Amphotericine B

- ✓ relatively poor penetration into tissues and fluids
- ✓ penetration into the brain virtually zero
- ✓ absorption from GI systém zero (i.v.!)
- ✓ binding to protein 90-95% (+ erythrocytes + cholesterol)
- ✓ serum half-life of 18-24 hours, elimination half-life of 15 days
- ✓ excreted unchanged in bile

Amphotericine B

- ✓ Aspergillosis (drug of 1st choice)
- ✓ Serious systemic mycoses with organ involvement (meningitis, endocarditis, pneumonia)
- ✓ Coccidiomycosis, histoplasmosis, blastomycosis

Amphotericine B

1. Acute symptoms:

✓ fever, chills, rigor, nausea, vomiting, headache, muscles, joints - production of PGE2, TNF and IL-1

1. Chronic symptoms:

✓ nephrotoxicity !! (up to 80% of patients) - failure of membrane cholesterol + vasoconstriction

✓ normocytic normochromic anemia

✓ thrombophlebitis

Amphotericine B - nephrotoxicity

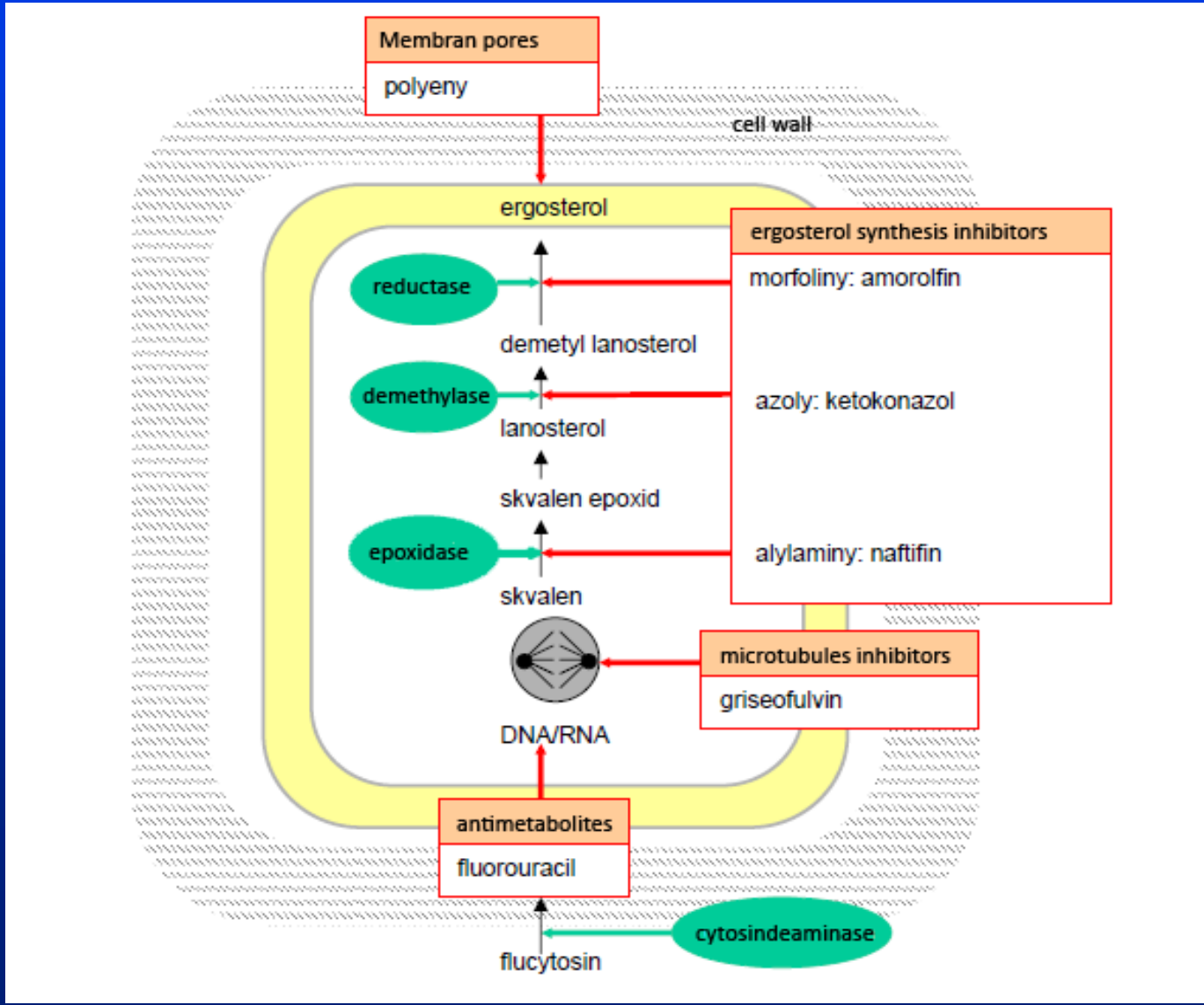
Synergic effects with flucytosin - ↓ dose of amphotecine B - ↓ nephrotoxicity

Liposomal forms : ABELCET i.v.

B. azole–based antimycotics: mechanism of action

- ✓ Inhibition of ergosterol synthesis
- ✓ Inhibitors of cytochrome P-450-dependent 14a-sterol demethylase

azole–based antimycotics



Azole-based antimycotic agents

- ✓ Systemic – p.o. or topical

  ketoconazol (NIZORAL)
  flukonazol (DIFLUCAN, MYCOMAX)

Azole-based antimycotic agents

- ✓ Systemic – i.v. (immunocompromised patients) – broader spectrum

  itraconazol (SPORANOX)

  voriconazol (VFEND)

  posaconazol (NOXAFIL)

Azole-based antimycotic agents

- ✓ Local (topical)

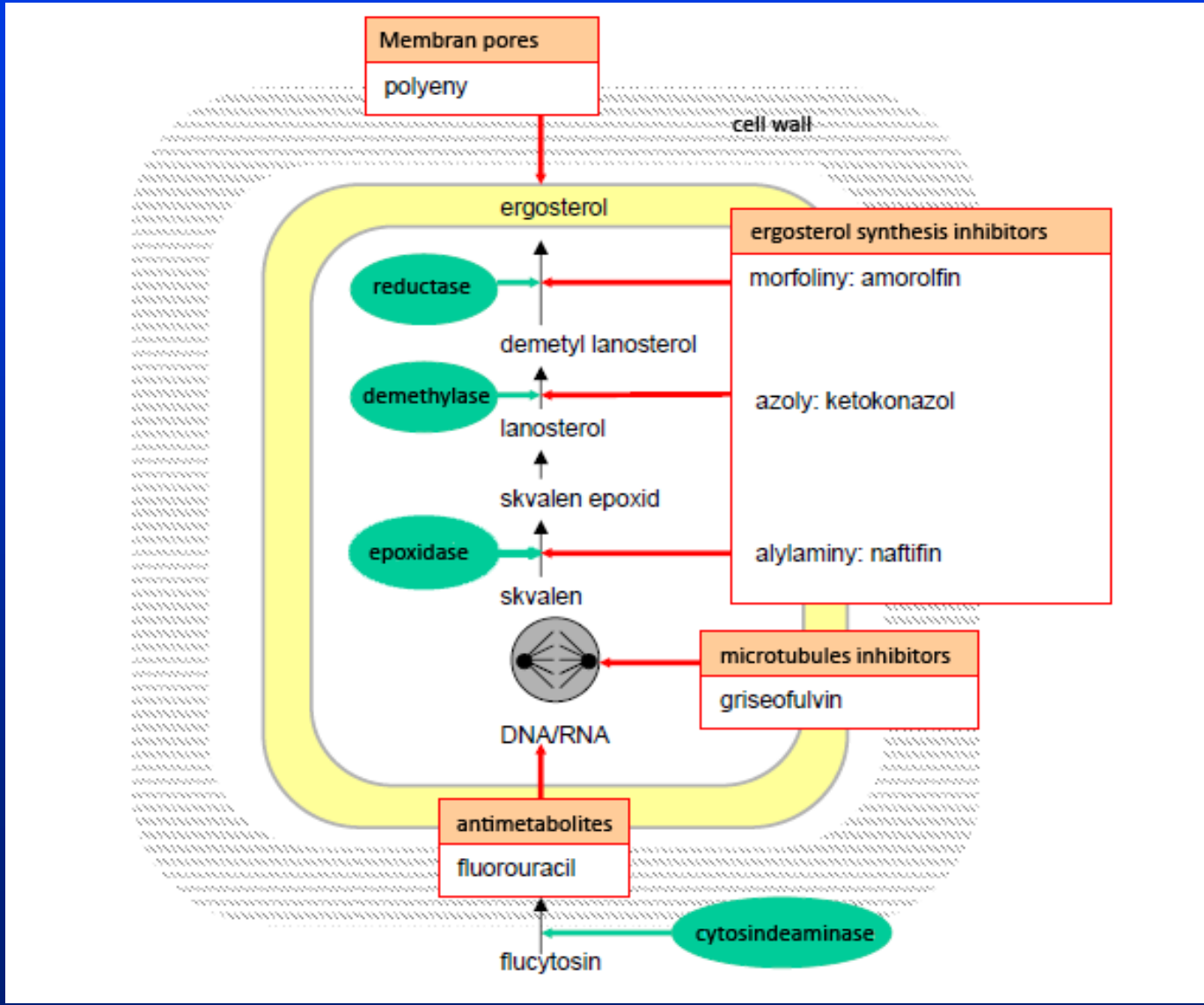
  clotrimazon (CANESTEN) – topical treatment

  mikonazol (LORAMYC) – local orophacial candidosis

3. Allyamines : mechanism of action

- ✓ Allylamines act by inhibiting early steps of ergosterol biosynthesis
- ✓ allylamine inhibition of sterol synthesis occurs at the point of squalene epoxidation, a reaction catalyzed by squalene epoxidase

Allyamines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fluorouracil
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flucytosin

3. Allyamines

- ✓ Terbinafin (LAMISIL – topical or oral)

Indication : dermatophytes

4. Others – 5-flucytosin (5-FC)

- ✓ 5-FC enters fungal cells aided by a permease enzyme. Once inside, it is converted to 5-fluorouracil (5FU) - RNA, DNA synthesis

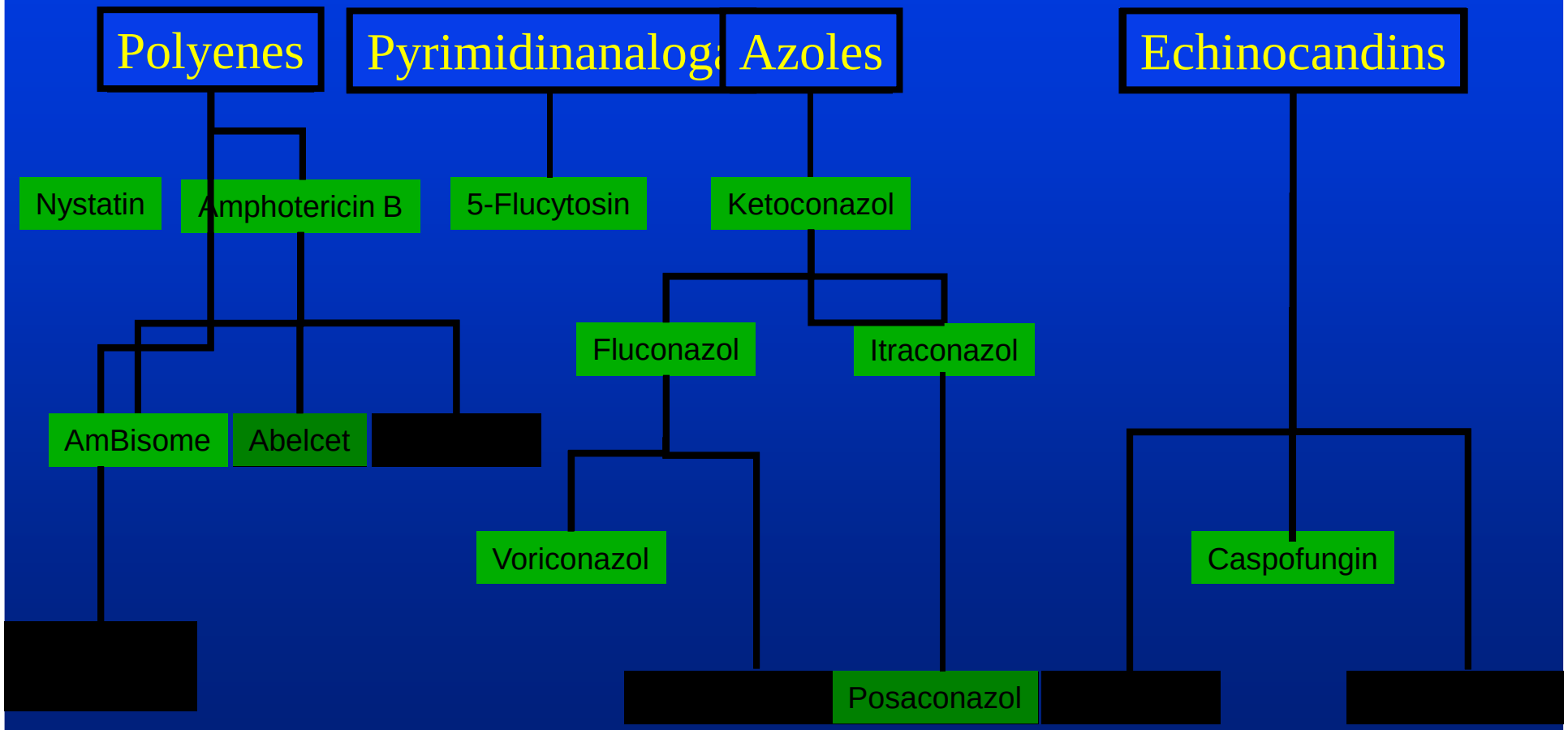
Indication : *Candida* and *Cryptococcus neoformans*

Synergic effects with amphotericin B

4. Others – griseofulvin

- ✓ Obsolent, not used in daily practice

Development of antifungals



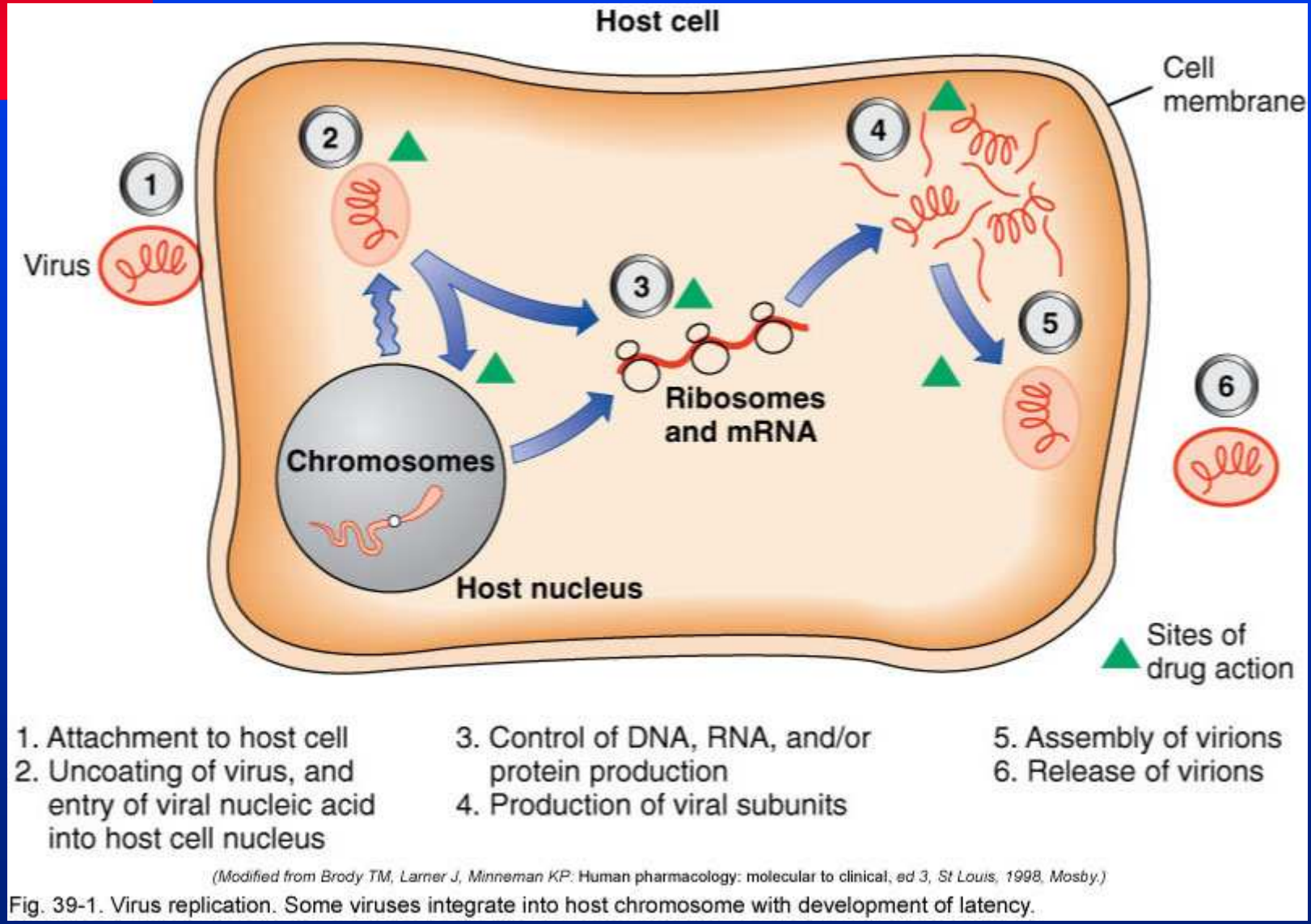
mod. nach R. Lewis, ICAAC 200

Antiviral drugs

Understanding Viruses - intracellular parasites

Viral replication

- Small inefective agents (20-30 nm)
- Incapable of reproduction outside their host cells
- It must attach to and enter a host cell
- It then uses the host cell's energy to synthesize protein, DNA, and RNA



(Modified from Brody TM, Larner J, Minneman KP: Human pharmacology: molecular to clinical, *ed 3, St Louis, 1998, Mosby.)*

Fig. 39-1. Virus replication. Some viruses integrate into host chromosome with development of latency.

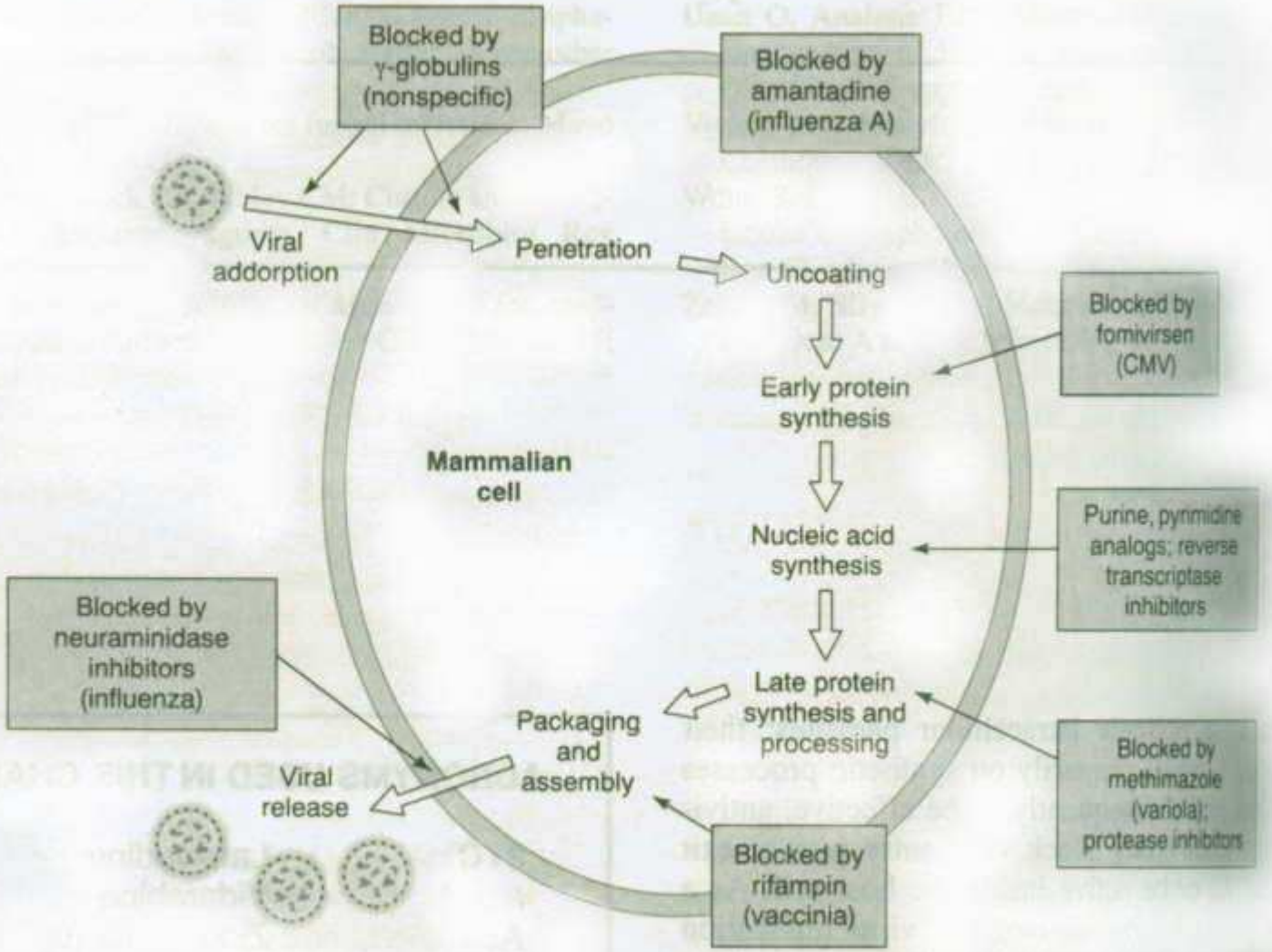


Figure 49–1. The major sites of antiviral drug action. (Modified and reproduced, with permission, from Katzung B, Trevor AT [editors]: *Pharmacology: Examination & Board Review*, 4th ed. Originally published by Appleton & Lange. Copyright © 1995 by The McGraw-Hill Companies, Inc.)

Key characteristics of antiviral drugs

Some drugs **interfere with ability of virus to bind to cells**

Able to enter the cells infected with virus

Interfere with viral nucleic acid **synthesis and/or regulation**

Some drugs **stimulate the body's immune system**

- **Best responses** to antiviral drugs are in **patients with competent immune systems**
- A **healthy immune system works synergistically with the drug** to eliminate or suppress viral activity

Viruses controlled by current antiviral therapy

- Influenza viruses (the “flu”)
- Cytomegalovirus (CMV)
- Hepatitis viruses
- Herpes viruses
- Human immunodeficiency virus (HIV)
- Influenza viruses (the “flu”)
- Respiratory syncytial virus (RSV)

Viral Infections

Competent immune system:

- Best response to viral infections
- A well-functioning immune system will eliminate or effectively destroy virus replication

Immunocompromised patients have frequent viral infections

- Cancer patients, especially leukemia or lymphoma
- Transplant patients, due to pharmacologic therapy
- AIDS patients, disease attacks immune system

Viral Infections

Opportunistic infections

- Occur in **immunocompromised patients**
- Infections that **would not normally harm an immunocompetent person**
- Require **long-term prophylaxis** and anti-infective drug therapy
- Can be other **viruses, fungi, bacteria, or protozoa**

Type of antivirotics therapy

1. **Antiviral drugs**
   - Used to treat infections caused by viruses other than HIV

2. **Antiretroviral drugs**
   - Used to treat infections caused by HIV, the virus that causes AIDS

Type of antivirotics therapy

1. Antiviral drugs

A. herpetic infection
B. Influenza
C. Cytomegaloviruses

Antivirals used for treatment of a. herpetic infection

Aciclovir /ZOVIRAX/ – DNA polymerase inhibitor

active in triphosphate form, acts as false substrate for specific viral DNA polymerase of the virus.

Administration: local, orally (20%) or i.v.

Indications: skin and systemic infections caused by herpes simplex, zoster.

Antivirals used for treatment of herpetic infection

Valaciclovir – prodrug, converted to aciclovir

Pencyclovir – prodrug famciclovir

Vidarabin (adenin arabinosid) : competitive inhibition od DNA-polymerase

ADRs: neurotoxicity

Herpes zoster-systemic

Herpes simplex-locally (cornea)

Antivirals used for treatment of b. influenza

Amantadine: also for the treatment of Parkinson disease

It inhibits the replication of influenza type A nucleic acid, used as systemic prophylaxy

Zanamivir: against influenza virus types A and B
it inhibits the viral neuraminidase
Local inhalation, intranasal application.

Antivirals used for treatment of c. cytomegaloviruses

Ganciclovir: in the triphosate-form inhibits viral DNA systhesis.
Selectivity is not only to viruses, damage. hematopoiesis, fertility

Cidofovir: a derivative of cytidine

Foscarnet: inhibition of viral DNA polymerase and influence of reverse transcriptase.
Indication: viruses resistent to aciclovir

Interferones

antiviral, immunomodulatory and antiproliferative effects

Interferon-α: produced by human lymphocytes
I: inf. hepatitis B, C

IFN-β: formed by fibroblasts.
I: Hepatitis B, C

Interferon-γ: in lymphocytes after stimulation with mitogens.

Type of antivirotics therapy

2. Antiretroviral drugs

- Used to treat infections caused by HIV, the virus that causes AIDS

HIV

Human immunodeficiency virus infection

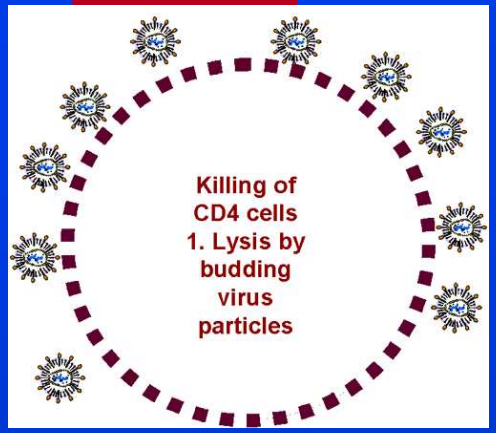
- **ELISA (enzyme-linked immunosorbent assay)**
  - **Detects HIV exposure** based on presence of human antibodies to the virus in the blood
- **RNA retrovirus, that contains ensyme *reverse transkriptase - RT***

- **Transmitted by:**
  - Sexual activity, intravenous drug use, perinatally from mother to child

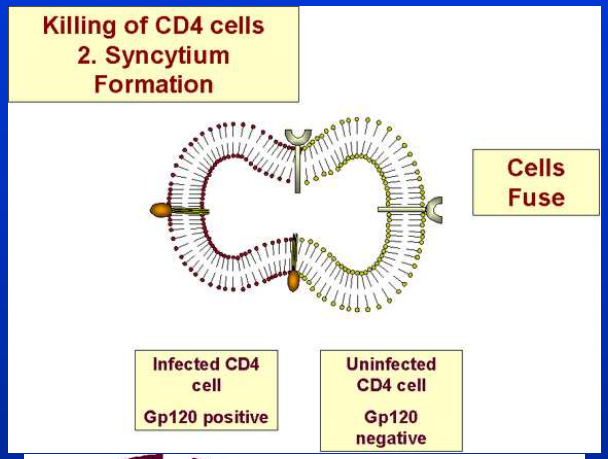
<u>Five Stages of HIV Infection</u>

- **Stage 1:** asymptomatic infection
- **Stage 2**: early, general symptoms of disease
- **Stage 3**: moderate symptoms
- **Stage 4**: severe symptoms, often leading to death

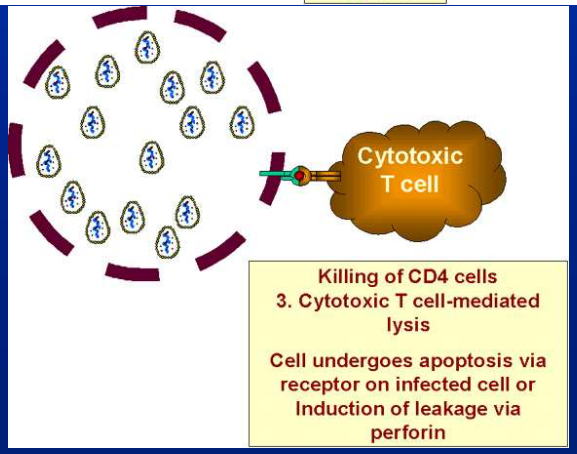
WHO model stages



1.HIV kills infected lymfocyte, because after replication it is released by budding and lysis of the host cell

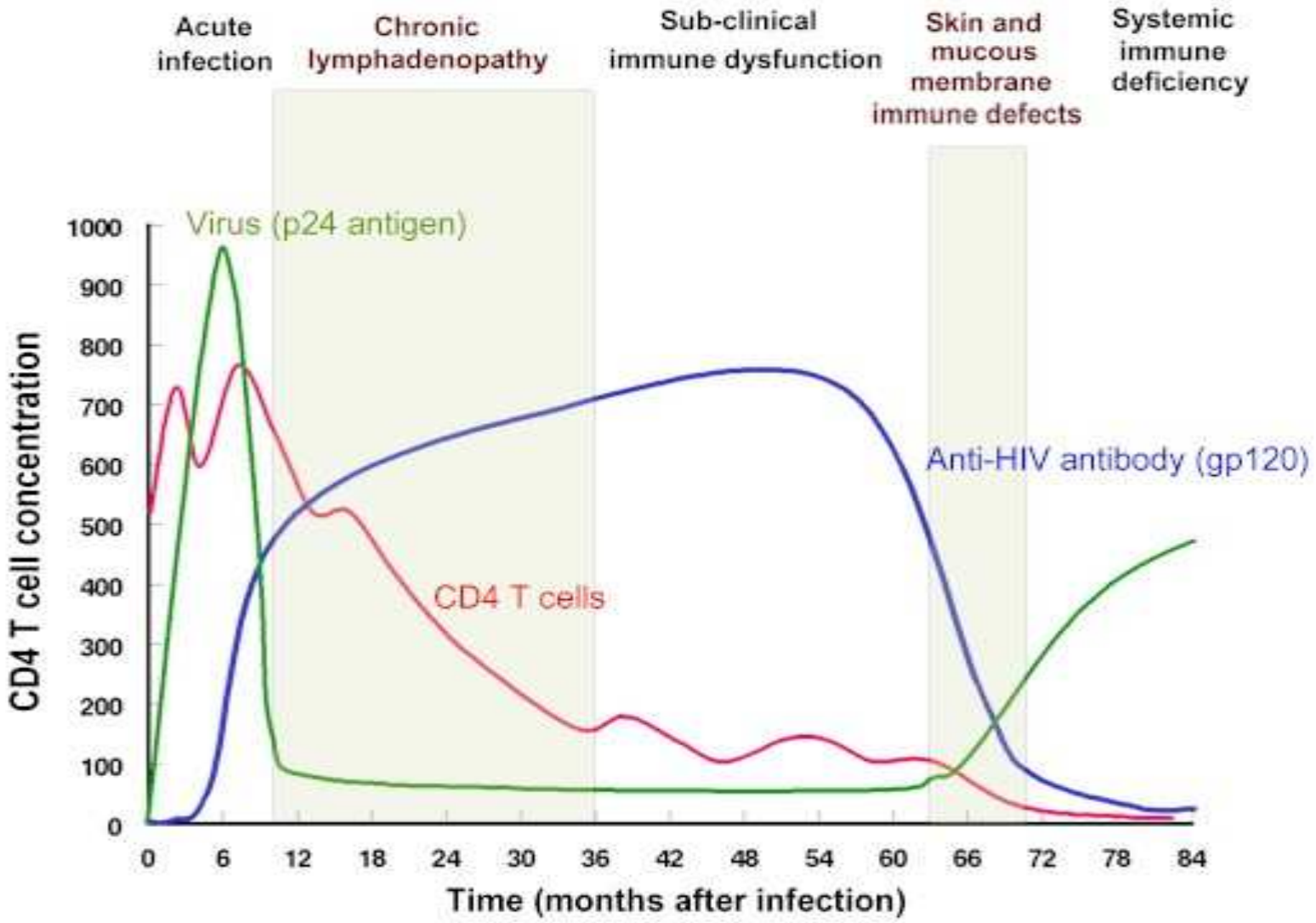


2.Infected and noninfected cell unify and form nets and syncytia of non functionnal lymfocytes



3 Immunocompetent cells do not recognise infected cells, which are foreign for them and they kill them

Depression of T cell quantity


Acute infection
Chronic lymphadenopathy
Sub-clinical immune dysfunction
Skin and mucous membrane immune defects
Systemic immune deficiency
Virus (p24 antigen)
Anti-HIV antibody (gp120)
CD4 T cells
CD4 T cell concentration
1000
900
800
700
600
500
400
300
200
100
0
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
Time (months after infection)

Antiretroviral Drugs

HAART - Highly active antiretroviral therapy

- Includes **at least three medications**
  - "cocktails"
- These **medications work in different ways to reduce the viral load**

Antiretroviral Drugs

- **Reverse transcriptase inhibitors (RTIs)**
  - Block activity of the enzyme reverse transcriptase, preventing production of new viral DNA

- **Examples**

abacavir (Ziagen)
didanosine (Videx)
stavudine (Zerit)
delavirdine (Rescriptor)
lamivudine (Epivir)
tenofovir (Viread)

Antiretroviral Drugs

- **Protease inhibitors (PIs)**
  - Inhibit the protease retroviral enzyme, preventing viral replication

  - Examples:

    amprenavir (Agenerase)
    indinavir (Crixivan)
    nelfinavir (Viracept)
    ritonavir (Norvir)
    saquinavir (Invirase)

Antiretroviral Drugs

- **Fusion inhibitors**
  - Inhibit viral fusion, preventing viral replication
  - Newest class of antiretroviral drugs
  - Example: enfuvirtide (Fuzeon)

Antiretroviral Drugs: Adverse Effects

- Numerous and vary with each drug

- Drug therapy may need to be modified because of
- adverse effects

- **Goal** is to find the regimen that will **best control the infection with a tolerable adverse effect profile**
- **Medication regimens change** during the course of the illness