Pharmacology of Antifungal and Antiviral Agents

This course is no longer offered for Continuing Education credit.

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Intended Audience: Dentists, Dental Hygienists, Dental Assistants, Dental Students, Dental Hygiene Students, Dental Assistant Students

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Introduction

The objectives of the course are to discuss antifungal and antiviral pharmacology and to provide evidence-based information for the use of antifungal agents for the treatment of oropharyngeal candidiasis and antiviral agents for the treatment of orolabial herpetic infections.

Conflict of Interest Disclosure Statement

- Dr. Ojeda Díaz reports no conflicts of interest associated with this course.
- Dr. Huber is a member of the dentalcare.com Advisory Board.

Course Contents

Overview

This continuing dental education course provides a clinical frame of reference when patients are taking antifungal or antiviral agents prescribed by physicians and discusses clinical indications for and prescription of antifungal and antiviral agents by oral healthcare providers.

Learning Objectives

Upon completion of this course, the dental professional should be able to:

- Discuss in general terms the pharmacology of antifungal and antiviral agents and indications for their use in medicine and dentistry.
- Prescribing antifungal agents for the treatment of oropharyngeal candidiasis based on best available evidence.
- Prescribing antiviral agents for the treatment of orolabial herpetic infections based on best available evidence.

Introduction

Oral healthcare providers treat an ever increasing number of medically and pharmacologically compromised patients. Consequently, clinicians can expect to face situations in the perioperative period that may threaten not only the physical well-being of their patients; but at times, even their own safety (e.g., the transmission of healthcare-associated infections). Potential risk factors are predicated on procedure-specific and patient- and provider-specific variables.

A patient's overall health status determines the patient's ability to undergo dental care. Patient-specific problems that may impact upon a patient's quality of life and/or the clinical process must be identified. Past and present illnesses, major hospitalizations, review of organ systems, drug allergies and other adverse drug reactions (ADRs), dietary supplements and special diets, and medications taken by a patient must be considered in determining perioperative risk.[1]

In the United States, there are approximately 500 active ingredients (drugs) in several thousand different formulations. **ClinCalc DrugStats** provides prescription drug utilization data estimates based on the Medical Expenditure Panel Survey (MEPS) conducted annually.[2] The data are invaluable in identifying patient-specific risks factors. The list of Top Prescription Drugs of 2017 is based on more than 3 billion out-patient prescriptions and reflects data collected in 2014.[2]

The Top 200 Prescription Drugs dispensed by U.S. community pharmacies represent 40% of the available 500 active ingredients and comprise 90% of all drugs taken by ambulatory patients.[2] The Top 300 Prescription Drugs represent 60% of the available 500 active ingredients and comprise 97% of all drugs taken by ambulatory patients.[2] It is axiomatic that the remaining 200 or 40% of all available active ingredients are taken by < 3% of ambulatory patients.

The Top 300 Prescription Drugs of 2017 include the antifungal agents fluconazole (#172), nystatin (#199) ketoconazole (#218), and the antiviral agents oseltamivir phosphate (#219); and acyclovir (#157) and valacyclovir (#192). Clearly, the volume of antifungal and antiviral agents dispensed by U.S. community pharmacies is very low.[2] It is also of note that while the largest numbers of available antiviral agents are anti-HIV drugs, not a single one is found in the top 300.

It is practical to think of drugs as falling into two categories: those prescribed by oral healthcare providers and those prescribed by other clinicians. Of those agents prescribed by oral healthcare providers minimum competency assumes knowledge in the following seven areas: (1) drug name (brand/generic), (2) mechanisms of action, (3) drug kinetics, (4) indication, (5) dosing, (6) familiarity with potential ADRs and monitoring parameters, and (7) contraindications.

In relation to those drugs prescribed by other clinicians, minimum competency by oral healthcare providers assumes knowledge in the following five areas: (1) recognition of those drugs most commonly taken by patients by name (brand/generic); (2) indications for their use, i.e., why a patient is taking the drug; (3) in some instances therapeutic dosages, e.g., corticosteroids and thyroids; (4) recognition of ADRs; and, importantly, (5) the use of informational resources.

Antifungal and antiviral agents are prescribed primarily by physicians. However, the treatment of oropharyngeal candidiasis and orolabial herpetic infections is, for the most part, the responsibility of oral healthcare providers. Consequently, the depth of information presented on selected antifungal and antiviral agents will reflect the expanded knowledge-base required by oral health care providers for minimum competency in prescribing such agents.

DailyMed is the official repository for FDA-approved package inserts, i.e., for individual drug-related knowledge base.[3] The information on this website is the most recent submitted to the FDA by manufacturers and may include strengthened warnings undergoing FDA review. The labeling information is accurate; whenever possible it is based on human experience, and does not contain promotional or misleading information such as implied claims for the use of a drug.

Pharmacology of Antifungal Agents

Fungi are free-living, eukaryotic (nucleated) organisms that exist as yeasts (round fungi), molds (filamentous fungi), or a combination of these two (dimorphic fungi). Although there are more than 100,000 fungal species, only a few are intrinsically pathogenic in humans (Table 1).[4] Most pathogenic fungi are saprophytic members of the soil microbial flora, i.e., they live on decaying organic matter. For these organisms, the respiratory system is the most common portals of entry.

Some of the other fungi, such as the *Candida* species, are opportunistic members of the normal human flora (Table 1).[4] These organisms are found typically on oral, vaginal, and gastrointestinal mucosa; or as residents on skin, and at times, on respiratory epithelium. Acquired or therapeutic immunosuppression (e.g., HIV infection, corticosteroids, and antimetabolites), diabetes mellitus, lymphoma, leukemia, and tuberculosis predispose patients to oropharyngeal and systemic candidal infections.

Mechanisms of Action of Antifungal Agents

Fungal and human cells, because of phylogenetic similarities, have homologous metabolic pathways to generate energy, to synthesize proteins, and for cell division. Currently available antifungal agents may be categorized according to their molecular targets. Primary molecular targets for antifungal agents are enzymes and other molecules involved in cell wall synthesis, plasma membrane synthesis, fungal DNA synthesis, and mitosis (Figure 1).[5]

Unlike human cells, fungal cells are surrounded by a cell wall. Its major components are chitin, B-(1,3)-D-glucan, B-(1,6)-D-glucan, and several glycoproteins. Chitins are linear polysaccharides that are bundled into microfibrils and serve as scaffolding for the fungal cell wall. B-(1,3)-D-glucan and B-(1,6)-D-glucan are glucan polymers that are covalently linked to the chitin scaffold. The **echinocandin** antifungal agents are **inhibitors of B-(1,3)-D-glucan synthase**.[5]

Another important biochemical difference between human and fungal cells is related to the sterol used to maintain plasma membrane structure and function. Human cells use cholesterol, whereas fungal cells use the structurally distinct ergosterol. The first step in the biosynthesis of ergosterol involves the conversion

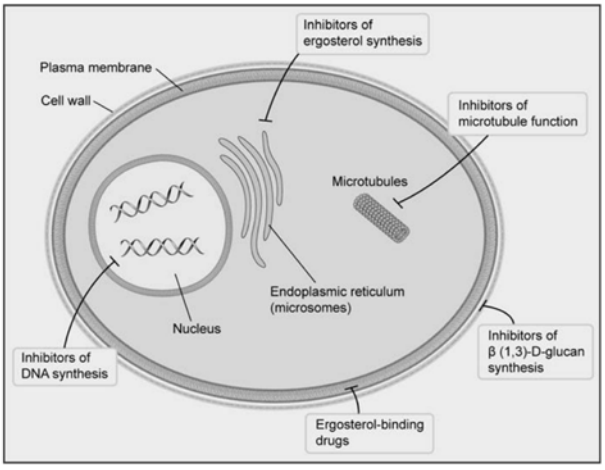

Figure 1. Molecular Targets for Antifungal Agents.

Table 1. Selected primary and opportunistic human mycoses.[4]

Organisms	Clinical Manifestations
Primary fungal infections	
Blastomycis dermatitidis	Pulmonary blastomycosis • Hematogenous dissemination
Coccidioides inimitis	Pulmonary coccidioidomycosis • Hematogenous dissemination
Histoplasma capsulatum	Pulmonary histoplasmosis • Hematogenous dissemination
Paracoccidioides brasiliensis	Paracoccidioidomycosis of the lungs, skin, mucous membrane, and lymph nodes • Hematogenous and lymphatic dissemination
Opportunistic fungal infections	
***Aspergillus* sp.**	Aspergillosis of the lungs, sinuses, and ear canals • Hematogenous dissemination
Candida* sp.** • ***C. albicans • ***C. dublinensis*** • ***C. glabrata*** • ***C. krusei*** • ***C. parapsilosis*** • ***C. tropicalis***	Mucocutaneous candidiasis • Hematogenous dissemination
***Mucor* sp.**	Mucormycosis of the nose and palate • Hematogenous dissemination
***Sporothix* sp.**	Lymphocutaneous sporotrichosis • Hematogenous dissemination

of squaline to lanosterol by squaline epoxidase. The **allylamine** and **benzylamine** antifungal agents are **inhibitors of squaline synthase**.[5]

The second step in plasma membrane synthesis is the conversion of lanosterol to ergosterol. This step is mediated by 14α-sterol demethylase, a fungus-specific cytochrome P450 enzyme. The **azole** antifungal agents are **inhibitors of 14α-sterol demethylase**.[5] Predictably, the allylamine, benzylamine, and azole antifungal agents sequentially inhibit ergosterol synthesis. The **polyene** antifungal agents **bind to ergosterol** and disrupt fungal plasma membrane stability.[5]

The antifungal agent **flucytosine** is absorbed via cytosine-specific permiases lacking in human cells. Flucytosine is metabolized to 5-fluorouracil, which is converted to 5-fluorodeoxyuridylic acid monophosphate (5-FdUMP). 5-FdUMP inhibits thymidylate

synthase; consequently, it **inhibits DNA synthesis** and **cell division**.[5] The antifungal agent **griseofulvin** inhibits microtubule function; consequently, it **disrupts the mitotic spindle**, and **inhibits mitosis**.[5]

Treatment of Fungal Infections

The treatment of most fungal infections is primarily the responsibility of physicians (Table 2).[5-7] However, the diagnosis and treatment of oropharyngeal candidal infections,

Table 2. Indications for Antifungal Chemotherapy.[5-7]

Mechanism of action	Drugs*	Indications*
Inhibitors of β-(1,3)-D-glucan synthase	Echinocandins Anidulafungin Caspofungin Micafungin	Candidiasis Aspergillosis
Inhibitors of squaline synthase	Allylamines and benzylamines Butenafine Naftifine Terbinafine	Tinea corporis or tinea cruris (all) Tinea capitis (terbinafine) Tinea pedis (butenafine)
Inhibitors of 14α-sterol demethylase	Imidazoles Butoconazole Clotrimazole Econazole Ketoconazole Luliconazole Miconazole Oxiconazole Sertaconazole	Candidiasis Cryptococcosis Coccidioidomycosis Histoplasmosis Blastomycosis
	Triazoles Fluconazole Itraconazole Posaconazole Terconazole Voriconazole Isavuconazole	Candidiasis Aspergillosis Blastomycosis Histoplasmosis
Inhibitors of fungal plasma membrane stability	Polyenes Amphotericin B Nystatin	Most fungal infections (amphotericin B) Mucocutaneous candidiasis
Inhibitor of fungal nucleic acid synthesis	Flucytosine	Candidiasis Cryptococcosis
Inhibitor of fungal mitosis	Griseofulvin	Fungal infections of the skin, hair, or nail caused by *Trichophton*, *Microsporum*, or *Epidermophyton*

*FDA-approved information on specific antiviral agents is available at DailyMed - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.[3]

to a great extent, falls within the purview of oral healthcare providers. The pathogenesis of candidal infections is based on interplay between host defense mechanisms and the pathogenicity of candida organisms. Patients with compromised immune defenses are at increased risk of infection.

Primary oropharyngeal candidiasis may appear in a variety of clinical forms. It is often asymptomatic, but patients may relate burning and altered taste. A classification system based on clinical criteria provides a clear distinction between primary forms of oropharyngeal candidiasis (Figures 2-7) and **secondary candidal infection** associated with keratinized primary lesions such as leukoplakia, lichen planus, and lupus erythematosus.[8]

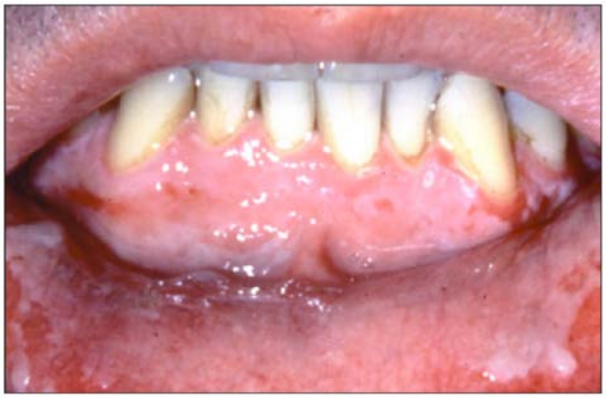

Figure 2. Acute pseudomembraneous candidiasis as a consequence of the extended use of a broad-spectrum antibacterial agent.

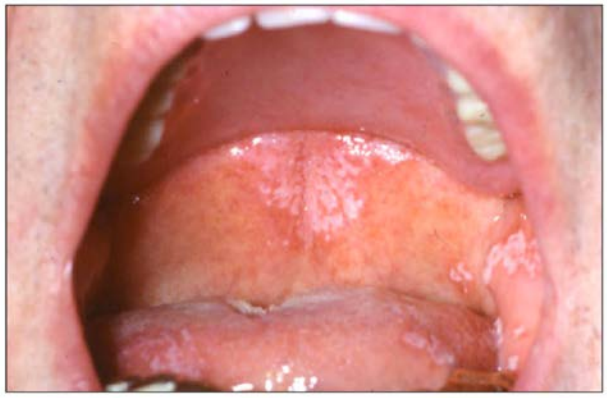

Figure 3. Chronic pseudomembraneous candidiasis as a consequence of inhaled corticosteroid use in the management of asthma.

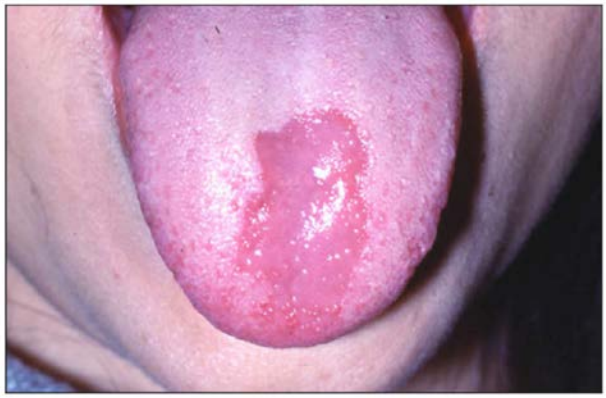

Figure 4. Erythematous candidiasis confirmed by cytology.

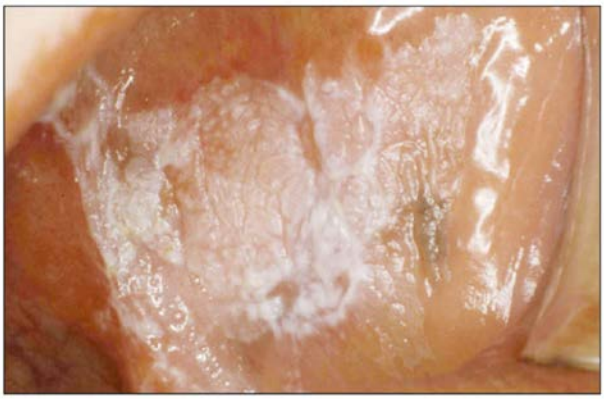

Figure 5. Hyperplastic candidiasis (candidal leukoplakia) confirmed by biopsy.

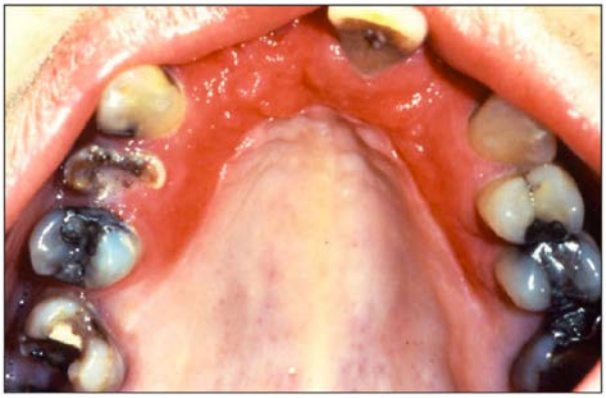

Figure 6. *Candida*-associated erythematous denture stomatitis.

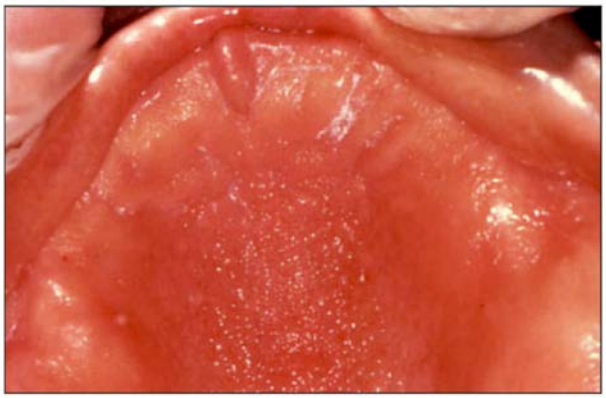

Figure 7. Granular or papillary *Candida*-associated denture stomatitis.

Other candidal infections include **median rhomboid glossitis** and **angular cheilitis**. The presence of oropharyngeal candidiasis and symptoms of dysphagia or odynophagia are the hallmark of **candidal esophagitis**. A rare condition observed in patients with an immune defect is **chronic mucocutaneous candidiasis** accompanied by chronic persistent onychomycosis. At times, hematogenous dissemination may lead to systemic candidal infection.

Oral healthcare providers must recognize oropharyngeal candidiasis and must be familiar with treatment strategies and patient management guidelines (Table 3).[6,7] Treatment with an antifungal agent can eliminate oropharyngeal infection and prevent systemic dissemination. Patients who fail to respond to antifungal therapy may have undiagnosed or inadequately treated predisposing conditions and are best managed by their physician.

Clotrimazole troches and **miconazole mucoadhesive tablets** are topical antifungal agents used to treat superficial candidal infections of squamous mucosa. Strong recommendation for their use to treat mild oropharyngeal candidiasis is based on high-quality evidence.[7] Rare ADRs include itching (pruritus), burning, and hypersensitivity (allergic) reactions.[3] Miconazole mucoadhesive tablets are contraindicated in patients with hypersensitivity to milk proteins.[3]

Nystatin oral suspension or **pastilles** may also be used to treat candidiasis of the oral mucosa. Strong recommendation for their use to treat mild oropharyngeal candidiasis is based on moderate-quality evidence.[7] Nystatin formulations are not absorbed systemically from the gastrointestinal tract or across the oral mucosa. Potential ADRs include rare hypersensitivity reactions (allergic contact mucositis) and Stevens-Johnson syndrome.[3]

Fluconazole has a nearly 100% bioavailability following oral administration and diffuses freely into saliva. Strong recommendation for its use to treat moderate-to-sever oropharyngeal candidiasis and for chronic suppressive therapy in recurrent infections is based on high-quality evidence.[7] Potential ADRs include nausea, vomiting, abdominal pain, and diarrhea; CYP3A4-related drug-drug interactions; and rare cases of liver toxicity and Stevens-Johnson syndrome.[3]

Itraconazole, **posaconazole**, and **voriconazole** have broader activity against Candida sp. Strong recommendation for their use to treat fluconazole-refractory moderate-to-severe oropharyngeal candidiasis is based on moderate-quality evidence.[7] Itraconazole solution or posaconazole suspension is to be prescribed first; voriconazole tablets are used when treatment with topical itraconazole or posaconazole has failed. ADRs are similar to those with fluconazole.[3]

Amphotericin B deoxycholate suspension is effective in some patients with moderate-to-severe fluconazole-refractory oropharyngeal candidiasis. Strong recommendation for its use is based on moderate-quality evidence. The suspension must be compounded by a pharmacist.[7] Weak recommendation for **intravenous amphotericin B deoxycholate** to treat moderate-to-severe fluconazole-refractory oropharyngeal candidiasis is based on moderate-quality evidence.[7]

Serious ADRs with intravenous administration of amphotericin B deoxycholate may include cytokine storm elicited by tumor necrosis factor-alpha (TNF-α) and interleukin-1(IL-1) released by cells of the immune system. Cytokine storm is characterized by fever, chills, rigors, and hypotension.[3] Other potential serious ADRs include renal toxicity; anemia, secondary to reduced production of erythropoietin; and Stevens-Johnson syndrome and toxic epidermal necrolysis.[3]

Table 3. Antifungal Agents for the Treatment of Oropharyngeal Candidiasis.[6,7]

Diagnosis	Drugs	Adult dosages
Mild disease	Clotrimazole*	10 mg torches 5 times daily for 14 days
	Miconazole*	50 mg mucoadhesive buccal tablets Once daily for 7-17 days
	Nystatin§	100,000 U/mL suspension 4 to 5 mL 4 times daily
	Nystatin§	200,000 U pastilles 1 or 2 pastilles 4 times daily for 7-14 days
Moderate-to-severe disease	Fluconazole*	100 mg oral tablets 1 to 2 tablets daily (3 mg/kg) for 7-14 days
Fluconazole-refractory disease	Itraconazole§	10 mg/mL oral solution 200 mg once daily for up to 28 days
	Posaconazole§	40 mg/mL oral suspension 400 mg twice daily for 3 days then 400 mg daily for up to 28
	Voriconazole§	200 mg tablets 200 mg twice daily for 7-21 days
	Amphotericin B deoxycholate§	100 mg/mL oral suspension 100 mg 4 times daily
	Caspofungin¶	70 mg loading dose, IV then 50 mg daily for 7-21 days
	Micafungin¶	100 mg daily IV
	Anidulafungin¶	50 mg, IV, 1x daily for 7-21 days
	Amphotericin B deoxylate¶	0.3 mg/kg daily, IV
Chronic suppressive therapy	Fluconazole*	100 mg oral tablets 100 mg 3 times weekly
Denture-related candidiasis	Based on moderate-quality evidence it is strongly recommended that in addition to antifungal chemotherapy, with denture-related candidiasis the prostheses be disinfected.	

*Strong recommendation - high-quality evidence
§Strong recommendation - moderate quality evidence
¶Weak recommendation - moderate quality evidence

Intravenous caspofungin, **micafungin**, or **anidulafungin** are used primarily to treat esophageal candidiasis. Weak recommendation for their use to treat fluconazole-resistant moderate-to-severe oropharyngeal candidiasis is based on moderate-quality evidence.[7] Since human cells lack a cell wall, the echinocandins have no serious systemic adverse effect. Potential ADRs include pruritus, rash, gastrointestinal disturbances, headache, and fever.[3]

Pharmacology of Antiviral Age

Viruses are obligate intracellular parasites called **virions** and consist of RNA or DNA genomes (Table 4).[9,10] The viral genome is surrounded by a virus-encoded protein shell **capsid**. In some cases, the capsid is surrounded by an **envelope**, a lipid bilayer membrane that contains additional virus-encoded proteins. With some variations, all virions have the same general **viral life cycle** and each stage is a potential target for pharmacological intervention (Figure 8).[10]

Mechanisms of Action of Antiviral Agents

Viral infections are initiated when virions attach to host cells. **Attachment** is mediated by capsid- or envelope-related viral proteins that bind specific receptors on host cell membranes. For example, the HIV envelope contains glycoproteins that mediate binding of the virus to CD4+ T lymphocytes that express CCR5 and/or CXCR4 receptors. A currently available **inhibitor**

Table 4. Selected Human RNA and DNA Viruses.[9]

Virus	Clinical manifestations
RNA viruses	
Influenza A and B	Influenza
Respiratory syncytial virus (RSV)	Upper respiratory tract infection
Human immunodeficiency virus 1 and 2 (HIV-1 and HIV-2)	AIDS
Hepatitis C virus (HCV)	Hepatitis C infection
DNA viruses	
Hepatitis B virus (HBV)	Hepatitis B infection
Herpes simplex virus 1 and 2 (HSV-1 and HSV-2)	Primary herpetic gingivostomatitis Genital herpes Neonatal herpes Herpes encephalitis Herpes keratoconjunctivitis Eczema herpeticum Herpes-associated erythema multiforme Recurrent herpetic infections
Varicella-zoster virus (VZV)	Chickenpox and herpes zoster infections
Human cytomegalovirus (HCMV)	Retinitis, esophagitis, and colitis

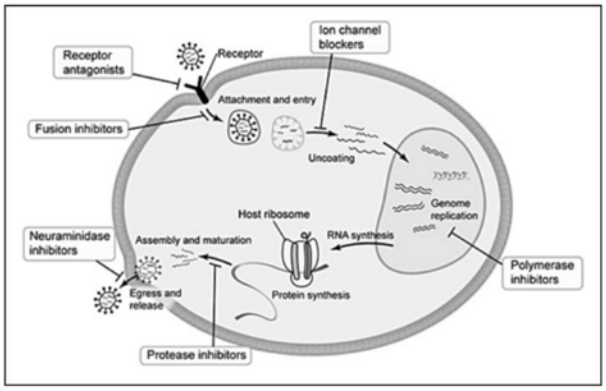

Figure 8. Stages of the viral life cycle and potential targets for antiviral agents.[10]

of viral attachment blocks HIV-specific CCR5 receptors on CD4+ T cell membranes.[10]

Viral entry across host cell membranes into the cytoplasm is mediated by other viral proteins. For example, the HIV envelope contains a protein (gp41) which promotes **fusion** of the viral envelope with target host cell (CD4+ T lymphocyte) membranes. A currently available **inhibitor of viral entry** blocks gp41-mediated fusion of the HIV envelope with the plasma membrane of host CD4+ T lymphocytes.[10]

Viral entry is followed by **uncoating**. This step refers to the removal/degradation or structural modification of the nucleocapsid, which results in the release of the viral genome into host cell cytoplasm and, in the case of DNA genomes, transport into host cell nuclei. Currently available **inhibitors of viral uncoating** block M2 proton channel in influenza A viruses and prevent pH-dependent disassociation of viral matrix proteins from the viral RNA.[10]

Following uncoating, the viral nucleic acid becomes available for **gene expression**, i.e., the **transcription** of viral RNA or DNA genome into mRNA, **translation** of mRNA into viral proteins, and **proteolytic cleavage** of viral polyproteins into their individual protein units. Currently available **inhibitors of viral gene expression** block HCV-related NS3/4A protease, essential for the expression of functional HCV proteins.[10]

Genome replication requires the generation of ribo- or deoxyribonucleoside triphosphates. Most RNA viruses replicate their genomes in host cell cytoplasm and most DNA viruses replicate their genomes in the nucleus of host cells. **Nucleoside analogues**, which when phosphorylated by viral or cellular kinases are incorporated into the growing viral genome and inhibit polymerase activity.[10] **Non-nucleoside polymerase inhibitors** directly inhibit RNA or DNA polymerases.[10]

The first step in HIV genome replication is reverse transcription, i.e., the viral RNA is first copied into DNA, which is then transcribed into mRNA. **Reverse transcriptase inhibitors** block the transcription of the HIV RNA genome into DNA.[10] The life cycle of the HIV also includes the additional step of integration, a process that binds HIV DNA to host cell DNA. **HIV integrase inhibitors** block the integration of viral genome into host cell genome.[10]

The next step in the viral life cycle is **assembly**, the process in which the immature virions are formed. Assembly is followed by **maturation**. This is the stage in the viral life cycle in which the new virions become infectious. The process involves proteolytic cleavage of one or more capsid- or envelop-related proteins by viral or host cell proteases. Currently available **inhibitors of viral maturation are inhibitors of HIV proteases**.[10]

Most viruses **egress** from infected host cells by cell lysis or by budding through the cell membrane. However, some virions require the additional step of **release**. For example, influenza A and B viruses require viral neuraminidase to effect their release from the extracellular surface of host cell membranes. Currently available **inhibitors of viral release or neuraminidase inhibitors** prevent the detachment the new influenza A and B virions from host cells.[10]

Treatment of Viral Infections

The treatment of most viral infections is primarily the responsibility of physicians (Table 5).[10-13] However, two of the known *Herpesviridae*, HSV-1 and HSV-2 are responsible for **primary** and **recurrent mucocutaneous herpetic infections** and HSV-1 is predominately associated with orolabial infections.[14] Consequently, the diagnosis and management of orolabial herpetic infections fall, to a great extent, within the purview of oral healthcare providers.

Table 5. Indications for Antiviral Chemotherapy.[10-13]

Mechanism of action	Drugs*	Indications
Inhibitors of viral attachment	Maravoric	CCR5-tropic HIV-1 infections
Inhibitors of viral entry	Enfuvirtide	HIV infections
	Docosanol	HSV infections
Inhibitors of viral uncoating	Amantadine Rimantadine	Influenza A infections
Inhibitors of viral gene expression	Boceprevir Ledipasvir Ombitasvir Paritaprevir Simeprevir Telaprevir	Chronic HCV (genotype 1) infections
Anti-herpesvirus nucleoside analogs	Acyclovir Valacyclovir	HSV and VZV infections
	Famciclovir Penciclovir	HSV infections
	Idoxuridine Trifulodine Vidarabine	HSV keratitis
	Ganciclovir Valganciclovir	HCMV infections
	Cidofovir	HCMV retinitis
Anti-HBV nucleoside analogs	Adefovir Emtricitabine Entecavir Lamivudine Telbivudine	HBV infections
Anti-HCV nucleoside analogs	Sofosbuvir	Chronic HCV infections
Anti-HIV nucleoside analogues (reverse transcriptase inhibitors)	Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir Zidovudine	HIV infections
Anti-herpesvirus non-nucleoside DNA polymerase inhibitors	Foscarnet	HSV and HCMV infections
Anti-HIV non-nucleoside reverse transcriptase inhibitors	Delaviridine Efavirenz Etravirine Nevirapine Rilpivirine	HIV infections
Anti-HCV non-nucleoside RNA polymerase inhibitors	Dasabuvir	HCV infections
Inhibitors of viral integration	Dolutegravir Raltegravir Elvitegravir	HIV infections
Inhibitors of viral maturation (protease inhibitors)	Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir	HIV infections
Inhibitors of viral release	Oseltamivir Zanamivir	Influenza A and B infections

*FDA-approved information on specific antiviral agents is available at DailyMed - the website is a user-friendly, look-up-and-download resource that provides comprehensive, up-to-date information on individual drugs.[3]

The most common initial presentation of orolabial HSV-1 infection is **primary herpetic gingivostomatitis** (Figures 9a and 9b). Following primary infection, the virions enter sensory nerve endings and are transported via retrograde axonal transport to regional sensory ganglia, i.e., the trigeminal ganglia. In the trigeminal ganglia the virus establishes latency in neuronal cell bodies and persists in an immunologically shielded state until reactivated.

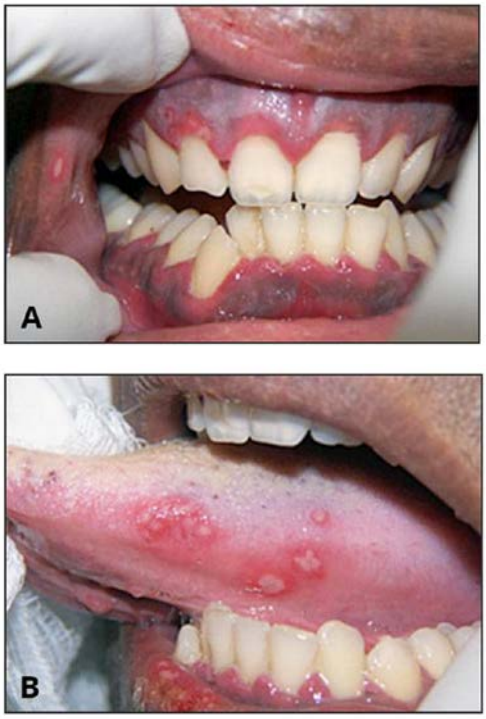

Figure 9. Primary herpetic gingivostomatitis in an immunocompetent patient.

Upon reactivation, the virions are delivered by anterograde axoplasmic transport to orolabial sites and manifest as recurrent infections. Recurrent orolabial HSV infections most commonly presents as **recurrent herpes labialis** (Figures 10a and 10b); less frequently, **recurrent herpetic stomatitis** (Figures 11a and 11b) attributed to traumatic triggers such as dental injections or thermal burns. Herpetic infections in immunocompromised patients tend to be more severe.

Herpetic whitlow may occur with either HSV-1 or HSV-2 inoculation into a finger. **Herpetic keratoconjunctivitis** in most adult is likely the result of autoinoculation. Less frequently, primary and recurrent HSV infection of the skin

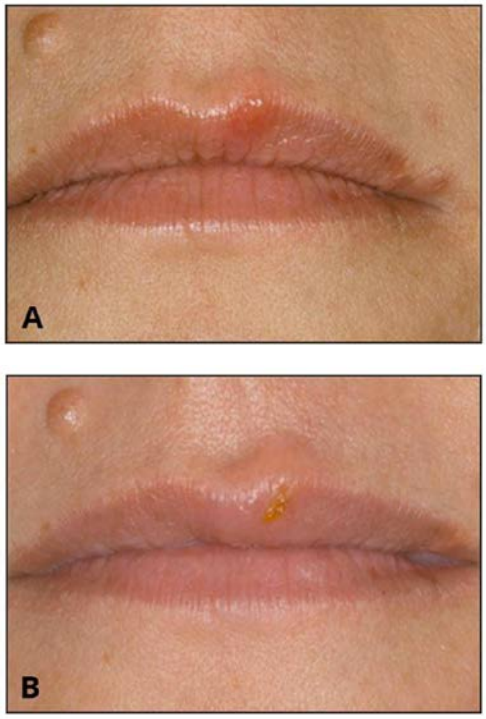

Figure 10. Recurrent herpes labialis in an immunocompetent patient.

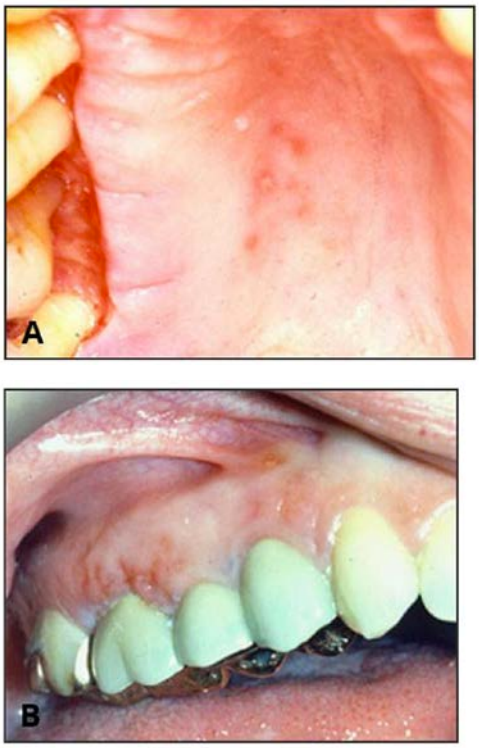

Figure 11. Recurrent herpes stomatitis in immunocompetent patients.

Table 6. Antiviral Agents for the Treatment and Prevention of Orolabial HSV Infections.[11,12,15-25]

Infection	Drug	Adult dosage
Moderate-to-severe primary herpetic gingivostomatitis • Immunocompetent patients	acyclovir	400 mg, PO, tid for 7-10 days OR 15 mg/kg (oral suspension), PO, 5x/day for 7 days
	famciclovir	500 mg, PO, bid/tid for 7-10 days
	valacyclovir	1 g, PO, bid for 7-10 days
Recurrent orolabial infections • Immunocompetent patient	docosanol*	10% cream, 5x/day until healed
	penciclovir*	1% cream, q2h while awake for 4 days
	acyclovir*	5% cream, 5x/day x 4 days
• Immunocompetent patients • Immunocompromised patient	famciclovir	1500 mg, PO, single dose
	valacyclovir	2 g, PO, 2x/day x 1 day
	acyclovir	400 m, PO, 5x/day for 5 days
Suppression of recurrences • Immunocompromised patients	acyclovir	400 mg,, PO, bid
	valacyclovir	500 mg, PO, once/day
	famciclovir	500 mg, PO, bid
Suppression of dental procedure-related recurrences • Immunocompetent patients	valacyclovir	2 g, PO, 2x/day, the day of procedure then 1 g, PO, 2x/day, the day after procedure
Mucocutaneous herpetic infections • Immunocompromised patients	acyclovir	400 mg, PO, 5x/day for 7/10days
	famciclovir	500 mg, PO, bid for 7-10 days
	valacyclovir	500 – 1000 mg, PO, bid for 7-10 days
Acyclovir-resistant mucocutaneous infections • Immunocompetent patients with moderate-to-severe primary herpetic gingivostomatitis • Immunocompromised patients	foscarnet	40 mg/kg, IV, q8h x 12-21 days

*Immunocompromised patients should not be treated with topical antiviral agents.

may present as **herpes gladiatorum** or **eczema herpeticum**. A substantial number of erythema multiforme cases are believed to be related to the herpes simplex virus (**herpes-associated erythema multiforme**).

Orolabial herpetic infections in immunocompetent patients are usually self-limiting. Treatment is palliative and supportive directed at controlling fever, dehydration, and pain; and monitoring for evidence of systemic viremia. Antiviral agents may be prescribed to patients with moderate-to-severe primary herpetic gingivostomatitis; to patients with recurrent orolabial herpetic infections; and to immunocompromised patient, who are inherently at risk of complications (Table 6).[11,12,15-25]

The recommendation of **oral acyclovir** for the treatment of moderate-to-severe primary herpetic gingivostomatitis in immunocompetent patients is based on limited-quality evidence.[12,15] In a placebo controlled study, children on acyclovir experienced reduction in the duration of lesions, fever, difficulty eating and drinking, and viral shedding. **Oral valacyclovir** or **famciclovir** are recommended as acceptable alternatives to oral acyclovir.[11]

The recommendation of **oral acyclovir**, **valacyclovir**, or **famciclovir** for the treatment of recurrent herpes labialis in immunocompetent and immunocompromised patients is based on good-quality evidence.[11,12,16-18] The drugs have been found to be effective in reducing viral shedding, pain, and healing time. Based on good-quality evidence, **oral acyclovir**, **valacyclovir**, or **famciclovir** are also recommended for the suppression of frequent recurrent infections.[11,22]

Oral acyclovir, valacyclovir, and famciclovir are well tolerated and associated adverse reactions are similar.[3] Common ADRs include nausea, vomiting, diarrhea, malaise, and headaches. Rare ADRs include myalgia, rash, Stevens-Johnson syndrome, tremors, lethargy, confusion, hallucinations, seizures, and coma. Resistance to acyclovir is uncommon, but HSV strains resistant to acyclovir are also resistant to valacyclovir and famciclovir.[11]

Topical docosanol, 10% cream, a 22-carbon saturated alcohol, is approved by the FDA as an over-the-counter agent for the treatment of recurrent herpes labialis in immunocompetent patients. Based on good-quality evidence the drug is somewhat effective. Treatment within 12 hours of prodromal signs and symptoms decreased pain (2.2 vs. 2.7 days) and healing time (4.1 vs. 4.8 days).[12,22] Common ADRs at the site of application include rash and pruritis.[3]

Topical penciclovir, 1% cream, based on good-quality evidence is helpful in the treatment of herpes labialis in immunocompetent adults.[12,23] The application of penciclovir versus placebo beginning within one hour of the first signs and symptoms of recurrence reduced median duration of pain (4.1 to 3.5 days) and healing time (5.5 to 4.8 days).[24] The drug did not affect the medial time for viral shedding (3 vs. 3 days). Systemic absorption of penciclovir is negligible.

Treatment with **topical acyclovir**, 5% cream, beginning within one hour of the onset of signs and symptoms of recurrence, based on good-quality evidence, has been shown in two parallel and independent trials to reduce the duration of recurrent herpes labialis in immunocompetent patients by about half a day.[12,25] In study 1, the mean duration of lesions was reduced from 4.8 to 4.3 days. In study 2, the mean duration of lesions was reduced from 5.2 to 4.6 days.[25]

Patients with moderate-to-severe primary herpetic gingivostomatitis and immunocompromised patients with acyclovir-resistant mucocutaneous herpetic infections may respond to **intravenous foscarnet**.[11] Potential ADRs include electrolyte imbalances; seizures; anemia and neutropenia; fever; nausea, vomiting, and diarrhea; headache; and reversible renal dysfunction, especially in patients with inadequate hydration, is not uncommon.[3]

Summary

Fungal processes that have been exploited in the development of antifungal agents include cell wall synthesis, plasma membrane synthesis and stability, nucleic acid synthesis, and mitosis. Primary line of treatment of oropharyngeal candidiasis includes topical and oral azole and polyene antifungal agents. Antiviral agents exploit the viral life cycle. Primary line of treatment of orolabial herpetic infections includes topical and oral anti-herpesvirus nucleoside analogs.

Course Test Preview

1. Which of the following statements related to the availability and utilization of drugs by ambulatory patients is correct?

a. In the United States, there are approximately 500 active ingredients (drugs) in several thousand different formulations.
b. The Top 200 Prescription Drugs dispensed by U.S. community pharmacies represent 40% of the available 500 active ingredients and comprise 90% of all drugs taken by ambulatory patients.
c. The Top 300 Prescription Drugs represent 60% of the available 500 active ingredients and comprise 97% of all drugs taken by ambulatory patients.
d. All of the above.

2. All of the following statements related to information available at *DailyMed* are correct EXCEPT which one?

a. *DailyMed* is the official repository for FDA-approved package inserts, i.e., for individual drug-related knowledge base.
b. The information on *DailyMed* contains promotional information such as implied claims (i.e., off label indications) for the use of a drug.
c. Drug information on *DailyMed* is the most recent submitted to the FDA by manufacturers and may include strengthened warnings undergoing FDA review.
d. The information on *DailyMed*, whenever possible it is based on human experience.

3. Which of the following statements related to primary and opportunistic fungal infections is correct?

a. Most pathogenic fungi are saprophytic members of the soil microbial flora; for these organisms, the respiratory system is the most common portals of entry.
b. Opportunistic fungi are found typically on oral, vaginal, and gastrointestinal mucosa; or as residents on skin, and at times, on respiratory epithelium.
c. Acquired or therapeutic immunosuppression predisposes patients to oropharyngeal and systemic candidal infections.
d. All of the above.

4. Which of the following antifungal agents inhibits fungal cell wall synthesis?

a. The echinocandin antifungal agents that inhibit β-(1,3)-D-glucan synthase.
b. The allylamine and benzylamine antifungal agents that inhibit squaline synthase.
c. The azole antifungal agents that inhibit of 14α-sterol demethylase.
d. The polyene antifungal agents that bind to ergosterol.

5. The spectrum of all of the following antifungal agents includes at least some members of the *Candida* sp. EXCEPT which one?

a. Echinocandins
b. Allylamines, benzylamines, and griseofulvin
c. Azoles (imidazoles and triazoles) and polyenes
d. Flucytosine

6. Which of the following antifungal agents is recommended, based on high-quality evidence, for the treatment of mild oropharyngeal candidiasis?

a. Clotrimazole touches
b. Miconazole mucoadhesive tablets
c. Nystatin oral suspension or pastilles
d. A and B are correct.

7. Which of the following statements related to fluconazole is correct?

a. It has a nearly 100% bioavailability following oral administration and diffuses freely into saliva.
b. Strong recommendation for its use to treat moderate-to-sever oropharyngeal candidiasis and for chronic suppressive therapy in recurrent infections is based on high-quality evidence.
c. Potential ADRs include nausea, vomiting, abdominal pain, and diarrhea; CYP3A4-related drug-drug interactions; and rare cases of liver toxicity and Stevens-Johnson syndrome.
d. All of the above.

8. Which of the following antifungal agents has broader activity against *Candida* sp.; and, based on moderate-quality evidence, is strongly recommendation for the treatment of fluconazole-refractory moderate-to-severe oropharyngeal candidiasis?

a. Itraconazole solution
b. Posaconazole suspension
c. Voriconazole tablets
d. All of the above.

9. All of the following statements related to the antifungal agent amphotericin B deoxycholate are correct EXCEPT which one?

a. Amphotericin B deoxycholate suspension is effective in some patient with moderate-to-sever fluconazole-refractory oropharyngeal candidiasis; strong recommendation for its use is based on moderate-quality evidence.
b. Strong recommendation for intravenous amphotericin B deoxycholate to treat moderate-to-sever fluconazole-refractory oropharyngeal candidiasis is based on moderate-quality evidence.
c. Following intravenous administration of amphotericin B deoxycholate, serious ADRs may include cytokine storm.
d. Following intravenous administration of amphotericin B deoxycholate, potential serious ADRs include renal toxicity; anemia, and Stevens-Johnson syndrome.

10. Which of the following statements related to intravenous caspofungin, micafungin, or anidulafungin is correct?

a. Intravenous caspofungin, micafungin, or anidulafungin are used primarily to treat esophageal candidiasis.
b. Weak recommendation for their use to treat fluconazole-resistant moderate-to-severe oropharyngeal candidiasis is based on moderate-quality evidence.
c. Potential ADRs include pruritus, rash, gastrointestinal disturbances, headache, and fever.
d. All of the above.

11. Which of the following statements related to viruses and viral pharmacology is correct?

a. Viruses are obligate intracellular parasites called virions and consist of an RNA or a DNA genome.
b. The viral genome is surrounded by a virus-encoded protein shell capsid; and, in some cases, the capsid is surrounded by an envelope.
c. With some variations, all virions have the same general viral life cycle and each stage is a potential target for pharmacological intervention.
d. All of the above.

12. All of the following statements related to mechanisms of action of antiviral agents are correct EXCEPT which one?

a. Inhibitors of viral attachment block specific receptors on host cell membranes.
b. Inhibitors of viral uncoating block the fusion of viral envelope with host cell plasma membrane and the release of the viral genome into host cell cytoplasm.
c. Nucleoside analogues are incorporated into the growing viral genome and inhibit polymerase activity.
d. Non-nucleoside polymerase inhibitors directly inhibit RNA or DNA polymerases.

13. All of the following statements related to anti-HIV agents are correct EXCEPT which one?

a. The first step in HIV genome replication is reverse transcription, i.e., the viral RNA is first copied into DNA, which is then transcribed into mRNA.
b. Reverse transcriptase inhibitors block the transcription of the HIV DNA genome into RNA.
c. HIV integrase inhibitors block the integration of viral genome into host cell genome.
d. Currently available inhibitors of viral maturation are inhibitors of HIV proteases.

14. Which of the following statements related to orolabial herpetic infections is correct?

a. Orolabial herpetic infections in immunocompetent patients are usually self-limiting.
b. Treatment orolabial herpetic infections in immunocompetent patients is primarily palliative and supportive directed at controlling fever, dehydration, and pain; and monitoring for evidence of systemic viremia.
c. Antiviral agents may be prescribed to immunocompetent patients with moderate-to-severe primary herpetic gingivostomatitis and to patients with recurrent orolabial herpetic infections; and to immunocompromised patient, who are inherently at risk of complications.
d. All of the above.

15. Which of the following statements related to the treatment of primary herpetic gingivostomatitis is correct?

a. The recommendation of oral acyclovir for the treatment of moderate-to-severe primary herpetic gingivostomatitis in immunocompetent patients is based on limited-quality evidence.
b. In a placebo controlled study, children on acyclovir experienced reduction in the duration of lesions, fever, difficulty eating and drinking, and viral shedding.
c. Oral valacyclovir or famciclovir are recommended as acceptable alternatives to oral acyclovir.
d. All of the above.

16. Which of the following statements related to recurrent herpes labialis is correct?

a. The recommendation of oral acyclovir, valacyclovir, or famciclovir for the treatment of acute episodes of herpes labialis in immunocompetent and immunocompromised patients is based on good-quality evidence.
b. Oral acyclovir, valacyclovir, or famciclovir have been found to be effective in reducing viral shedding, pain, and healing time.
c. Based on good-quality evidence, oral acyclovir, valacyclovir, or famciclovir are also recommended for the suppression of frequent recurrent infections.
d. All of the above.

17. All of the following statements related to oral acyclovir, valacyclovir, and famciclovir are correct EXCEPT which one?

a. Oral acyclovir, valacyclovir, and famciclovir are well tolerated and associated adverse reactions are similar.
b. Common ADRs include nausea, vomiting, diarrhea, malaise, and headaches.
c. Rare ADRs include myalgia, rash, Stevens-Johnson syndrome, tremors, lethargy, confusion, hallucinations, seizures, and coma.
d. Resistance to acyclovir is common, but HSV strains resistant to acyclovir are susceptible to valacyclovir and famciclovir.

18. Which of the following statements related to docosanol is correct?

a. Topical docosanol, 10% cream, a 22-carbon saturated alcohol, is approved by the FDA as an over-the-counter agent for the treatment of recurrent herpes labialis in immunocompetent patients.
b. The drug is somewhat effective - treatment within 12 hours of prodromal signs and symptoms decreased pain (2.2 vs. 2.7 days) and healing time (4.1 vs. 4.8 days).
c. Common ADRs at the site of application include rash and pruritis.
d. All of the above.

19. All of the following statements related to penciclovir are correct EXCEPT which one?

a. Topical penciclovir, 1% cream, appears to be helpful in the treatment of herpes labialis in immunocompetent adults.
b. The application of penciclovir versus placebo beginning within one hour of the first signs and symptoms of recurrence reduced the median duration of pain (4.1 to 3.5 days) and healing time (5.5 to 4.8 days).
c. The drug significantly reduces the medial time for viral shedding.
d. Systemic absorption of penciclovir after topical use is negligible.

20. All of the following statements related to intravenous foscarnet are correct EXCEPT which one?

a. Patients with moderate-to-severe primary herpetic gingivostomatitis with acyclovir-resistant infections may respond to intravenous foscarnet.
b. Immunocompromised patients with acyclovir-resistant mucocutaneous infections may respond to intravenous foscarnet.
c. Potential ADRs include electrolyte imbalances; seizures; anemia and neutropenia; fever; nausea, vomiting, and diarrhea; headache.
d. Uncommon ADRs include reversible renal dysfunction, especially in patients with inadequate hydration.

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