Pharmacology/Therapeutics I Block V Handouts – 2015-16

50. Pharmacotherapy of Anemia & Cytopenias – Kini
51. Immunomodulation Therapy – Clipstone
52. Anti-Mycobacterials – Cook
53. Antifungal Agents – Clipstone
54. Drugs used in the Treatment of Allergies & Asthma - Moorman
Pharmacotherapy of Anemias and Hematopoietic Growth Factors

Date: Friday, November, 6, 2015 – 10:30 am


KEY CONCEPTS & LEARNING OBJECTIVES

1. To discuss the basic pharmacology, clinical indications for use, and toxicity of the following agents used in the therapy of anemia:
   - Iron
   - Vitamin B₁₂
   - Folic Acid

2. To discuss the basic pharmacology, clinical indications for use, and toxicity of the following growth factors used in the therapy of cytopenias:
   - Erythropoietin
   - G-CSF
   - GM-CSF
   - IL-11
   - Romiplostim
   - Eltrombopag
Pharmacotherapy of Anemias and Hematopoietic Growth Factors

I. Agents used in anemias

A. Iron

1. Basic pharmacology
   a) Approximate distribution
      (1) 70% in hemoglobin
      (2) 10% in myoglobin
      (3) 10-20% stored as ferritin and hemosiderin
      (4) <1% in enzymes (e.g. cytochromes), and transferrin
   b) Intake
      -Average US diet contains 10-15 mg of which 0.5-1 mg is absorbed
   c) Absorption
      (1) Heme iron is absorbed intact from duodenum and jejunum
      (2) Non-heme iron must be reduced to ferrous iron (Fe^{2+})
      (3) The ferrous form is absorbed through DMT1 by active transport
      (4) Within mucosal cell, ferrous iron is converted to ferric (Fe^{3+})
      (5) Iron leaves the mucosal cell by passing through ferroportin
      (6) Hepcidin downregulates ferroportin and regulates iron absorption
   d) Fate
      (1) In case of demand, ferric iron is bound to transferrin for immediate transport via the blood to bone marrow
      (2) Stored as ferritin or hemosiderin in liver and spleen
      (3) Ferritin in plasma is in equilibrium with body storage and can be used to estimate total body stores
   e) Iron balance
      (1) Maintained by changes in absorption regulated by the concentrations of transferrin and ferritin in mucosal cells
      (2) In iron deficiency transferrin goes up, ferritin goes down
      (3) In iron overload transferrin goes down, ferritin goes up

2. Indication for iron therapy-Prevention or treatment of iron deficiency anemia (microcytic hypochromic anemia)
   a) Increased requirements
      (1) Frequently present in premature infants
(2) Children during rapid growth period
(3) Pregnant and lactating women
b) Inadequate absorption: post-gastrectomy or severe small bowel disease
c) Blood loss
   (1) Menstruation
   (2) Occult gastrointestinal bleeding

3. Iron therapy
   a) Oral preparations
      (1) Only ferrous salts (sulfate, gluconate, fumarate)
      (2) Response within a week, normal in 1-3 months
      (3) Adverse effects: GI distress (take with or after meals); black stool may obscure
          recognition of GI bleeding
   b) Parenteral iron therapy
      (1) Usually iron dextran, deep i.m. or i.v. infusion (also iron-sucrose and iron sodium
          gluconate)
      (2) Indicated post-gastrectomy/small bowel resection, malabsorption syndromes,
          intolerance of oral preps
      (3) Adverse effects: local pain and tissue staining with i.m., headache, fever, nausea,
          vomiting, back pain, arthralgias, urticaria, bronchospasm, anaphylaxis/death (rare)

4. Clinical toxicity
   a) Acute: accidental ingestion of iron tablets
      (1) May be fatal in small children
      (2) Necrotizing gastroenteritis
      (3) After short improvement, metabolic acidosis, coma and death
      (4) Treatment:
          (a) Gastric aspiration, lavage with phosphate or carbonate solution
          (b) Activated charcoal is ineffective
          (c) Deferoxamine, a potent iron chelating substance, i.m. or i.v.
   b) Chronic (iron overload)
      (1) Seen in an inherited disorder, hemochromatosis
      (2) Patients receiving repeated red cell transfusions
      (3) Excess iron deposited in heart, liver pancreas leading to organ failure
      (4) Treatment:
          (a) Intermittent phlebotomy (in the absence of anemia)
          (b) Iron chelation: deferoxamine (parenteral) or deferasirox (oral)

B. Vitamin B\textsubscript{12} and folic acid

1. Basic pharmacology
   a) Chemistry and pharmacokinetics of vitamin B\textsubscript{12}
      (1) Deoxyadenosylcobalamin and methylcobalamin are the active forms
      (2) Cyanocobalamin and hydroxycobalamin (therapeutic drugs) are converted to the
          active forms
      (3) Absorption
          (a) Vitamin B\textsubscript{12} is absorbed only after complexing with "intrinsic factor"
          (b) Absorption (1-5 µg/day) occurs in the distal ileum by a specific transport system
          (c) Deficiency often caused by lack of intrinsic factor or bowel disease (transport)
          (d) Absorbed vitamin B\textsubscript{12} is bound to plasma transcobalamin II for distribution
**II. Hematopoietic growth factors**

**A. Erythropoietin**

1. Basic pharmacology
   a) 34-39 kDa glycoprotein
   b) Functions:
      (1) Stimulates proliferation and differentiation of erythroid cells
      (2) Promotes release of reticulocytes from bone marrow
   c) Produced by the kidney
   d) Usually inverse relationship between hemoglobin level and serum erythropoietin level, but not in chronic renal failure
e) Recombinant human erythropoietin (epoetin alfa) is produced in a mammalian cell expression system

2. Indication for erythropoietin therapy
   a) Chronic renal failure
   b) Some patients with aplastic anemia, hematologic malignancies, anemias associated with AIDS, cancer
      (1) In these patients, erythropoietin is most effective if endogenous erythropoietin levels are disproportionately low
      (2) Higher doses required than in chronic renal failure, but responses are still incomplete
   c) Treatment of anemia of prematurity
   d) Post phlebotomy

3. Erythropoietin therapy
   a) Given IV or subcutaneously
   b) Increase in reticulocyte count seen in about 10 days
   c) Increase in hemoglobin seen in 2-6 weeks

4. Clinical toxicity
   a) Hypertension
   b) Thrombotic complications
   c) Allergic reactions
   d) Increased risk of tumor progression in cancer patients

B. G-CSF and GM-CSF

1. Basic pharmacology
   a) G-CSF (granulocyte colony stimulating factor) and GM-CSF (granulocyte-macrophage colony stimulating factor) are myeloid growth factors
   b) Recombinant human G-CSF (filgrastim) is produced in a bacterial expression system
   c) Recombinant human GM-CSF (sargramostim) is produced in a yeast expression system
   d) Pegfilgrastim: Filgrastim conjugated to polyethylene glycol-longer half-life
   e) Functions:
      (1) Both G-CSF and GM-CSF stimulate proliferation and differentiation of myeloid cells
      (2) G-CSF promotes release of hematopoietic stem cells from bone marrow (GM-CSF is less efficient)
      (3) GM-CSF also stimulates proliferation and differentiation of erythroid and megakaryocytic precursors

2. Indication for G-CSF/GM-CSF therapy
   a) After intensive myelosuppressive chemotherapy
      (1) Accelerates rate of neutrophil recovery
      (2) Reduces duration of neutropenia
      (3) Reduces febrile neutropenia, antibiotic use, days of hospitalization
   b) Can also be used after chemotherapy for acute myeloid leukemia (AML)
      (1) Accelerates neutrophil recovery, reduces infection
      (2) No evidence for increased relapse rate
   c) Treatment of congenital neutropenia, cyclic neutropenia, neutropenia associated with myelodysplasia and aplastic anemia
   d) High dose chemotherapy with autologous stem cell rescue
   e) Mobilization of peripheral blood stem cells for autologous transplant

3. Clinical toxicity
   a) G-CSF preferred since it is better tolerated in general
b) G-CSF can cause bone pain, splenic rupture (very rare)
c) GM-CSF can cause fever, arthralgia, myalgia, peripheral edema, pleural/pericardial effusion
d) Allergic reactions

C. Interleukin-11

1. Basic pharmacology
   a) IL-11 is produced by stromal cells in the bone marrow
   b) Recombinant human IL-11 (oprelvekin) is produced in a bacterial expression system
   c) Stimulates growth of megakaryocytic progenitors
   d) Increases peripheral platelets

2. Indication for IL-11 therapy
   a) Patients with thrombocytopenia after cytotoxic chemotherapy
      (1) Can be used if platelet transfusions are refractory, or to prevent adverse reactions of transfusions
      (2) Usually given for 14-21 days after chemotherapy, or until the platelet count rises above 50,000/uL

3. Clinical toxicity
   a) Fatigue
   b) Headache
   c) Dizziness
   d) Cardiovascular effects (dyspnea, atrial arrhythmia)
   e) Hypokalemia

D. New agents for thrombocytopenia

a) Romiplostim- A novel protein known as a “peptibody” with two domains; a peptide domain that binds the thrombopoietin receptor (MPL), and an antibody Fc domain that increases half-life. Romiplostim is FDA approved for the treatment of idiopathic thrombocytopenia purpura (ITP). Adverse effects include headache, myalgia, and bone marrow fibrosis (reversible).

b) Eltrombopag-A small molecule thrombopoietin receptor agonist of the thrombopoietin receptor, approved for the treatment of ITP. Adverse effects are the same as for romiplostim. Eltrombopag has now received FDA approval for the treatment of aplastic anemia.
- Immunopharmacology

Date: Wednesday November 11th, 2015

Reading Assignment: Katzung 13th edition: Ch 55 p. 946-969

LEARNING OBJECTIVES

1. List the indications, clinical uses and contraindications for the major classes of immunosuppressive and immunomodulatory drugs

2. Describe the mechanisms of action for each of the major classes of immunosuppressive and immunomodulatory drugs

3. List the major adverse effects for each of the major classes of immunosuppressive and immunomodulatory drugs

4. Identify any clinically significant drug interactions associated with each of the major classes of immunosuppressive and immunomodulatory drugs

5. Apply your knowledge of the pharmacology of the major classes of immunosuppressive and immunomodulatory drugs to select the most appropriate medication(s) for the successful pharmacotherapy of a specific patient based upon patient-specific and disease criteria.
Drugs covered in this lecture

A. Glucocorticoids/Steroids
   Prednisone/Prednisolone

B. Proliferation inhibitors and Anti-metabolites
   Azathioprine
   Mycophenolate mofetil

C. Immunophilin-binding drugs: Inhibitors of T cell signaling pathways
   Calcineurin inhibitors: Cyclosporin & Tacrolimus

   mTOR inhibitors: Sirolimus and Everolimus

D. Antibodies for induction immunosuppression
   Rabbit polyclonal anti-thymocyte globulin
   Alemtuzumab
   Basiliximab

E. Miscellaneous immunosuppressive drugs used in the treatment of Relapsing-Remitting Multiple Sclerosis
   Fingolimod
   Natalizumab
   Interferon
   Glatiramer

F. Passive Immunization Ig
   IVIG
   Rho(D) Ig
   Hyperimmune Ig

G. Immune checkpoint inhibitors
   Ipilimumab
   Nivolumab & Pembrozilmb
### Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Immunoglobulin for Passive Immunization</th>
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<tbody>
<tr>
<td><strong>Basilmab</strong></td>
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<tr>
<td><strong>Alentuzumab</strong></td>
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<tr>
<td><strong>Rabbit Antithymocyte Globulin</strong></td>
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<td><strong>IVIG</strong></td>
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### Indications & Clinical Uses

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<thead>
<tr>
<th>Adverse Effects</th>
<th>Mechanism of action</th>
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<tr>
<td><strong>Basilmab</strong></td>
<td>Induction immunoregulatory</td>
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<tr>
<td><strong>Alentuzumab</strong></td>
<td>Induction immunoregulatory</td>
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<tr>
<td><strong>Rabbit Antithymocyte Globulin</strong></td>
<td>Induction immunoregulatory</td>
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### Hypertumore

- To provide aid to early-stage immunotherapy
- To provide aids to early-stage immunotherapy
- To provide aids to early-stage immunotherapy
- To provide aids to early-stage immunotherapy

### Miscellaneous

- Treatment of early-stage immunotherapy
- Treatment of early-stage immunotherapy
- Treatment of early-stage immunotherapy
- Treatment of early-stage immunotherapy

### Immune Checkpoint Inhibitors

- Nivolumab
- Pembrolizumab
- Ipilimumab

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<thead>
<tr>
<th>Immune checkpoint</th>
<th>Function</th>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>Treats early-stage immunotherapy</td>
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<tr>
<td>Pembrolizumab</td>
<td>Treatment for early-stage immunotherapy</td>
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<tr>
<td>Ipilimumab</td>
<td>Treatment for early-stage immunotherapy</td>
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- Treatment of early-stage immunotherapy
- Treatment of early-stage immunotherapy
- Treatment of early-stage immunotherapy
- Treatment of early-stage immunotherapy

### Rh(D) (d)

- To complement Rh negative RBC's
- To complement Rh negative RBC's
- To complement Rh negative RBC's
- To complement Rh negative RBC's

### IVIG

- Provides short-term humoral immunity
- Provides short-term humoral immunity
- Provides short-term humoral immunity
- Provides short-term humoral immunity
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Interferon</td>
<td>Multiple targets</td>
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<tr>
<td>Glatiramer</td>
<td>Treatment of Multiple Tissues</td>
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<td>Natalizumab</td>
<td>Treatment of Multiple Tissues</td>
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<td>fingolimum</td>
<td>Treatment of Multiple Tissues</td>
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| Miscellaneous Immunosuppressive Drugs Used in the Treatment of MS |

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<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Chlorambucil</td>
<td>Treatment of Multiple Tissues</td>
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<td>Cyclophosphamide</td>
<td>Treatment of Multiple Tissues</td>
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<tr>
<td>Methotrexate</td>
<td>Treatment of Multiple Tissues</td>
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<tr>
<th>Adverse Effects</th>
<th>Additional &amp; Promising Agents (less commonly used in transplantation)</th>
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ANTIFUNGAL DRUGS

Date: Thursday, December 3rd, 2015 8:30-9:30am

Optional Reading Assignment: Basic and Clinical Pharmacology
Katzung, 12th Edition
Chapter 48 pp 849-857

Key Concepts and Learning Objectives.

1. List the indications and contraindications for the major classes of antifungal agents

2. Describe the spectrum of activity and principal clinical uses for the major classes of antifungal agents.

3. Describe the mechanism of action for the major classes of antifungal agents.

4. List the major adverse effects associated with the use of the major classes of antifungal agents.

5. Discuss the principal pharmacokinetic parameters (e.g. absorption, distribution & elimination) of the major classes of antifungal agents and the effects that these have on the clinical use of these drugs.

6. Distinguish the major differences between the members of the azole class of antifungals based upon their spectrum of activity, pharmacokinetic parameters and major adverse effects.

7. Identify those antifungal drugs that pose significant risk of major drug interactions and describe the likely effects on the serum concentration of any co-administered drug

8. Apply your knowledge of the pharmacology of the major classes of antifungal drug agents to select the most appropriate medication for a specific patient based upon the presence of both a specific fungal pathogen and patient-specific criteria.

9. Identify the recommended antifungal agents used in the treatment of specific systemic, localized and cutaneous fungal pathogens
Drugs covered in this lecture

I. Systemic antifungal drugs for systemic infections
   
   A. Polyene Antifungal agents
      Amphotericin B*
   
   B. Fluorinated pyrimidine
      5-Flucytosine*
   
   C. Azole antifungal agents
      Imidazoles: Ketoconazole
      Triazoles: Fluconazole*, Itraconazole*, Voriconazole*, Posaconazole*

   D. Echinocandins
      Caspofungin*, Micafungin & Anidulofungin

II Systemic antifungal drugs for cutaneous fungal infections

   Griseofulvin*
   Terbinafine*

III Topical antifungal drugs for cutaneous fungal infections

   Polyene: Nystatin
   Azoles: Miconazole, Clotrimazole & Terconazole
   Allylamines and Benzyllamines: Terbinafine, Naftifine & Butenafine

Note: The most important antifungal drugs are highlighted in bold with an asterix.
I. Systemic antifungal drugs for systemic infections

A. AMPHOTERICIN B

Overview
a) Naturally occurring polyene macrolide antibiotic from Streptococcus nodosus
b) Broader spectrum of all antifungal agents
c) Associated with significant toxicities
   - alternative liposomal formulations reduce side effects
d) Despite the presence of newer drugs, Ampho B remains the standard therapy for treatment of life-threatening mycoses

Mechanism of Action
a) Primarily fungicidal
b) Binds to ergosterol in the plasma membrane of sensitive fungal cells causing pores to form that disrupt membrane function allowing electrolytes (K+) and small molecules to leak out causing cell death.
c) Binds ergosterol with much greater affinity than to cholesterol present in the plasma membrane of mammalian cells

Spectrum of Activity
Amphotericin B has the broadest spectrum of all antifungal agents

Effective against:
- Candida sp (except C. lusitaniae)
- Cryptococcus
- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Aspergillus sp
- Fusarium
- Zygomycosis/Mucormycosis

Not active against:
- Pseudallescheria boydii (Scedosporium apiospermum)

Resistance is infrequent and is usually associated with decreased ergosterol content of fungal membranes
Pharmacokinetics
a) Not orally absorbed from GI tract
b) Administration is via IV infusion
c) Oral Ampho B is only effective against fungi within the lumen of the GI tract
d) Drug is highly hydrophobic. The standard formulation is a colloidal suspension with sodium deoxycholate (C-AMB). Alternative liposomal formulations are associated with increased efficacy and decreased toxicity (L-AMB, ABLC & ABCD), although are considerably more expensive (~ $600-1000/day vs ~ $25/day for C-AMB)
e) Drug is widely distributed throughout the body
f) Long serum half-life ~ 15hrs
g) 2-3% of drug distributes to CNS, although drug is effective in treatment of meningitis
h) Intrathecal injection can be used to treat fungal meningitis in severely ill patients, but is poorly tolerated (seizures/neurological sequelae)
i) No dosage adjustment required in Renal/hepatic impairment

Clinical Uses
a) All life-threatening mycotic infections:
   - fungal infections in immunosuppressed patients
   - severe fungal pneumonia
   - severe cryptococcal meningitis
   - disseminated infections of endemic mycoses
   - Patients not responding to AZOLE-treatment of invasive Aspergillus

b) Used as initial induction therapy to reduce initial fungal burden and is then replaced by one of the newer/less toxic AZOLE drugs for chronic therapy and prevention of relapse
c) Often given as prophylactic therapy to patients with profound neutropenia and fever who have not responded to broad spectrum antibacterial agents over 5-7 days
d) Treatment of choice for Zygomycosis/Mucormycosis
e) Topical and localized administration:
   - Mycotic corneal ulcers
   - Fungal arthritis (local injection)
   - Candiduria- bladder irrigation (no systemic toxicity)

******NOTE: Only antifungal agents that is approved for use in the treatment of pregnant and/or breast feeding women.

Adverse Effects (Low therapeutic index)
Infusion-related toxicities (Ampho-terrible):
   nearly universal
   Fever, chills, muscle spasms, vomiting, headache and hypotension
   - Slow infusion rate/decrease daily dose
   - Pre-emptive medication: antipyretic, anti-histamine, corticosteroids

Cumulative toxicities:
 a) Nephrotoxicity (common)
   Reversible- ↓Renal perfusion via vasoconstriction
   Maybe reduced with Na+ loading
Irreversible- Renal tubule injury (with prolonged administration)
  - Tubular acidosis and severe K+ and Mg++ wasting
  - More common in presence of diuretic volume depletion or other nephrotoxic medications
    e.g. aminoglycosides or cyclosporin

b) Hepatoxicity (occasional)- increase in liver enzymes

c) Anemia– reversible suppression of erythrocyte production due to ↓erythropoietin

Drug Interactions:
Ampho B should not be given concurrently with other nephrotoxic agents e.g. aminoglycosides or cyclosporin

B. FLUCYTOSINE
Overview
  a) 5-fluorocytosine is a synthetic pyrimidine (originally developed as an anti-metabolite chemotherapy agent, although not effective)
  b) Use is restricted due to high incidence of primary and acquired resistance
  c) Typically used in combination with other antifungal drugs (Ampho B)

Mechanism of Action
  a) Fungistatic
  b) Enters the cell via a specific cytosine-specific permease not found in mammalian cells
  c) Within the cell it is sequentially converted to 5-fluorouracil by the enzyme cytosine deaminase and then to 5-fluoroxyuridine monophosphate (5-FdUMP) and 5-fluouridine trisphosphate (5-FUTP)
    - 5-FdUMP inhibits thymidylate synthase a key enzyme in nucleotide/DNA synthesis
    - 5-FUTP inhibits RNA synthesis
  d) Note: Mammalian cells do not express cytosine deaminase
  e) Ampho B increases cell permeability to Flucytosine

Mechanism of action of Flucytosine

Spectrum of Activity and Clinical use
a) Narrow spectrum: Cryptococcus neoformans, Candida sp
Agents of chromoblastomycosis
e.g. Fonsecaea pedrosol, Fonsecaea compacta, Phialophora verrucosa and Cladosporium carrionii

b) Use is restricted due to high incidence of primary and acquired resistance
c) Resistance due to mutations in cytosine permease, cytosine deaminase, uracil phosphoribosyl transferase (5-FU to 5-FUMP), or ▲ production of endogenous cytosine
d) Emergence of resistance is reduced with combination therapy
e) Typically used in combination with either Amphotericin B or itraconazole
   Flucytosine + Ampho B ➔ Candidiasis or Cryptococcosis
   Flucytosine + itraconazole ➔ Chromoblastomycosis

Pharmacokinetics
a) Good oral absorption
b) Wide distribution
c) Penetrates well into the CSF (useful for Cryptococcal meningitis)
d) Renal elimination
e) t1/2 ~ 6 hrs, but > 200 hrs in renal failure
f) Dosage adjustment required with renal impairment

Adverse effects
a) Is metabolized by gut microflora to 5-flurouracil (Toxic anti-metabolite)
   - GI (frequent): nausea, vomiting, diarrhea
   - Bone marrow toxicity (anemia, leukopenia & thrombocytopenia)
   - More common in those with underlying hematological disorder or receiving radiation or chemotherapy

b) Should not be used in PREGNANCY

C. AZOLE ANTIFUNGAL AGENTS
General overview of Drug Class
a) New class of antifungals
b) Widely used clinically
c) Generally broad spectrum of activity
d) Less serious side effects compared to Ampho B
e) Major inhibitors of CYP450 enzymes make drug interactions a significant problem

Two major chemical classes:
Imidazoles  Ketoconazole (Oral, systemic fungal infections)
           Clotrimazole, miconazole (Topical, superficial fungal infections)
Triazoles  Fluconazole (Oral, systemic fungal infections)
           Itraconazole (Oral, systemic fungal infections)
           Voriconazole (Oral, systemic fungal infections)
           Posaconazole (Oral, systemic fungal infections)
Mechanism of action

a) Azoles are primarily fungistatic

b) All azoles inhibit the 14α-sterol demethylase, a CYP450 enzyme involved in the conversion of lanosterol into ergosterol.

Results in ↓ ergosterol and ↑ 14α-methylsterol content of fungal membranes, which affects the biophysical structure of the phospholipids bilayer causing increased membrane permeability and reduced activity of critical membrane-associated proteins such as those involved in electron transport.

Spectrum of activity

Each specific drug exhibits a unique spectrum of activity, although all exhibit activity against most Candida species and Cryptococcus neoformans.

Common Adverse effects of Azole antifungals

a) GI distress,

b) Hepatotoxicity – requires hepatic enzyme monitoring

c) Should not be used in pregnancy

Azole-drug interactions

a) All azoles are either substrates or inhibitors of CYP450 enzymes. Therefore many potential drug interactions

SPECIFIC AZOLE ANTIFUNGAL AGENTS

C1. KETOCONAZOLE (Prototype)

Overview

a) 1st oral azole antifungal introduced (also available as topical formulation)

b) Broad spectrum of activity includes: Candida, Coccidioides, C. neoformans, H. capsulatum, B. dermatitidis and dermatophytes

c) However, poor PK and Adverse effect profile limit its clinical use

   Oral ketoconazole requires acidic environment for absorption drug penetrates poorly into CSF and urine

d) Many adverse effects due to inhibition of mammalian CYP450 enzymes involved in adrenal and gonadal steroid synthesis-

   ↓ cortisol and ↓ testosterone
gynecomastia, ↓ libido, impotence, menstrual irregularities,
Orthostatic hypotension & fatigue
e) Many drug interactions due to inhibition of CYP450 enzymes
f) Oral ketoconazole now largely replaced by itraconazole (broader spectrum, greater potency, fewer adverse effects)
g) Topical ketoconazole used to treat common dermatophyte infections

C2. FLUCONAZOLE
Overview
a) Available as ORAL or IV
b) Well absorbed
c) Cheap, well-tolerated, high therapeutic index
d) Excellent penetration into CSF
e) Fewest drug interactions of all azoles
f) >80% of drug eliminated unchanged in the urine
   - Dosage adjustment required in renal insufficiency

Spectrum of activity and Clinical Uses:
a) Equivalent to Ampho B for Candida albicans
b) Antifungal agent most commonly used for mucocutaneous candidiasis
c) Poor activity towards C. glabrata and no activity towards C.krusei
d) Treatment of choice for Cryptococcal meningitis (Ampho B induction and maintenance therapy)
e) Drug of choice for Coccidioidal meningitis (good CSF penetration/less morbidity than intrathecal Ampho B)
f) Limited activity against endemic fungi (EXCEPT Coccidioides)
   i.e. limited activity against Histoplasmosis, Blastomycosis, Sporotrichosis
   less potent than itraconazole
   Can be used if itraconazole contraindicated, although high dose required
g) NOT EFFECTIVE for treatment of: Aspergillosis or Zygomycosis/Mucormycosis

Adverse effects
a) Well tolerated with only minor adverse effects
   - nausea, headache, skin rash, GI
   - Alopecia (reversible) has been associated with long duration high dose therapy

C3. ITRACONAZOLE
Overview
a) Oral solution/Capsules- requires acidic environment for absorption
b) Broader spectrum of activity than fluconazole
c) Has now largely replaced ketoconazole
d) Long half-life/once daily dosing
e) Extensively metabolized in the liver/inactive metabolites eliminated in urine/feces
f) Poor penetration of CSF and the eye
g) Strong inhibitor of CYP3A4 – many drug interactions

Spectrum of activity and Clinical Uses:
a) Treatment of choice for dermatophytes/onchomycosis
b) Preferred agent for non-meningeal Blastomyces, Histoplasmosis, Sporothrix and Coccidioidomycosis
c) Active against Ampho B-resistant Pseudallescheriasis
d) Effective against Candida, although more side effects than fluconazole
e) Active against *Aspergillus*, although less effective than Voriconazole (DOC)

f) Not recommended as maintenance/salvage therapy of Cryptococcal meningitis due to poor penetration of CSF and frequent relapse

g) NOT ACTIVE against either Fusarium or Mucor

**Adverse Effects**

a) Typical Azole Adverse effects: GI distress, hepatotoxicity

b) Should not be used in pregnancy

c) Itraconazole-specific effects:
   - Triad of hypertension, hypokalemia and peripheral edema
   - Can cause congestive heart failure in patients with ventricular dysfunction
   - Should not be used for the treatment of simple fungal infections in patients with a history of ventricular dysfunction or CHF

**C4. VORICONAZOLE**

**Overview**

a) Newer Azole

b) Extended spectrum anti-fungal

c) Oral and IV formulations

d) Absorption inhibited by fatty meal

e) Well absorbed, broadly distributes into tissues including CSF

f) Inhibitor of CYP 2C19, 2C9 and 3A4 - many drug interactions

g) Less toxic than Ampho B

h) Undergoes extensive hepatic metabolism - no active metabolites

i) <2% excreted in urine unchanged No need for dosage reduction in renal insufficiency

j) Exhibits non-linear metabolism 50% increase in dose can result in 150% increase in serum concentration (important since some adverse effects are dose dependent)

**Spectrum of activity and Clinical Uses:**

a) Similar to Itraconazole in spectrum

b) Excellent activity against Candida sp. including fluconazole-resistant *C. glabrata* and *C. krusei*

c) Good activity against dimorphic fungi:

   *Blastomyces, Histoplasmosis, Coccidioides & Paracoccidioides*

d) Enhanced activity against *Aspergillus* and *Fusarium*

e) Treatment of choice for invasive *Aspergillus* (less toxic than Ampho B)

f) Treatment of *Pseudoallescheria boydii*

g) NOT ACTIVE against Mucor

**Adverse Effects**

a) Generally well tolerated - Occasional GI distress and Hepatotoxicity

b) Teratogenic and should not be used in pregnancy

c) Unique side effects

   Minor
   
   (i) Periostitis (Bone Pain) – inflammation of the periosteum

   (ii) Transient vision changes (Visual blurring/changes in color vision)

      Affects ~ 30% of patients

      Occurs within 30 mins of dose/lasts 30-60 mins

      Observed after first dose- symptoms diminish with time
(iii) Photosensitivity/Rash - rarely Steven’s Johnson’s Syndrome

More Serious (Associated with high serum concentration > 5.5 mcg/ml)
(i) Visual/Auditory hallucinations
(ii) Seizures

C5. POSACONAZOLE

Overview
a) Newest Azole
b) Brodest spectrum of azole family
c) Oral formulation only (lack of IV formulation limits use in severely ill patients)
d) Requires acidity for absorption
e) Readily distributes to tissues, but POOR penetration of CSF and urine
f) Unchanged drug eliminated in the feces – not necessary to reduce dosage in renal insufficiency
g) Inhibitor of CYP3A4 therefore many potential drug interactions

Spectrum of activity and Clinical Uses:
a) Brodest spectrum of azole family similar to voriconazole
b) Primarily used in treatment and prophylaxis of invasive fungal infections (e.g. Candida/Aspergillus)
c) Used for antifungal prophylaxis in patients with:
   - prolonged neutropenia due to chemotherapy
   - severe Graft-versus-host-disease
d) ONLY azole active against Zygomycosis/Mucormycosis (used as a salvage agent)

Adverse Effects
a) Good safety profile
b) Nausea, vomiting, diarrhea- most common
c) Fetal abnormalities- Not to be used in pregnancy
D. ECHINOCANDINS: Caspofungin, Micafungin & Anidulafungin

Overview
a) Newest class of antifungal agents
b) First agents to target the fungal cell wall
c) Large lipopetides/Poor oral availability
d) Must be administered IV
e) Long half-lives
f) Poor penetration of CSF
g) Very expensive compared to other agents
h) Echinocandins are not significant substrates or inhibitors of CYP450 therefore few drug interaction

Mechanism of Action
a) Echinocandins non-competitively inhibit $\beta$(1-3)-D-glucan synthase complex involved in the synthesis of $\beta$(1-3) glucan- the principal building block of the fungal cell wall.
b) Inhibiting glucan synthesis impairs structural integrity of the cell wall resulting in osmotic instability and cell death.

Spectrum of activity and Clinical Uses:
a) Candida sp (Fungicidal) including C. glabrata and C. krusei
   - Frequently used as first line treatment for invasive Candida
     (especially critically ill/neutropenic patients)
   - Major advantage fungicidal with minimal associated adverse effects
b) Aspergillus sp. (Fungistatic)
   - Salvage therapy for invasive Aspergillus infections that fail Ampho B treatment
c) NO SIGNIFICANT ACTIVITY towards Cryptococcus or dimorphic fungi

Adverse effects
a) Well tolerated, few adverse effects, safest antifungals available
b) Histamine-like effects (skin itching) with rapid infusion

II Systemic antifungal drugs for cutaneous fungal infections
For treatment of superficial skin and nail infections with dermatophytes:
Microsporum, Epidermophyton & Trichophyton
Tinea pedis (foot)
Tinea cruris (groin)
Tinea corpora (body)
Tinea captis (scalp)
Onchomycosis (nail)

II. E. GRISEOFULVIN (ORAL)
Overview
a) Very insoluble fungistatic drug
b) Administered in a microcrystalline form
c) Absorption is improved with a fatty meal
d) Only used for mycotics infection of the skin, nails and hair due to Microsporum, Epidermophyton & Trichophyton
e) No activity against other fungi
f) Therapeutic use is limited by the availability of topical/oral antifungal agents with fewer side effects
g) Now largely replaced by terbinafine for treatment of onchomycosis

Mechanism of Action
a) The drug is fungistatic and binds to fungal tubulin thereby inhibiting fungal microtubule function, preventing the formation of the mitotic spindle and blocking fungal mitosis
b) Griseofulvin accumulates in keratin-producing precursor cells when these cells first differentiate and binds tightly to keratin making these newly differentiated cells resistant to fungal infection
c) This allows the new growth of hair, nails and skin to be free of dermatophyte infection
d) Infected skin, nail and hair cells are gradually exfoliated and replaced by uninfected new cells
e) Successful treatment with Griseofulvin typically requires longterm treatment (nails- 6-12 months; skin, 2-6 weeks)

Adverse effects
a) A large number of adverse effects, although serious side effects are rare

   (i)    Headache common
   (ii)   Nervous system- lethargy, vertigo, blurred vision
   (iii)  Hepatotoxicity (rare)
   (iv)   Augments effects of alcohol
(v) Leukopenia, neutropenia and monocytosis have been reported
(vi) Skin - urticaria, photosensitivity, rash and skin eruptions
(vii) Should not be taken during pregnancy due to fetal abnormalities

Drug Interactions
Griseofulvin induces hepatic CYP450 enzymes – can increase the metabolism of certain drugs e.g. warfarin and oral contraceptives

II.F. TERBINAFINE (ORAL)
Overview
a) An Allylamine antifungal agent
b) Low oral bioavailability due to significant 1st pass effect
c) Deposits in skin, nails, hair and fat
d) Long half-life (200-400 hrs)
e) Extensively hepatically metabolized and renally-excreted- not recommended for patients with hepatic/renal insufficiency

Spectrum of activity and Clinical use
a) Limited to dermatophytes and Candida albicans
b) Used in the treatment of tinea capitis, tinea corporis, tinea cruris, tinea pedis and Onychomycosis
c) Cure rate is ~90%- more effective then either griseofulvin or itraconazole

Mechanism of action
a) The drug is fungicidal
b) It inhibits fungal squalene epoxidase, an enzyme involved in the synthesis of ergosterol
   - decreased ergosterol synthesis impairs fungal membrane function
   - Causes accumulation of squalene, which is toxic resulting in fungal cell death

Adverse effects
a) Well tolerated
b) Low incidence of GI distress, headache or rash
c) Rarely terbinafine may cause hepatotoxicity, neutropenia or Stevens-Johnson syndrome
d) Few significant drug interactions
III Topical antifungal drugs for cutaneous fungal infections

III.G. NYSTATIN
   a) Similar structure and mechanism of action to Ampho B
   b) Too toxic for IV administration
   c) Available in gels, creams ointments and suppositories
   d) Not significantly absorbed from skin, mucus membranes or GI tract
      - little toxicity when given topically
   e) Used for the treatment of oral Candidiasis (swish and swallow)
      - drug is not absorbed and is quantitatively excreted in the feces
   f) Not effective against dermatophytes
   g) Few adverse effects as drug is not absorbed

III.H. TOPICAL AZOLES: Clotrimazole, Miconazole and Terconazole
   a) Available as creams, lozenges and suppositories
   b) Clinical uses: Oral and Vulvovaginal candidiasis & Dermatophyte infections
   c) Absorption negligible- Adverse effects rare

III.I TOPICAL ALLYAMINES AND BENZYLAMINES
   Allylamines: Terbinafine & Naftifine
   Benzylamines: Butenafine
   a) All drugs act to inhibit squalene epoxidase and are fungicidal
   b) Spectrum of activity limited to *Candida albicans* and dermatophytes
   c) Used in the treatment of Tinea cruris, Tinea corporis and Tinea pedis

SUMMARY MATERIAL
# Summary of major antifungal drug classes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>MOA</th>
<th>Adverse Effects</th>
<th>Misc.</th>
</tr>
</thead>
</table>
| **Amph B** | • Broad Spectrum  
  • All-life-threatening mycotic infections  
  Candida, Cryptococcus Histoplasma, Blastomyces, Coccidioides, Aspergilus, Fusarium, Mucor  
  Not C. lusitaniae  
  Not Pseudallescheria boydii  
  • TOC Mucormycosis | Binds to ergosterol in fungal plasma membrane and forms pores causing increased membrane permeability and loss of cytoplasmic K+ | Infusion related (Ampho-terrible)  
  Fever, Chills, spasms, vomiting  
  Cumulative  
  Nephrotoxicity/Hepatotoxicity/Anemia | • Only Antifungal drug approved for use in pregnancy  
  • Used for initial induction therapy followed by consolidation therapy with less toxic Azole |
| **Flucytosine** | • Narrow spectrum  
  Cryptococcus neoformans  
  especially cryptococcal meningitis  
  Candida sp  
  Agents of chromblastomycosis | Taken up via cytosine permease and converted by fungal-specific cytosine deaminase to 5-FU analogs that inhibit thymidylate synthase and RNA synthesis | GI (frequent) nausea/vomiting/diarrhea  
  BM toxicity- more common in those with blood disorder  
  Tetratogenic | • Good CSF penetration  
  • Used in combination with Amph B  
  • Frequent resistance  
  • Dosage adjustment in Renal failure  
  • Not to be used in pregnancy |
| **Echinocandins** | Candida  
  in C. glabrata/C. krusei  
  Treatment of invasive Candida  
  Treatment of invasive Aspergillus  
  No activity for Cryptococcus or Dimorphic fungi | Acts on fungal cell wall  
  Inhibits β(1-3) D glucan synthase complex  
  Impairs membrane structure  
  Increases osmotic instability | Well tolerated  
  Histamine-like effect with Rapid infusion | Poor CSF penetration  
  Not to be used in pregnancy |
| **Griseofulvin** | Treatment of mycotic infections of Skin, nail and hair due to dermatophytes | Fungistatic  
  Binds fungal microtubules and inhibits mitotic spindle  
  Accumulates in newly differentiated Keratin producing cells preventing fungal growth | Many adverse effects  
  Headache, lethargy, vertigo, blurred vision  
  Urticaria, photosensitivity, rash  
  Hepatotoxicity  
  Leukopenia, neutropenia, monocyteosis  
  Fetal abnormalities | Very insoluble  
  Strong CYP450 inducer  
  - many drug interactions  
  Not to be used during pregnancy |
| **Terbinafine** | Treatment of onychomycosis and superficial skin infections  
  • Candida Albicans  
  • Dermatophytes | Inhibits fungal squaletone epoxidase resulting in formation of toxic products and inhibition of ergosterol synthesis | Well tolerated  
  Adverse effects rare  
  Hepatotoxicity  
  Neutropenia  
  Stevens Johnson | • Long half life (> 200 hrs)  
  • Not recommended in hepatic/renal insufficiency |
<table>
<thead>
<tr>
<th>MOA</th>
<th>Ketoconazole</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectrum of Activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF Penetration</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Renal Dose Adjustment</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>****</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Endocrine effects</td>
<td>Minor adverse effects</td>
<td>Photosensitivity, rash, pneumonitis, visual change</td>
<td>None</td>
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<tr>
<td>Clinical Uses</td>
<td>Largely replaced by azoles</td>
<td>Cheaper, 2nd line agent</td>
<td>Treatment of invasive fungal infections</td>
<td>Treatment of aspergillosis, fusariosis</td>
</tr>
</tbody>
</table>

**Pharmacology & Therapeutics**

**Antifungal Drugs**

**Thursday, December 3rd, 2015**

**Neil Clipstone, Ph.D.**
### Summary of Spectrum of activity of Antifungal agents for Systemic Infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antifungal agent</th>
<th>AZOLES</th>
<th>AmB</th>
<th>Flu</th>
<th>Itra</th>
<th>Vori</th>
<th>Pos</th>
<th>Echocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida sp</td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td>C. glabrata</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>C. krusei</td>
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<td>+</td>
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<td>+/-</td>
<td>+/</td>
<td>+</td>
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<td>C. lusitaniae</td>
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<td>Cryptococcus neoformans</td>
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<td>Coccidioides sp</td>
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<td>Blastomyces sp</td>
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<tr>
<td>Histoplasma sp</td>
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<td>+</td>
<td></td>
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<tr>
<td>Aspergillus sp</td>
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<td></td>
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<tr>
<td>Fusarium sp</td>
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<tr>
<td>Pseudallerischeri boydii/</td>
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<tr>
<td>Scedosporium apiospermum</td>
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<tr>
<td>Zygomycetes/Mucor</td>
<td></td>
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</tr>
</tbody>
</table>

### Treatment of Dermatophyte infections and Onchomycosis

- **Oral Griseofulvin** (long safety history)
- **Oral Terbinafine**
- **Oral fluconazole/Itraconazole**

**Note:** Topical antifungals are ineffective

- **Topical antifungals**
  - e.g. **AZOLES** or **Terbinafine**
  - **NOT NYSTATIN**
    - (not active against dermatophytes)

- **Oral terbinafine/Itraconazole/fluconazole**

**Note:** Topical antifungals are ineffective

- **Oral terbinafine or Itraconazole**

**2nd line:** Oral fluconazole or griseofluvin
<table>
<thead>
<tr>
<th>Fungal Disease</th>
<th>Type</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endemic Mycoses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild/moderate</td>
<td>An Azole-e.g. Itraconazole (preferred)</td>
</tr>
<tr>
<td></td>
<td>Severely ill/</td>
<td>Amph B (induction)</td>
</tr>
<tr>
<td></td>
<td>disseminated</td>
<td>An Azole (consolidation/maintenance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Note: Fluconazole can be used to treat Coccidioidmycosis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>and is DOC for Disseminated disease/meningitis</em></td>
</tr>
<tr>
<td><strong>Candidiasis</strong></td>
<td>Mucocutaneous</td>
<td>Initially a topical Agent: Nystatin or an azole</td>
</tr>
<tr>
<td></td>
<td>Oral/vaginal/rash</td>
<td>OR oral Fluconazole if topical treatment is unsuccessful</td>
</tr>
<tr>
<td></td>
<td>Mild/moderate</td>
<td>Fluconazole OR another Azole</td>
</tr>
<tr>
<td></td>
<td>Severe disease</td>
<td>Amph B OR an Azole OR an Echinocandin</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
<td>Amph B +/- Flucytosine (induction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole (consolidation/maintenance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>NOT AN ECHINOCANDIN- poor CNS penetration</em></td>
</tr>
<tr>
<td><strong>Cryptococcosis</strong></td>
<td>Pulmonary/skin</td>
<td>Fluconazole OR Amph B</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
<td>Amph B +/- Flucytosine (induction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluconazole (consolidation/maintenance)</td>
</tr>
<tr>
<td><strong>Aspergillosis</strong></td>
<td>Pulmonary/skin</td>
<td>Itraconazole</td>
</tr>
<tr>
<td></td>
<td>Invasive</td>
<td>Voriconazole OR Amph B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Itraconazole- maintenance/Alt. agent</td>
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<tr>
<td></td>
<td></td>
<td>Echinocandins/Posaconazole- salvage</td>
</tr>
<tr>
<td><strong>Mucormycosis</strong></td>
<td></td>
<td>Amph B OR Posaconazole (salvage)</td>
</tr>
<tr>
<td><strong>Fusariosis</strong></td>
<td></td>
<td>Amph B OR Voriconazole/Posaconazole (salvage)</td>
</tr>
</tbody>
</table>
ANTIFUNGAL DRUGS

Date: Thursday, December 3rd, 2015 8:30-9:30am

Optional Reading Assignment: Basic and Clinical Pharmacology
Katzung, 12th Edition
Chapter 48 pp 849-857

Key Concepts and Learning Objectives.

1. List the indications and contraindications for the major classes of antifungal agents

2. Describe the spectrum of activity and principal clinical uses for the major classes of antifungal agents.

3. Describe the mechanism of action for the major classes of antifungal agents.

4. List the major adverse effects associated with the use of the major classes of antifungal agents.

5. Discuss the principal pharmacokinetic parameters (e.g. absorption, distribution & elimination) of the major classes of antifungal agents and the effects that these have on the clinical use of these drugs.

6. Distinguish the major differences between the members of the azole class of antifungals based upon their spectrum of activity, pharmacokinetic parameters and major adverse effects.

7. Identify those antifungal drugs that pose significant risk of major drug interactions and describe the likely effects on the serum concentration of any co-administered drug

8. Apply your knowledge of the pharmacology of the major classes of antifungal drug agents to select the most appropriate medication for a specific patient based upon the presence of both a specific fungal pathogen and patient-specific criteria.

9. Identify the recommended antifungal agents used in the treatment of specific systemic, localized and cutaneous fungal pathogens
Drugs covered in this lecture

I. Systemic antifungal drugs for systemic infections

A. Polyene Antifungal agents
   Amphotericin B*

B. Fluorinated pyrimidine
   5-Flucytosine*

C. Azole antifungal agents
   Imidazoles: Ketoconazole
   Triazoles: Fluconazole*, Itraconazole*, Voriconazole*, Posaconazole*

D. Echinocandins
   Caspofungin*, Micafungin & Anidulofungin

II Systemic antifungal drugs for cutaneous fungal infections

Griseofulvin*
Terbinafine*

III Topical antifungal drugs for cutaneous fungal infections

Polyene: Nystatin
Azoles: Miconazole, Clotrimazole & Terconazole
Allylamines and Benzylamines: Terbinafine, Naftifine & Butenafine

Note: The most important antifungal drugs are highlighted in bold with an asterix.
I. Systemic antifungal drugs for systemic infections

A. AMPHOTERICIN B

Overview
a) Naturally occurring polyene macrolide antibiotic from Streptococcus nodosus
b) Broadest spectrum of all antifungal agents
c) Associated with significant toxicities
   - alternative liposomal formulations reduce side effects
d) Despite the presence of newer drugs, Ampho B remains the standard therapy for treatment of life-threatening mycoses

Mechanism of Action
a) Primarily fungicidal
b) Binds to ergosterol in the plasma membrane of sensitive fungal cells causing pores to form that disrupt membrane function allowing electrolytes (K+) and small molecules to leak out causing cell death.
c) Binds ergosterol with much greater affinity than to cholesterol present in the plasma membrane of mammalian cells

Spectrum of Activity
Amphotericin B has the broadest spectrum of all antifungal agents

Effective against:
- Candida sp (except C. lusitaniae)
- Cryptococcus
- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Aspergillus sp
- Fusarium
- Zygomycosis/Mucormycosis

Not active against: Pseudallescheria boydii (Scedosporium apiospermum)

Resistance is infrequent and is usually associated with decreased ergosterol content of fungal membranes
Pharmacokinetics

a) Not orally absorbed from GI tract
b) Administration is via IV infusion
c) Oral Ampho B is only effective against fungi within the lumen of the GI tract
d) Drug is highly hydrophobic. The standard formulation is a colloidal suspension with sodium deoxycholate (C-AMB). Alternative liposomal formulations are associated with increased efficacy and decreased toxicity (L-AMB, ABLC & ABCD), although are considerably more expensive (~ $600-1000/day vs ~ $25/day for C-AMB)
e) Drug is widely distributed throughout the body
f) Long serum half-life ~ 15hrs
g) 2-3% of drug distributes to CNS, although drug is effective in treatment of meningitis
h) Intrathecal injection can be used to treat fungal meningitis in severely ill patients, but is poorly tolerated (seizures/neurological sequelae)
i) No dosage adjustment required in Renal/hepatic impairment

Clinical Uses

a) All life-threatening mycotic infections:
   - fungal infections in immunosuppressed patients
   - severe fungal pneumonia
   - severe cryptococcal meningitis
   - disseminated infections of endemic mycoses
   - Patients not responding to AZOLE-treatment of invasive Aspergillus
b) Used as initial induction therapy to reduce initial fungal burden and is then replaced by one of the newer/less toxic AZOLE drugs for chronic therapy and prevention of relapse
c) Often given as prophylactic therapy to patients with profound neutropenia and fever who have not responded to broad spectrum antibacterial agents over 5-7 days
d) Treatment of choice for Zygomycosis/Mucormycosis
e) Topical and localized administration:
   - Mycotic corneal ulcers
   - Fungal arthritis (local injection)
   - Candiduria- bladder irrigation (no systemic toxicity)

******NOTE: Only antifungal agents that is approved for use in the treatment of pregnant and/or breast feeding women.

Adverse Effects (Low therapeutic index)

Infusion-related toxicities (Ampho-terrible):
   nearly universal
   Fever, chills, muscle spasms, vomiting, headache and hypotension
   - Slow infusion rate/decrease daily dose
   - Pre-emptive medication: antipyretic, anti-histamine, corticosteroids

Cumulative toxicities:
a) Nephrotoxicity (common)
   Reversible- ↓Renal perfusion via vasoconstriction
   Maybe reduced with Na+ loading
Irreversible- Renal tubule injury (with prolonged administration)
- Tubular acidosis and severe K+ and Mg++ wasting
- More common in presence of diuretic volume depletion or other nephrotoxic medications
  e.g. aminoglycosides or cyclosporin
b) Hepatoxicity (occasional)- increase in liver enzymes
c) Anemia– reversible suppression of erythrocyte production due to ↓erythropoietin

Drug Interactions:
Ampho B should not be given concurrently with other nephrotoxic agents e.g. aminoglycosides or cyclosporin

B. FLUCYTOSINE

Overview
a) 5-flurocytosine is a synthetic pyrimidine (originally developed as an anti-metabolite chemotherapy agent, although not effective)
b) Use is restricted due to high incidence of primary and acquired resistance
c) Typically used in combination with other antifungal drugs (Ampho B)

Mechanism of Action
a) Fungistatic
b) Enters the cell via a specific cytosine-specific permease not found in mammalian cells
  c) Within the cell it is sequentially converted to 5-flurouracil by the enzyme cytosine deaminase and then to 5-flurodeoxyuridine monophosphate (5-FdUMP) and 5-flourouridine trisphosphate (5-FUTP)
    - 5-FdUMP inhibits thymidylate synthase a key enzyme in nucleotide/DNA synthesis
    - 5-FUTP inhibits RNA synthesis
d) Note: Mammalian cells do not express cytosine deaminase
e) Ampho B increases cell permeability to Flucytosine

Spectrum of Activity and Clinical use
a) Narrow spectrum: *Cryptococcus neoformans*,
*Candida sp*
Agents of chromoblastomycosis
e.g. *Fonsecaea pedrosol, Fonsecaea compacta, Phialophora verrucosa and Cladosporium carrionii*
b) Use is restricted due to high incidence of primary and acquired resistance
c) Resistance due to mutations in cytosine permease, cytosine deaminase, uracil phosphoribosyl transferase (5-FU to 5-FUMP), or ↑ production of endogenous cytosine
d) Emergence of resistance is reduced with combination therapy
e) Typically used in combination with either Amphotericin B or itraconazole
   Flucytosine + Ampho B ⇒ Candidiasis or Cryptococcosis
   Flucytosine + itraconazole ⇒ Chromoblastomycosis

**Pharmacokinetics**
a) Good oral absorption
b) Wide distribution
c) Penetrates well into the CSF (useful for Cryptococcal meningitis)
d) Renal elimination
e) \( t_1/2 \approx 6 \) hrs, but > 200 hrs in renal failure
f) Dosage adjustment required with renal impairment

**Adverse effects**
a) Is metabolized by gut microflora to 5-flurouracil (Toxic anti-metabolite)
   - GI (frequent): nausea, vomiting, diarrhea
   - Bone marrow toxicity (anemia, leukopenia & thrombocytopenia)
   - More common in those with underlying hematological disorder or receiving radiation or chemotherapy
b) Should not be used in PREGNANCY

**C. AZOLE ANTIFUNGAL AGENTS**

**General overview of Drug Class**
a) New class of antifungals
b) Widely used clinically
c) Generally broad spectrum of activity
d) Less serious side effects compared to Ampho B
e) Major inhibitors of CYP450 enzymes make drug interactions a significant problem

**Two major chemical classes:**

**Imidazoles**
- Ketoconazole (Oral, systemic fungal infections)
- Clotrimazole, miconazole (Topical, superficial fungal infections)

**Triazoles**
- Fluconazole (Oral, systemic fungal infections)
- Itraconazole (Oral, systemic fungal infections)
- Voriconazole (Oral, systemic fungal infections)
- Posaconazole (Oral, systemic fungal infections)
Mechanism of action

a) Azoles are primarily fungistatic

b) All azoles inhibit the 14α-sterol demethylase, a fungal CYP450 enzyme involved in the conversion of lanosterol into ergosterol.

Results in ↓ergosterol and ↑14α-methylsterol content of fungal membranes, which affects the biophysical structure of the phospholipids bilayer causing increased membrane permeability and reduced activity of critical membrane-associated proteins such as those involved in electron transport.

Spectrum of activity

Each specific drug exhibits a unique spectrum of activity, although all exhibit activity against most Candida species and Cryptococcus neoformans.

Common Adverse effects of Azole antifungals

a) GI distress,
b) Hepatotoxicity – requires hepatic enzyme monitoring
c) Should not be used in pregnancy

Azole-drug interactions

a) All azoles are either substrates or inhibitors of CYP450 enzymes. Therefore many potential drug interactions

SPECIFIC AZOLE ANTIFUNGAL AGENTS

C1. KETOCONAZOLE (Prototype)

Overview

a) 1st oral azole antifungal introduced (also available as topical formulation)
b) Broad spectrum of activity includes: Candida, Coccidioides, C. neoformans, H. capsulatum, B. dermatitidis and dermatophytes
c) However, poor PK and Adverse effect profile limit its clinical use
   Oral ketoconazole requires acidic environment for absorption drug penetrates poorly into CSF and urine
d) Many adverse effects due to inhibition of mammalian CYP450 enzymes involved in adrenal and gonadal steroid synthesis-
   ↓cortisol and ↓testosterone
   gynecomastia, ↓libido, impotence, menstrual irregularities,
   Orthostatic hypotension & fatigue
e) Many drug interactions due to inhibition of CYP450 enzymes
f) Oral ketoconazole now largely replaced by itraconazole (broader spectrum, greater potency, fewer adverse effects)
g) Topical ketoconazole used to treat common dermatophyte infections

C2. FLUCONAZOLE
Overview
a) Available as ORAL or IV
b) Well absorbed
c) Cheap, well-tolerated, high therapeutic index
d) Excellent penetration into CSF
e) Fewest drug interactions of all azoles
f) >80% of drug eliminated unchanged in the urine
   - Dosage adjustment required in renal insufficiency

Spectrum of activity and Clinical Uses:
a) Equivalent to Ampho B for Candida albicans
b) Antifungal agent most commonly used for mucocutaneous candidiasis
c) Poor activity towards C. glabrata and no activity towards C.krusei
d) Treatment of choice for Cryptococcal meningitis (Ampho B induction and maintenance therapy)
e) Drug of choice for Coccidioidal meningitis (good CSF penetration/less morbidity than intrathecal Ampho B)
f) Limited activity against endemic fungi (EXCEPT Coccidioides)
   i.e. limited activity against Histoplasmosis, Blastomycosis, Sporotrichosis
   less potent than itraconazole
   Can be used if itraconazole contraindicated, although high dose required
g) NOT EFFECTIVE for treatment of: Aspergillosis or Zygomycosis/Mucormycosis

Adverse effects
a) Well tolerated with only minor adverse effects
   - nausea, headache, skin rash, GI
   - Alopecia (reversible) has been associated with long duration high dose therapy

C3. ITRACONAZOLE
Overview
a) Oral solution/Capsules- requires acidic environment for absorption
b) Broader spectrum of activity than fluconazole
c) Has now largely replaced ketoconazole
d) Long half-life/once daily dosing
e) Extensively metabolized in the liver/inactive metabolites eliminated in urine/feces
f) Poor penetration of CSF and the eye
g) Strong inhibitor of CYP3A4 – many drug interactions

Spectrum of activity and Clinical Uses:
a) Treatment of choice for dermatophytes/onchomycosis
b) Preferred agent for non-meningeal Blastomyces, Histoplasmosis, Sporothrix and Coccidioidomycosis
c) Active against Ampho B-resistant Pseudallescheriasis
d) Effective against Candida, although more side effects than fluconazole
e) Active against *Aspergillus*, although less effective than Voriconazole (DOC)

f) Not recommended as maintenance/salvage therapy of Cryptococcal meningitis due to poor penetration of CSF and frequent relapse

g) NOT ACTIVE against either Fusarium or Mucor

Adverse Effects

a) Typical Azole Adverse effects: GI distress, hepatotoxicity

b) Should not be used in pregnancy

c) Itraconazole-specific effects:
   - Triad of hypertension, hypokalemia and peripheral edema
   - Can cause congestive heart failure in patients with ventricular dysfunction
   - Should not be used for the treatment of simple fungal infections in patients with a history of ventricular dysfunction or CHF

C4. VORICONAZOLE

Overview

a) Newer Azole

b) Extended spectrum anti-fungal

c) Oral and IV formulations

d) Absorption inhibited by fatty meal

e) Well absorbed, broadly distributes into tissues including CSF

f) Inhibitor of CYP 2C19, 2C9 and 3A4 - many drug interactions

g) Less toxic than Ampho B

h) Undergoes extensive hepatic metabolism - no active metabolites

i) <2% excreted in urine unchanged No need for dosage reduction in renal insufficiency

j) Exhibits non-linear metabolism 50% increase in dose can result in 150% increase in serum concentration (important since some adverse effects are dose dependent)

Spectrum of activity and Clinical Uses:

a) Similar to Itraconazole in spectrum

b) Excellent activity against Candida sp. including fluconazole-resistant C. glabrata and C. krusei

c) Good activity against dimorphic fungi:
   *Blastomyces, Histoplasmosis, Coccidioides & Paracoccidioides*

d) Enhanced activity against *Aspergillus* and Fusarium

e) Treatment of choice for invasive *Aspergillus* (less toxic than Ampho B)

f) Treatment of *Pseudoallescheria boydii*

g) NOT ACTIVE against Mucor

Adverse Effects

a) Generally well tolerated - Occasional GI distress and Hepatotoxicity

b) Tetraamethicogenic and should not be used in pregnancy

c) Unique side effects

   Minor
   
   (i) Periostitis (Bone Pain) – inflammation of the periosteum
   
   (ii) Transient vision changes (Visual blurring/changes in color vision)
       
       Affects ~ 30% of patients
       
       Occurs within 30 mins of dose/lasts 30-60 mins
       
       Observed after first dose - symptoms diminish with time
(iii) Photosensitivity/Rash - rarely Steven’s Johnson’s Syndrome

More Serious (Associated with high serum concentration > 5.5 mcg/ml))

(i) Visual/Auditory hallucinations
(ii) Seizures

C5. POSACONAZOLE
Overview
a) Newest Azole
b) Broader spectrum ofazole family
c) Oral formulation only (lack of IV formulation limits use in severely ill patients)
d) Requires acidity for absorption
e) Readily distributes to tissues, but POOR penetration of CSF and urine
f) Unchanged drug eliminated in the feces – not necessary to reduce dosage in renal insufficiency
g) Inhibitor of CYP3A4 therefore many potential drug interactions

Spectrum of activity and Clinical Uses:
a) Broader spectrum ofazole family similar to voriconazole
b) Primarily used in treatment and prophylaxis of invasive fungal infections (e.g. Candida/Aspergillus)
c) Used for antifungal prophylaxis in patients with:
   - prolonged neutropenia due to chemotherapy
   - severe Graft-versus-host-disease
d) ONLY azole active against Zygomycosis/Mucormycosis (used as a salvage agent)

Adverse Effects
a) Good safety profile
b) Nausea, vomiting, diarrhea - most common
c) Fetal abnormalities - Not to be used in pregnancy
D. ECHINOCANDINS: Caspofungin, Micafungin & Anidulafungin

Overview
a) Newest class of antifungal agents
b) First agents to target the fungal cell wall
c) Large lipopeptides/Poor oral availability
d) Must be administered IV
e) Long half-lives
f) Poor penetration of CSF
g) Very expensive compared to other agents
h) Echinocandins are not significant substrates or inhibitors of CYP450 therefore few drug interaction

Mechanism of Action
a) Echinocandins non-competitively inhibit \(\beta(1-3)\)-D-glucan synthase complex involved in the synthesis of \(\beta(1-3)\) glucan- the principal building block of the fungal cell wall.

b) Inhibiting glucan synthesis impairs structural integrity of the cell wall resulting in osmotic instability and cell death.

Spectrum of activity and Clinical Uses:
a) *Candida sp* (Fungicidal) including *C. glabrata* and *C. krusei*
   - Frequently used as first line treatment for invasive Candida
     (especially critically ill/neutropenic patients)
   - Major advantage fungicidal with minimal associated adverse effects

b) *Aspergillus sp.* (Fungistatic)
   - Salvage therapy for invasive *Aspergillus* infections that fail Ampho B treatment

c) NO SIGNIFICANT ACTIVITY towards *Cryptococcus* or dimorphic fungi

Adverse effects
a) Well tolerated, few adverse effects, safest antifungals available
b) Histamine-like effects (skin itching) with rapid infusion

II Systemic antifungal drugs for cutaneous fungal infections

For treatment of superficial skin and nail infections with dermatophytes:
*Microsporum, Epidermophyton & Trichophyton*
- *Tinea pedis* (foot)
- *Tinea cruris* (groin)
Tinea corpora (body)
Tinea capitis (scalp)
Onchomycosis (nail)

II. E. GRISEOFULVIN (ORAL)
Overview
a) Very insoluble fungistatic drug
b) Administered in a microcrystalline form
c) Absorption is improved with a fatty meal
d) Only used for mycotics infection of the skin, nails and hair due to Microsporum, Epidermophyton & Trichophyton
e) No activity against other fungi
f) Therapeutic use is limited by the availability of topical/oral antifungal agents with fewer side effects
g) Now largely replaced by terbinafine for treatment of onchomycosis

Mechanism of Action
a) The drug is fungistatic and binds to fungal tubulin thereby inhibiting fungal microtubule function, preventing the formation of the mitotic spindle and blocking fungal mitosis
b) Griseofulvin accumulates in keratin-producing precursor cells when these cells first differentiate and binds tightly to keratin making these newly differentiated cells resistant to fungal infection
c) This allows the new growth of hair, nails and skin to be free of dermatophyte infection
d) Infected skin, nail and hair cells are gradually exfoliated and replaced by uninfected new cells
e) Successful treatment with Griseofulvin typically requires longterm treatment (nails- 6-12 months; skin, 2-6 weeks)

Adverse effects
a) A large number of adverse effects, although serious side effects are rare
   (i) Headache common
   (ii) Nervous system- lethargy, vertigo, blurred vision
   (iii) Hepatotoxicity (rare)
   (iv) Augments effects of alcohol
Leukopenia, neutropenia and monocytosis have been reported. Skin- urticaria, photosensitivity, rash and skin eruptions. Should not be taken during pregnancy due to fetal abnormalities.

**Drug Interactions**
Griseofulvin induces hepatic CYP450 enzymes – can increase the metabolism of certain drugs e.g. warfarin and oral contraceptives.

**II.F. TERBINAFINE (ORAL)**

**Overview**
- An Allylamine antifungal agent
- Low oral bioavailability due to significant 1st pass effect
- Deposits in skin, nails, hair and fat
- Long half-life (200-400 hrs)
- Extensively hepatically metabolized and renally-excreted- not recommended for patients with hepatic/renal insufficiency

**Spectrum of activity and Clinical use**
- Limited to dermatophytes and *Candida albicans*
- Used in the treatment of tinea captis, tinea corporis, tinea cruris, tinea pedis and Onchomycosis
- Cure rate is ~90%- more effective then either griseofulvin or itraconazole

**Mechanism of action**
- The drug is fungicidal
- It inhibits fungal squalene epoxidase, an enzyme involved in the synthesis of ergosterol
  - decreased ergosterol synthesis impairs fungal membrane function
  - Causes accumulation of squalene, which is toxic resulting in fungal cell death

**Adverse effects**
- Well tolerated
- Low incidence of GI distress, headache or rash
- Rarely terbinafine may cause hepatotoxic, neutropenia or Stevens-Johnson syndrome
- Few significant drug interactions
III Topical antifungal drugs for cutaneous fungal infections

III.G. NYSTATIN
   a) Similar structure and mechanism of action to Ampho B
   b) Too toxic for IV administration
   c) Available in gels, creams ointments and suppositories
   d) Not significantly absorbed from skin, mucus membranes or GI tract
      - little toxicity when given topically
   e) Used for the treatment of oral Candidiasis (swish and swallow)
      - drug is not absorbed and is quantitatively excreted in the feces
   f) Not effective against dermatophytes
   g) Few adverse effects as drug is not absorbed

III.H. TOPICAL AZOLES: Clotrimazole, Miconazole and Terconazole
   a) Available as creams, lozenges and suppositories
   b) Clinical uses: Oral and Vulvovaginal candidiasis & Dermatophyte infections
   c) Absorption negligible- Adverse effects rare

III.I TOPICAL ALLYAMINES AND BENZYLAMINES
   Allylamines: Terbinafine & Naftifine
   Benzylamines: Butenafine
   a) All drugs act to inhibit squalene epoxidase and are fungicidal
   b) Spectrum of activity limited to Candida albicans and dermatophytes
   c) Used in the treatment of Tinea cruris, Tinea corporis and Tinea pedis

SUMMARY MATERIAL
# Summary of major antifungal drug classes

<table>
<thead>
<tr>
<th>Indications</th>
<th>MOA</th>
<th>Adverse Effects</th>
<th>Misc.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amph B</strong></td>
<td>Broad Spectrum&lt;br&gt;• All-life-threatening mycotic infections&lt;br&gt;• Candida, Cryptococcus Histoplasma, Blastomyces, Coccidioides, Aspergillus, Fusarium, Mucor&lt;br&gt;• Not C. lusitaniae&lt;br&gt;• Not Pseudallescheria boydii&lt;br&gt;• TOC Mucormycosis</td>
<td>Binds to ergosterol in fungal plasma membrane and forms pores causing increased membrane permeability and loss of cytoplasmic K+&lt;br&gt;Infusion related (Ampho-terrible)&lt;br&gt;Fever, Chills, spasms, vomiting&lt;br&gt;Cumulative Nephrotoxicity/Hepatotoxicity/Anemia</td>
<td>• Only Antifungal drug approved for use in pregnancy&lt;br&gt;• Used for initial induction therapy followed by consolidation therapy with less toxic Azole</td>
</tr>
<tr>
<td><strong>Flucytosine</strong></td>
<td>Narrow spectrum&lt;br&gt;• Cryptococcus neoformans&lt;br&gt;• Especially cryptococcal meningitis&lt;br&gt;• Candida sp&lt;br&gt;• Agents of chromblastomycosis</td>
<td>Taken up via cytosine permease and converted by fungal-specific cytosine deaminase to 5-FU analogs that inhibit thymidylate synthase and RNA synthesis</td>
<td>• GI (frequent) nausea/vomiting/diarrhea&lt;br&gt;• BM toxicity- more common in those with blood disorder&lt;br&gt;• Tetratogenic</td>
</tr>
<tr>
<td><strong>Echinocandins</strong>&lt;br&gt;Caspofungin&lt;br&gt;Micafungin&lt;br&gt;Anidulafungin</td>
<td>Candida&lt;br&gt;• in C. glabrata/C. krusei&lt;br&gt;• Treatment of Invasive Candida&lt;br&gt;• Treatment of Invasive Aspergillus</td>
<td>Acts on fungal cell wall&lt;br&gt;• Inhibits ( {(1-3) \ D \text{ glucan synthase complex} )&lt;br&gt;• Impairs membrane structure&lt;br&gt;• Increases osmotic instability</td>
<td>• Well tolerated&lt;br&gt;• Histamine-like effect with Rapid infusion</td>
</tr>
<tr>
<td><strong>Griseofulvin</strong></td>
<td>Treatment of mycotic infections of Skin, nail and hair due to dermatophytes</td>
<td>Fungistatic&lt;br&gt;• Binds fungal microtubules and inhibits mitotic spindle&lt;br&gt;• Accumulates in newly differentiated Keratin producing cells preventing fungal growth</td>
<td>• Many adverse effects&lt;br&gt;• Headache, lethargy, vertigo, blurred vision&lt;br&gt;• Urticaria, photosensitivility, rash&lt;br&gt;• Hepatotoxicity&lt;br&gt;• Leukopenia, neutropenia, monocytois&lt;br&gt;• Fetal abnormalities</td>
</tr>
<tr>
<td><strong>Terbinafine</strong>&lt;br&gt;Treatment of onychomycosis and superficial skin infections&lt;br&gt;• Candida Albicans&lt;br&gt;• Dermatophytes&lt;br&gt;Treatment of tinea capitis, tinea carpi, tinea cruris &amp; tinea pedis</td>
<td>Inhibits fungal squaletene epoxidase resulting in formation of toxic products and inhibition of ergosterol synthesis</td>
<td>• Well tolerated&lt;br&gt;• Adverse effects rare&lt;br&gt;• Hepatotoxicity&lt;br&gt;• Neutropenia&lt;br&gt;• Stevens Johnson</td>
<td>• Long half life (&gt; 200 hrs)&lt;br&gt;• Not recommended in hepatic/renal insufficiency</td>
</tr>
<tr>
<td><strong>Pharmacology &amp; Therapeutics</strong></td>
<td>Antifungal Drugs</td>
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<tr>
<td><strong>Thursday, December 3rd, 2015</strong></td>
<td>Neil Clipstone, Ph.D</td>
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<table>
<thead>
<tr>
<th><strong>Antifungal Drug</strong></th>
<th><strong>Spectrum of Activity</strong></th>
<th><strong>MOA</strong></th>
<th><strong>CSF Penetration</strong></th>
<th><strong>Renal Dose Adjustment</strong></th>
<th><strong>Drug Interactions</strong></th>
<th><strong>Adverse Effects</strong></th>
<th><strong>Clinical Uses</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketoconazole</strong></td>
<td></td>
<td>Ketoconazole</td>
<td></td>
<td></td>
<td></td>
<td>Minor adverse effects, Alopecia, Headache, GI</td>
<td>Largely replaced by itraconazole, Cheaper 2nd line agent</td>
</tr>
<tr>
<td><strong>Fluconazole</strong></td>
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<td>Fluconazole</td>
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<td><strong>itraconazole</strong></td>
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<td>Itraconazole</td>
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<tr>
<td><strong>Posaconazole</strong></td>
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<td>Posaconazole</td>
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<tr>
<td><strong>Voriconazole</strong></td>
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<td>Voriconazole</td>
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<tr>
<td><strong>Fusidic acid</strong></td>
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<td>Fusidic acid</td>
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**MOA**
- Inhibition of 14α-sterol demethylation involved in the synthesis of ergosterol, an essential component of fungal membranes
- **Spectrum of Activity**
  - Dermatophytes
  - Candida sp
  - Cryptococcus
  - Histoplasma
  - Blastomyces
- **CSF Penetration**
- **Renal Dose Adjustment**
- **Drug Interactions**
- **Adverse Effects**
- **Clinical Uses**
  - Treatment of invasive fungal infections
  - Candida and Aspergillus
  - Treatment of Pseudallescheria boyalii infections
  - Salvage therapy for mucormycosis
  - Treatment of cryptococcal meningitis
  - Treatment of Blastomyces and Histoplasma infections
### Summary of Spectrum of activity of Antifungal agents for Systemic Infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antifungal agent</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>AZOLES</td>
</tr>
<tr>
<td></td>
<td>AmB</td>
</tr>
<tr>
<td>Candida sp</td>
<td>+</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>+</td>
</tr>
<tr>
<td>C. krusei</td>
<td>+</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>-</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>+</td>
</tr>
<tr>
<td>Coccidioides sp</td>
<td>+</td>
</tr>
<tr>
<td>Blastomyces sp</td>
<td>+</td>
</tr>
<tr>
<td>Histoplasma sp</td>
<td>+</td>
</tr>
<tr>
<td>Aspergillus sp</td>
<td>+</td>
</tr>
<tr>
<td>Fusarium sp</td>
<td>+</td>
</tr>
<tr>
<td>Pseudallerischeri boydii/</td>
<td>-</td>
</tr>
<tr>
<td>Scedosporium apiospermum</td>
<td></td>
</tr>
<tr>
<td>Zygomycetes/Mucor</td>
<td>+</td>
</tr>
</tbody>
</table>

### Treatment of Dermatophyte infections and Onchomycosis

**Tinea captis**  
*(ringworm of the scalp)*

|                                | Oral Griseofulvin  |
|                                | (long safety history) |
|                                | Oral Terbinafine |
|                                | Oral fluconazole/Itraconazole |

Note: Topical antifungals are ineffective

**Tinea pedis**  
**Tinea corporis**  
**Tinea cruris**

Topical antifungals  
e.g. AZOLES or Terbinafine

**NOT NYSTATIN**  
*(not active against dermatophytes)*

**Chronic/extensive disease**  
**Immunocompromized patient**

|                                | Oral terbinafine/Itraconazole/fluconazole |

**Onchomycosis**

|                                | Oral terbinafine or Itraconazole |

2nd line: Oral fluconazole or griseofluvin

Note: Topical antifungals are ineffective
<table>
<thead>
<tr>
<th>Fungal Disease</th>
<th>Type</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endemic Mycoses</strong></td>
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<tr>
<td></td>
<td>Mild/moderate</td>
<td>An Azole-e.g. Itraconazole (preferred)</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td></td>
<td></td>
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<tr>
<td>Blastomycosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coccidioidmycosis</td>
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<td></td>
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<tr>
<td></td>
<td>Severe ill/</td>
<td>Amph B (induction)</td>
</tr>
<tr>
<td></td>
<td>disseminated</td>
<td>An Azole (consolidation/maintenance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Note: Fluconazole can be used to treat Coccidioidmycosis and is DOC for Disseminated disease/meningitis</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Candidiasis</strong></td>
<td>Mucocutaneous</td>
<td>Initially a topical Agent: Nystatin or an azole OR oral Fluconazole if topical treatment is unsuccessful</td>
</tr>
<tr>
<td></td>
<td>Oral/vaginal/rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild/moderate</td>
<td>Fluconazole OR another Azole</td>
</tr>
<tr>
<td></td>
<td>Severe disease</td>
<td>Amph B OR an Azole OR an Echinocandin</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
<td>Amp B +/- Flucytosine (induction) Fluconazole (consolidation/maintenance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>NOT AN ECHINOCANDIN- poor CNS penetration</strong></td>
</tr>
<tr>
<td><strong>Cryptococcosis</strong></td>
<td>Pulmonary/skin</td>
<td>Fluconazole OR Amph B</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
<td>Amph B +/- Flucytosine (induction) Fluconazole (consolidation/maintenance)</td>
</tr>
<tr>
<td><strong>Aspergillosis</strong></td>
<td>Pulmonary/skin</td>
<td>Itraconazole</td>
</tr>
<tr>
<td></td>
<td>Invasive</td>
<td>Voriconazole OR Amph B OR Itraconazole - maintenance/Alt. agent Echinocandins/posaconazole- salvage</td>
</tr>
<tr>
<td><strong>Mucormycosis</strong></td>
<td></td>
<td>Amph B OR Posaconazole (salvage)</td>
</tr>
<tr>
<td><strong>Fusariosis</strong></td>
<td></td>
<td>Amph B OR Voriconazole/Posaconazole (salvage)</td>
</tr>
</tbody>
</table>
TB and NTM Therapy

I. Understand the basic principles of TB therapy

II. Know about the key drugs used in the initial and continuation phases of TB therapy

III. Understand the types of TB drug resistance

IV. Understand the concepts behind the main treatment regimens for pansusceptible TB

V. Understand the basic approach to treatment of MDR and XDR TB

VI. Know about the drugs and approaches for treatment of latent TB infection (LTBI)

VII. Know the difference in the general approach to treatment of TB and NTM infections

VIII. Know that different drug regimens are used to treat leprosy, in contrast to TB

Drugs covered re: TB therapy
Isoniazid (isonicotinic acid hydrazide, INH)
Rifampin (rifampicin)
Ethambutol
Pyrazinamide
Streptomycin

Drugs mentioned only to point out differences between TB and NTM therapy
Cefoxitin
Imipenem
Clarithromycin
Azithromycin
Levofloxacin
Moxifloxacin

Drugs mentioned only to point out differences between TB and leprosy therapy
Dapsone (only to note differences from TB therapy)
Clofazamine (only to note differences from TB therapy)
Anti-TB Drugs
Isoniazid, Ethambutol, Rifampin, Pyrazinamide, Streptomycin

I. Principles of TB therapy
   A. Multiple drugs are used (except in latent TB), to which the TB is susceptible
   B. Drugs must be taken consistently to avoid emergence of TB resistance
   C. Duration of therapy must be sufficient for cure – so far, 6 months of therapy is the standard of therapy (highest cure, lowest relapse rates); still seeking a way to shorten therapy to 4 months or less to increase adherence with therapy and cost.

II. INH (Isoniazid, Isonicotinic Acid Hydrazide)
   A. Clinical use – never used as a single drug for active disease (only for latent TB)
      1. First line drug for active pulmonary TB
      2. Used in combination with at least one other active anti-TB drug
      3. The primary drug for treatment for latent TB infection
   B. Mechanism of action
      1. Isoniazid is a “prodrug” (i.e., it must be converted to its active form)
      2. Activated by catalase peroxidase, which is regulated by the TB katG gene
      3. Targets the TB inhA gene product – enoyl-(acyl carrier protein) reductase – and therefore inhibits synthesis of mycolic acid in the TB cell wall
      4. Bactericidal for replicating organisms; bacteriostatic for “resting organisms”
      6. Active against intracellular and extracellular organisms
      7. Active against M. kansasii but not other non-tuberculous mycobacteria (NTM)
   C. Resistance mechanisms
      1. Many mutations in katG gene result in inactivation of catalase-peroxidase
      2. Mutation in regulatory region of inhA gene, which is involved in mycolic acid synthesis (also results in resistance to ethionamide – “cross resistance”)
   D. Pharmacokinetics
      1. Metabolism – INH acetylation in liver by N-acetyltransferase
         a. Non-acetylated INH is excreted in urine
         b. Acetylation rate in humans is genetically controlled:
            ▪ Slow or rapid “acetylators” – determines blood level after dose
            ▪ Slow acetylators - 6 hrs after 4mg/kg dose, INH level > 0.8 µg/ml
            ▪ Rapid acetylators - 6 hrs after 4mg/kg dose, INH level < 0.2 µg/ml
            ▪ Acetylator status - no effect treatment outcome, because all levels are above bacterial inhibitory concentrations for INH-susceptible TB
      2. Distribution - wide including CSF - CSF levels 20% plasma levels but may equal plasma levels with meningeal inflammation
E. Toxicity
1. Hepatotoxicity – 10-20% of patients have elevation of transaminases within the first month of therapy in
   a. Rate of symptomatic hepatitis with INH ~0.6%
   b. Increased incidence with: increasing age, pre-existing liver disease, EtOH consumption, pregnancy (and up to 3 mos. post-partum) and co-Rx with other hepatotoxic drugs.
2. Neurotoxicity
   a. Peripheral neuritis more common in slow acetylators who have higher levels of the unaltered drug
   b. Pyridoxine (vitamin B6) therapy reduces incidence
3. Hypersensitivity reaction, with fever, rash, lupus-like syndrome; positive ANA

F. Drug Interactions
1. Dilantin toxicity
2. INH plus rifampin increases occurrence of hepatitis
3. Decreases itraconazole
4. Decreases levodopa

III. Rifampin (rifampicin) - semisynthetic derivative of a complex macrocyclic antibiotic rifamycin B produced by Streptomyces mediterranei. Rifabutin and rifapentine are in the same class but have different pharmacokinetics

A. Clinical use
1. First line drug for TB – always used in combination with other drugs
2. Gram positive organisms, e.g., Staph aureus, but always used in combination
3. N. meningitides – prophylaxis meningococcal meningitis – single drug therapy

   Note: Cannot be used alone as an antibacterial agent (other than for meningitis prophylaxis) because of rapid development of resistance

B. Mechanisms of action and resistance
1. Inhibits DNA-dependent RNA polymerase encoded by the rpoB gene
2. Bactericidal to all population of organisms
3. rpoB mutations can cause rifampin resistance

C. Pharmacokinetics
1. Metabolized in the liver
2. Distribution – penetrates well into most tissues, CSF levels 0.5 µg/ml with normal meninges and 4-8x increase with inflamed meninges

D. Toxicity
1. Most common - GI upset
2. Hepatotoxicity increased with use of other hepatotoxic drugs, including INH
3. Red discoloration urine, tears, other secretions. Note: permanent discoloration of soft contacts
4. Acute renal failure, interstitial nephritis
5. Influenza syndrome – more common with intermittent dosing
6. Thrombocytopenia
7. Cholestatic jaundice

E. Drug interactions
1. Induces hepatic microsomal enzymes and therefore interacts with 100 drugs
2. For example accelerates the clearance and reduces the effective serum concentrations of: methadone, coumadin, corticosteroids, estrogen, oral hypoglycemic agents, digoxin, anti-arrhythmic drugs, theophylline, anticonvulsants, ketoconazole, cyclosporine, antiretroviral drugs

IV. Ethambutol – only active against mycobacteria

A. Clinical use
1. First line tuberculosis therapy
2. Always used in combination with other anti-TB drugs
3. Used to inhibit the development of resistance to other agents

B. Mechanism of action
1. Inhibits synthesis mycobacterial arabinosyl transferase encoded by embB
2. Effects cell wall synthesis
3. Bacteriostatic

C. Pharmacokinetics
1. Reduce dose in renal failure
2. Distributed throughout the body. Cerebrospinal levels low even in inflamed meninges.

D. Toxicity
1. Ocular - optic neuritis – symptoms: blurred vision, central scotomata, red-green color vision loss, dose-related, < 1% incidence
2. Don’t use in children too young for assessment of visual acuity and color testing
3. Peripheral neuropathy less common – feet, hands

V. Pyrazinamide (PZA)

A. Clinical use
1. First line tuberculosis therapy
2. Always used in combination with other anti-TB drugs
3. Used in the first two months of TB therapy; not of much value thereafter

B. Mechanism of action and resistance
1. PZA is a “prodrug” (i.e., it must be converted to its active form)
2. **Activated by pyrazinamidase**, encoded by the TB *pncA* gene
3. Resistance results from a variety of *pncA* gene mutations
4. Bactericidal

C. Pharmacokinetics
   1. Best avoided in renal failure because metabolic products excreted largely in urine
   2. Distribution good, CSF in tuberculous meningitis

D. Toxicity
   1. Hepatitis, worse in patients with preexisting liver disease
   2. Skin rash and gastrointestinal intolerance
   3. Arthralgia, increased serum uric acid levels, but acute gout is uncommon

VI. **Streptomycin** - first line bactericidal agent for extracellular organisms

A. Clinical use: second line TB drug

B. Mechanism of action and resistance
   1. Inhibits protein synthesis by binding to ribosome
   3. Resistance – mutation of ribosomal binding protein or ribosomal binding site
   4. Isolates resistant to streptomycin are **not** cross resistant to amikacin, kanamycin or capreomycin

C. Pharmacokinetics
   1. Excretion renal – reduce dose in renal failure
   2. Enters CSF only in the presence of meningeal inflammation

D. Toxicity
   1. Ototoxicity – primarily vestibular function, but also hearing loss
   2. Nephrotoxicity
VII. Types of TB drug resistance

A. Primary (acquired) resistance
1. TB is resistant to the drug at the time of infection
2. This results from exposure to and infection by a source case with drug-resistant TB

B. Secondary (evolved) resistance
1. Results from ineffective therapy (poor treatment design or adherence), e.g.:
   a. Single drug TB therapy for active disease with high bacterial numbers
   b. Too few drugs to prevent emergence of resistance
   c. Suboptimal drug dosing
   d. Suboptimal drug absorption – with resultant subtherapeutic drug levels
2. Rationale for treatment with multiple anti-tuberculous drugs:
   a. Cavitary lesions can contain $10^7$–$10^9$ bacteria
   b. There is a spontaneous rate of mutation within any TB bacterial population that results in resistance to different TB drugs, i.e.:
      - Ethambutol $= 1.0 \times 10^{-7}$
      - Streptomycin $= 2.3 \times 10^{-8}$
      - INH $= 2.6 \times 10^{-8}$
      - Rifampin $= 3.3 \times 10^{-9}$
   c. Therefore, for example, with single drug therapy, it is possible to select for drug resistance in a large bacterial population (e.g., in a lung cavity)
   d. The risk of development of resistance to two drugs is the product of the risk of the development of resistance to each drug – e.g., if the risk for INH $= \sim 10^{-8}$ and the risk for Rifampin $= \sim 10^{-9}$, then the risk for both INH and Rifampin, used in combination is $10^{-8} \times 10^{-9} = 10^{-17}$

C. Cross resistance – resistance to drugs of a similar class and/or structure – e.g.:
1. rifampin – rifabutin
2. kanamycin – amikacin
3. INH – ethionamide (a second line TB drug)

D. Multi-drug resistant TB (MDR-TB)
1. Definition = resistance to both INH and rifampin
2. More common in HIV infected patients
3. Associated with nosocomial transmission and a high mortality in HIV infected patients
4. Note: Rifampin resistance eliminates the option of short-course (6 month) TB therapy and therefore requires therapy for at least 18-24 months.

E. Extensively Drug Resistant TB (XDR-TB)
1. Definition = resistance to all of the following
   a. INH and Rifampin
   b. Resistance to a fluoroquinolone antibiotic
   c. Resistance to one of three injectable antibiotics (amikacin, kanamycin, capreomycin)
2. XDR-TB is rare in the US.
3. Requires treatment for at least 18-24 months with multiple second line TB drugs and has a poor treatment outcome

VIII. Treatment Regimens and Outcomes

A. Effective therapy of TB – 95% cure rate; <5% relapse rate
1. 4-drug regimen (so-called RIPE therapy = Rifampin-INH-PZA-Ethambutol)
2. Initial phase Rx: RIPE. Continuation phase Rx: RI (Note: Ethambutol can be dropped in initial phase if TB is susceptible to all 4 drugs.).

Regimen examples from the CDC:
   a. Initial: daily-8 wks (56 dose). Continuation: daily (126 dose) or 2x/wk (36 dose) for 18 wks – Total doses: either 182 or 92
   b. Initial: daily-2 wks (14 dose), then 2x/wk-6 wks (12 dose). Continuation: 2x/wk-8 wks (36 dose) – Total doses: 62
   c. Initial: 3x/wk-8wks (24 dose). Continuation: 3x/wk-18wks (54 dose). Total doses: 78
   2. Note: Intermittent (2-3 times per week) therapy can be used for INH/rifampin phase of therapy – BUT only when administered through directly observed therapy (DOT)
   3. 6-month therapy can used with a high success rate, if:
      a. Adherence to treatment regimen is high
      b. Sputum cultures convert to negative by 2 months of treatment
      c. There is not major cavitary lung disease
      d. Note: if cavitary disease and/or continued sputum culture positive at 2 months, extend duration to 9 month therapy and check adherence to therapy, drug absorption (and possibly serum drug levels), HIV status

B. Treatment of monoresistant TB:
   1. INH monoresistant TB – rifampin, ethambutol, PZA therapy can be used for 6 month therapy, with good outcome
   2. Rifampin monoresistant TB (uncommon; e.g., in AIDS pts) – INH, ethambutol, PZA can be used, but must be extended to 12-18 month therapy.
      Note: Loss of rifampin from the regimen means loss of the option for short-course (6 month) TB therapy.
   3. Ethambutol or streptomycin monoresistant TB (uncommon) – does not reduce the efficacy of therapy or require prolongation of treatment beyond 6 months.
   4. PZA monoresistant TB – (uncommon for TB; most PZA-resistant strains turn out to be M. bovis) – loss of PZA as an effective drug does not reduce treatment efficacy but requires extension of therapy to 9 months.

C. Treatment of MDR and XDR TB:
   1. Drug selection – Use at least two drugs to which the patient’s TB strain is susceptible, as determined by laboratory testing.
   2. Treatment history is critical – Use drugs that have never before been used to treat the patient.
IX. Treatment of Late NTB Infection (LTBI)
   A. INH monotherapy for 9 months is highly effective
      1. Low bacterial burden; therefore, low likelihood of emergence of INH resistance
      2. The problem is sustaining adherence to therapy for such a long duration of
treatment in an asymptomatic patient – adherence can be as low as 20%
completion for a 9 month course of therapy
   B. INH + Rifapentene – 3 month,12-dose, once weekly, DOT regimen
      1. As effective as 9 month therapy with INH
      2. “100%” adherence if treatment is done by directly observed therapy (DOT)
   C. Rifampin – 4 month, daily therapy
      1. As effective as 9 month therapy with INH
      2. Higher drug cost than INH, but increased adherence rate to shorter course of
therapy and arguably overall cost of treatment, if monitoring and other costs are
included.

X. Treatment of non-tuberculous mycobacterial (NTM) infections
   A. Somewhat different treatment from TB – INH and PZA are inactive against many
NTM.
   B. Mycobacterium avium-intracellular (MAI, MAC)
      1. Resistant to INH and PZA
      2. Standard regimen: rifampin, ethambutol + either clarithromycin or azithromycin
      3. Amikacin may be added initially (1-3 months) for cavitary lung disease
      4. Usual duration of therapy: 1 year after sputum culture conversion to negative.
   C. Mycobacterium kansasii
      1. Resistant to PZA
      2. Standard regimen: INH, rifampin, ethambutol
      3. Amikacin may be added initially (1-3 months) for cavitary lung disease
      4. Alternative regimens: rifampin, ethambutol + either (clarithromycin or
azithromycin) or fluoroquinolone (e.g., levofloxacin or moxifloxacin)
      5. Usual duration of therapy: 1 year after sputum culture conversion to negative.
   D. Rapidly growing mycobacteria (e.g., Mycobacterium abscessus)
      1. Resistant to all first-line TB drugs (i.e., RIPE)
      2. Standard regimen:
         a. Initiation phase: 1-3 months of either cefoxitin/amikacin or imipenem/amikacin
         b. Continuation phase: 12-18 months of (clarithromycin or azithromycin) +
fluoroquinolone (e.g., levofloxacin or moxifloxacin)
XI. Treatment of leprosy (*Mycobacterium leprae* infection)

A. Very different treatment from TB treatment

B. “Paucibacillary” leprosy (intermediate, borderline tuberculoid or tuberculoid)
   1. US recommendation: rifampin + dapsone daily for 12 months
   2. WHO recommendations: rifampin + dapsone daily unsupervised + rifampin 1x/mo. supervised

C. “Multibacillary” leprosy (borderline, borderline-lepromatous, lepromatous)
   1. US recommendation: rifampin + dapsone + clofazimine daily for 24 months
   2. WHO recommendation: dapsone + clofazimine (daily, unsupervised) + rifampin + clofazimine (1x/mo., supervised) for 12 months

XII. List of drugs covered in the lecture

**Main drugs covered re: TB therapy**
Isoniazid (Isonicotinic Acid Hydrazide, INH)
Rifampin (rifampicin)
Ethambutol
Pyrazinamide
Streptomycin

**Drugs mentioned only to point out differences between TB and NTM therapy**
Cefoxitin
Imipenem
Clarithromycin
Azithromycin
Levofloxacin
Moxifloxacin

**Drugs mentioned only to point out differences between TB and leprosy therapy**
Dapsone (only to note differences from TB therapy)
Clofazamine (only to note differences from TB therapy)
Key Concepts and Learning Objectives

1. To know the mechanism of action, route of administration, therapeutic use and side effects of the beta2 adrenergic agonists.

2. To know the mechanism of action, route of administration, therapeutic use and side effects of the muscarinic antagonists.

3. To know the mechanism of action, route of administration, therapeutic use and side effects of the glucocorticosteroids.

4. To know the mechanism of action, route of administration, therapeutic use and side effects of the leukotrienes.

5. To understand when to use the different classifications of drugs in the treatment of asthma.

6. To know the pharmacology of the 1st and 2nd generation antihistamines.

7. To identify the first line of treatment in patients with nasal rhinitis due to allergy.
Drugs for the Treatment of Asthma

I. Asthma treatment overview
   A. Affects millions of people worldwide
   B. Caused by narrowing of the airways
   C. Can be treated successfully

II. Controlling Asthma Triggers
   A. Allergens
   B. Respiratory infections
   C. Irritants
   D. Physical activity
   E. Medications
   F. Stress

III. Monitoring Asthma Symptoms
   A. Regular doctor visits
   B. Pulmonary function monitoring
   C. Medication adjustments
   D. Ongoing education

IV. Categories of Asthma Symptoms- Medications used for the treatment of asthma vary according to age, severity of asthma and the level of symptom control Treatment plans must be reviewed and adjusted on a regular basis.
A. Intermittent asthma - Patients who have the following characteristics:

1. Symptoms of asthma that occur two or fewer days per week
2. Asthma that does not interfere with daily activities

3. Awakening at night with symptoms 2 or fewer night per month
4. Oral steroid treatment needed no more than once per year

B. Persistent asthma – Patients with regular symptoms that may limit daily activities

1. Coughing, wheezing, shortness of breath
2. Nighttime symptoms that awaken you from sleep
3. Symptoms that need treatment with a bronchodilator
4. Symptoms that affect your ability to participate in normal activities

V. Pharmacotherapy goals

A. Relief of symptoms
B. Prevention of acute asthmatic attack
C. Improved quality of life

VI. Beta2 Adrenergic Agonists

A. Short acting agents

1. Albuterol (Meta)
2. Terbutaline (Brethaire®)
3. Metaproterenol
4. Bitolterol (Tornalate®)

B. Long acting agents

1. Salmeterol
Pharmacology & Therapeutics

Drugs for the Treatment of Asthma and Allergies

December 9, 2015

D. Moorman, Ph.D.

2. Formoterol

3. Vilanterol

C. Mechanism of action

1. Stimulates adenylyl cyclase

2. Increases cAMP in smooth muscle

3. Increased cAMP results in a powerful bronchodilation

D. Route of administration

1. Metered inhaler

2. Nebulizer

3. Oral

E. Pharmacokinetics – See below

Pharmacokinetics of Bronchodilators

<table>
<thead>
<tr>
<th>Agent</th>
<th>Inhalation Route</th>
<th>Oral Route</th>
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<tbody>
<tr>
<td></td>
<td>Onset of action (mins)</td>
<td>Duration of action (hr)</td>
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<tr>
<td>Metaproterenol</td>
<td>&lt;1</td>
<td>1-3</td>
</tr>
<tr>
<td>Bitolterol</td>
<td>3-4</td>
<td>5-8</td>
</tr>
<tr>
<td>Albuterol</td>
<td>5-15</td>
<td>3-6</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>15-30</td>
<td>3-6</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>10-20</td>
<td>12</td>
</tr>
</tbody>
</table>

F. Side effects

1. Skeletal muscle tremors

2. Tachycardia

3. Anxiety, restlessness and apprehension

G. Other long acting bronchodilators
1. Theophylline-oral and IV
2. Inhibits phosphodiesterase
3. Frequent side effects- Rarely used

VII. Muscarinic Antagonists for asthma
Ipratropium and Tiotropium
A. Slow onset of action
B. Achieve less bronchodilation
C. Competitively blocks muscarinic receptors in the airway and prevents bronchoconstriction
D. Side effects are minimal. If dosed to high can have atropine like effects

VIII. Corticosteroids
A. Route of administration
   1. Inhalation
      a. Beclomethasone (Venceril®)
      b. Flunisolide (Aerobid®)
      c. Triamcinolone (Azmacort®)
   2. Oral Administration
      a. Prednisone (Meticorten®)
   3. IV administration
      a. Methylprednisolone
B. Pharmacokinetics
   1. Onset of action; 3 hours
   2. Duration of action: inhaled 10-12hrs, oral 6-12hrs
3. Effects are not seen rapidly

C. Mechanism of action
   1. Reduction in the synthesis of arachidonic acid by inhibiting phospholipase A2
   2. Thereby inhibiting the synthesis of leukotrienes and prostaglandins

D. Therapeutic use
   1. First line of treatment for prophylactic therapy
   2. A short course of oral corticosteroids combined with an inhaled steroid

E. Side effects
   1. Short term use- increased energy, insomnia, hunger, agitation and mood alterations
   2. Long term use- osteoporosis, cataracts, myopathy, etc.

IX. Combined therapy- contain both bronchodilator and steroid

X. Cromolyn
   A. Alternate to low dose glucocorticoids
   B. Mechanism of action- decrease the release of histamine and leukotrienes
   C. Less effective than steroids
   D. Must be use 3-4 times/day

XI. Leukotriene Antagonists
   A. Montelukast, zafiriukast- antagonists to LTD₄ and LTE₄
   B. Zileuton- inhibitor of 5-lipoxygenase
   C. Mechanism of action
      1. Open narrowed airways
2. Decrease inflammation and mucus production

D. Oral administration

E. Side effects- include mood alterations and rarely depression

XII. Monoclonal antibodies – Omalizumab

A. Monoclonal antibody to IgE

B. Mechanism of action- forms a complex with free IgE which lowers serum levels

C. High cost
Drugs for the Treatment of Allergies

I. Overview

A. The management of allergic rhinitis involves

1. Allergen avoidance

2. Pharmacotherapy

3. Allergen immunotherapy

B. Management of allergic rhinitis is influenced by

1. Frequency and severity of symptoms

2. Age of patient

3. Presence of concurrent conditions

C. Treatment in young children

1. Cromolyn sodium- nasal spray, less effective than glucocorticoid sprays

2. Second generation antihistamines
D. Treatment for older children and Adults- mild symptoms

1. Second generation oral antihistamines
   a. Certirizine
   b. Loratadine
   c. Fexofenadine

2. Antihistamine nasal spray
   a. Azelastine
   b. Olopatadine

3. Glucocorticoid nasal spray
   a. Mometasone
   b. Fluticasone
   c. triamcinolone

4. Cromolyn nasal spray
E. Treatment of moderate to severe symptoms

1. Glucocorticoid nasal sprays

2. A second agent can be added including an antihistamine spray or oral antihistamines

3. Patients with concomitant asthma add montelukast

F. Glucocorticoid nasal sprays

1. First generation agents (10-50% bioavailability)
   
a. Beclomethasone

b. Flunisolide

2. Second generation agents (<2% bioavailability)

   a. Mometasone

   b. Fluticasone

   c. Ciclesonide

3. Mechanism of action-down regulate inflammation by binding to intracellular glucocorticoid receptors

4. Side effects- nose bleeds, irritation of nasal mucosa

5. Drug interaction- Fluticasone and strong inhibitors of CYP3A4 (ritonavir, itraconazole) have been reported
G. Antihistamines – Pharmacology

1. 1\textsuperscript{st} generation antihistamines
   
a. Cause significant sedation
   
b. They are lipophilic and cross the blood brain barrier

2. 2\textsuperscript{nd} generation antihistamines
   
a. Lack central nervous effects
   
b. May cause weight gain

3. Pharmacology of Antihistamines- (see table)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanisms of Action</th>
<th>Therapeutic Use</th>
<th>Route of Administration</th>
<th>Major Side effects</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine (Benedryl\textsuperscript{*})</td>
<td>Blocks histamine H\textsubscript{1} receptors</td>
<td>Allergic rhinitis, Urticaria and adjunctive therapy in anaphylactic reactions</td>
<td>Oral and Intravenous</td>
<td>Marked sedation or agitation due to muscarinic receptor blockade</td>
<td>Histamine H\textsubscript{1} receptor antagonist– 1\textsuperscript{st} generation</td>
</tr>
<tr>
<td>Chlorpheniramine (Chlortrimeton\textsuperscript{*})</td>
<td>Blocks histamine H\textsubscript{1} receptors</td>
<td>Allergic rhinitis, Common ingredient in OTC medications</td>
<td>Oral</td>
<td>Slight sedation or agitation due to muscarinic receptor blockade</td>
<td>Histamine H\textsubscript{1} receptor antagonist– 1st generation</td>
</tr>
<tr>
<td>Fexofenadine (Allegra\textsuperscript{*})</td>
<td>Blocks histamine H\textsubscript{1} receptors</td>
<td>Allergic rhinitis, Idiopathic chronic urticaria</td>
<td>Oral</td>
<td></td>
<td>Histamine H\textsubscript{1} receptor antagonist– 2nd generation</td>
</tr>
<tr>
<td>Loratidine (Claritin\textsuperscript{*})</td>
<td>Blocks histamine H\textsubscript{1} receptors</td>
<td>Allergic rhinitis, allergic reactions to blood, andadjunctive therapy in anaphylactic reactions</td>
<td>Oral</td>
<td>Nausea, fatigue, headache</td>
<td>Histamine H\textsubscript{1} receptor antagonist– 2nd generation</td>
</tr>
</tbody>
</table>
4. Antihistamine nasal sprays
   
a. Rapid onset of action

b. Combination therapy - Glucocorticoid/antihistamine

5. Combination therapy
   
a. Oral antihistamine/decongestant- better symptom relief than antihistamines alone

b. Decongestants have a variety of adverse effects

H. Other Agents

1. Cromolyn- very safe, but its utility is limited by frequent dosing and lower efficacy.

   Used when other agents can’t be tolerated.

2. Montelukast –useful in patients who can’t tolerate nasal sprays and in patients with coexistent allergic rhinitis and asthma or coexistent nasal polyposis.

3. Oral glucocorticoids- short courses can be used when symptoms are preventing the patient form sleeping and work.