
Fungi More or Less Obligately Associated with Humans

- a. a few dermatophytes (the “anthropophilic species”)
- b. *Malassezia furfur*
- c. *Candida albicans*
- d. *Lacazia (Loboa) loboi**⁺
- e. *Pneumocystis jirovecii**⁺

*recently confirmed molecularly to be a fungus

⁺name recently changed from *P. carinii* for human agent

⁺not culturable

Requirements for Designating a Mycosis*

1. presentation of adequate clinical history that suggests fungal infection; usually provided by patient
2. observation of fungus in clinical specimens; serology or molecular detection can substitute today, sometimes even CT or MRI data for initial ID
3. fungus observed is compatible with disease state reported
4. adequate evidence is presented that causative agent is actually a fungus that was properly identified

*1979 - 174 species of fungi met these requirements

Today - many more again (250 - 400??), and increasing by the month.

Reasons for Paucity of Awareness

1. general lack of government reporting requirements*
2. relative difficulty in documenting the existence of fungal disease: for all but relative few, need to culture
3. fungal diseases are generally not communicable⁺
4. exact mycosis or relevance of mycosis is often difficult to establish
5. some organisms only recently defined as fungi

*only 2 are required to be reported to CDC (histoplasmosis & coccidioidomycosis).

⁺exception may be *Pneumocystis jirovecii*

MAIN POINTS OF FIRST LECTURE(S)

1. Mycoses are more or less accidental.
2. Reservoir of infecting units is usually nature (endemic vs epidemic - communicable)
3. More and more species of fungi are being implicated in mycoses.
4. More and more cases of life-threatening mycoses are being diagnosed each year.
5. Mycoses are not all that rare*.
6. Mycoses are probably worthy of more attention and earlier consideration during diagnosis than they often receive

* and it is scientifically dishonest to say they are.

Why Increased Number of Cases?

- a. an increased awareness, and better and more specific mycological training among professionals;
- b. an increase in the number of human hosts that are being compromised or otherwise becoming more susceptible.

Note: Fungi are probably not becoming more virulent. However, some are starting to develop antifungal resistance.

Some Factors Predisposing Humans to Fungal Infections

1. prolonged antibiotic therapy
 2. underlying disease (HIV infection, cancer, diabetes, etc.)
 3. age
 4. surgical procedures
 5. immunosuppressive drugs
 6. radiation therapy
 7. indwelling catheters
 8. obesity
 9. drug addiction
 10. transplants
 11. burns
 12. travel, heatstroke, etc.
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Host Deficiencies in Bone Marrow Transplant Recipients

- Lymphopenia and T and B cell dysfunction for several months
 - Neutropenia for 1 month
 - Breakdown of mucosal barriers
 - Deficient neutrophil chemotaxis and killing of intracellular organisms
 - Dysfunction of pulmonary macrophages
 - Graft-versus-host disease and its therapy perpetuate host deficiencies
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**Two Groups of Pathogenic Fungi
Based on Virulence**

1. **"Primary Pathogens": Fungi that are free-living and commonly pathogenic in normal hosts and severely pathogenic in compromised or otherwise predisposed hosts.**
2. **"Secondary Pathogens": Fungi that are free-living or exo-/endo-symbionts and are generally, but not exclusively, pathogenic only in compromised hosts (so-called secondary or opportunistic pathogens; distinction often blurred).**

What Fungus Must Do to Infect

1. **Gain entry to body interior via**
 - a) **lungs or other orifices**
 - b) **traumatic implantation**
 - c) **invasion of deeper tissue to produce systemic infection**
2. **Multiply or grow in volume in the host to sufficient numbers/extent to yield symptoms**
3. **Resist (or at least not stimulate) host defenses**
4. **Live by utilizing host tissue &/or fluids as a food source**
 - a. **produces tissue damage (necrosis)**
 - b. **produces tissue irritation (rash, inflammation, granuloma formation, etc.)**

Factors that Affect Host-Fungus Interactions

- a) **Those that allow fungus to enter host and cause disease***
- b) **Those of the host that either limit the growth or the survival of the fungus in tissue****

***virulence factors**

****host factors**

Reasons* Why Some Fungi are Pathogenic

1. able to grow at elevated temperatures (35 - 40 or 41 °C; a few at 45 °C or slightly higher)**
2. able to grow under reduced oxidation/reduction potentials
3. able to avoid efficient, innate and cell-mediated immunity systems of humans, or at least not stimulate them***

* primary virulence factors?

** dermatophytes slightly lower (32 - 34 °C)

*** involves secondary virulence factors (area of intense research)

Miscellaneous Virulence Factors*

1. Dimorphism ? Polymorphism? (vegetative)
2. Capsules**
3. Cell walls
 - β-glucans
 - chitin**
 - chitosan
 - melanin**
 - mannoprotein
 - surface hydrophobicity
 - surface antigens
4. Siderophores/Fe³⁺ reductases
5. Unique membranes
6. Secretory enzymes
 - phospholipases**
 - proteases**
- 7.???????

*secondary virulence factors? **well established in mouse models for some fungi

REVIEW

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Early Diagnosis of Invasive Fungal Infections

Benefits

- Early diagnosis permits therapy of maximal effectiveness
- Early intervention with antifungal therapy may help decrease the high mortality rate associated with serious systemic mycoses

Obstacles

- Because of immunosuppression, typical signs and symptoms of infection are frequently absent
- Few clinical features are uniquely specific for systemic fungal infection
- Sputum and blood cultures are frequently negative
- Invasive procedures
 - May be necessary for definitive diagnosis
 - Are often contraindicated in severely immunocompromised patients