

Topic 18: Aspergillosis

Aspergillosis

An opportunistic mycosis that comprises a variety of syndromes involving a form-species of the form-genus *Aspergillus**

Main agents:

1. *Aspergillus fumigatus* (80%)
2. *A. flavus***
3. *A. niger***
4. *A. terreus*** 18-19%
5. *A. ochraceus*
6. *A. nidulans*
7. *A. clavatus*
8. Other species ~ 1-2%

-Cause about 5000+ hospitalizations/yr in US with > 300 deaths/yr;** autopsy data* 1978 - 1982 indicated 0.5% multiorgan cases; 1980 - 1992 14-fold increase; 1993-to-date, some increase in AIDS-related cases***

*large form-genus⁺ with phialidic anamorphs; when teleomorphs/holomorphs known are Plectomycetes, Eurotiales. Incidence of infection 4-→38%; of fungal infection deaths, 85%.

** next most common

*** extremely conservative estimate

⁺some suggest over 600 form-species (probably only about 100 "good" species)

History - very old

- 1815 - possibly first valid description from bird infection (most early descriptions too)
- 1847- 1st human case possibly Sluyter** (or Bennett***, 1842)
- 1850- Fresenius* - coined aspergillosis for infection due to *Aspergillus* in a buzzard (*Aspergillus*, Micheli, 1729, after aspergillum)
- 1856- Virchow - 4 cases → best early descriptions of bronchial & pulmonary forms – isolated *A. fumigatus*

* named many species, including *A. fumigatus*

** named Pityriasis versicolor

*** worked with Berg on thrush in newborns

1897- Renon - occupational hazard association-*

1. pigeon handlers
2. handlers of moldy grain
3. wig cleaners
4. farmers working with moldy hay (Farmers' lung)

*often chronic

1924- Cleland - association with debilitation (opportunistic disease)

1952 until today- Opportunistic forms most important*

1. high % of deaths among leukemia patients/neutropenic
2. significant complications in organ transplant situations (e.g. BM transplants)
3. many outbreaks in hospital environments
4. AIDS

Clinical Syndromes Aspergillosis

Broad Classification

1. Toxicity - due to ingestion of moldy food (e.g. aflatoxicosis) (*Aspergillus* mycotoxicosis)
2. Allergy & sequelae to the presence of conidia or transient hyphal growth in body orifices (e.g. nasal & lung)
3. Colonization without invasion into preformed cavities or debilitated tissue
- 4.* Chronic invasive, inflammatory, granulomatous, necrotizing disease of lungs & other tissue
- 5.* Systemic and fatal dissemination disease

*True pathogenesis (ubiquitous & opportunistic)

	Main Predisposing Factor	
oxidative micro- biocidal killers no, H ₂ O ₂ , O, etc	Neutropenia: normally	PMNs
	←*neutrophils* = 40-60%	<u>white cell count;</u>
	eosinophils = 1 to 3%	<u>leukocytes</u>
	basophils = 0.5 to 1%	
	lymphocytes = 20 to 40% T&B cells	
	monocytes = 4 to 8%	MΦ

Laboratory Identification

Traditionally by morphological characteristics of anamorphs

1. Colony morphology
color (most often because of spore color)
2. Conidiophore & phialide
morphology (uniserate or biserate)
3. Conidium morphology
with *A. fumigatus*
thermotolerance (45°C)
other species 37-40°C

Teleomorphs* (homothallic &/or heterothallic)
cleistothecial structure - pseudoparenchymatous**
Eurotiales
Eurotiaceae

*unknown for four most common pathogens

**vs prosenchymatous of Onygenales

Clinical Categories of "Infectious" Aspergillosis

- | | | |
|----|------------------------------|---|
| | | Asthma |
| | | Allergic Alveolitis |
| | | Allergic broncho-pulmonary |
| A. | Pulmonary | |
| | 1) allergic | |
| | 2) colonizing (Aspergilloma) | usually |
| | 3) invasive* | primary |
| B. | Disseminated* | |
| C. | CNS | usually |
| D. | Cutaneous | secondary |
| E. | Nasal | |
| F. | Iatrogenic | (any adverse** condition due to medical intervention) |
| G. | Otomycosis | |

*1) due to lowered resistance caused by disease or drugs, neutropenic; granulocytopenia; (GCSF therapy)[†]

**2) barrier breaks - e.g., surgery, 3) disruption of normal flora due to antibiotics or steroids, 4) etc.

[lots of cases initiated in operating room setting; started to show up in 1970's (or be documented)]

[†]Granulocyte Colony Stimulating Factor

Pulmonary Forms of Aspergillosis

1. Allergic
 - a. asthma - the least serious & a response to conidia; conidia seldom germinate.
symptoms- cough, wheezing, chills, aches, pains, rare fever; no skin test reaction of arthus type (immediate*); but DTH*** detected by skin test
 - b. allergic alveolitis- usually found in individuals having repeated exposure to large #s of conidia & hyphal fragments (usually occupational: farmer's lung disease)
symptoms- cough, fever, chills
- occur within 6 hrs
- X-ray infiltration common
- Arthus-type skin test***
- Repeated exposures → granulomatous disease
 - c. allergic bronchopulmonary (more serious extension of allergic Alveolitis)
 - 1) bronchoscopy may show fungus patches (rare) in bronchi
 - 2) conidiophores and conidia often observed in lungs
 - 3) sputum has fungus and conidia
 - 4) positive sputum throughout disease course
 - 5) Arthus type skin test**
 - 6) sputum may become bloody
 - 7) often restricted to upper lung lobes
- *IgE-mediated or immunocomplex type
**CMI-mediated or immunocomplex type
***2 - 4 hrs., & mediated by ppt antibodies (see notes p24)
2. Colonizing aspergillosis (aspergilloma)
 - a. development of large fungus balls* throughout lungs or cavities caused by other disease
 - b. symptoms as above - but more severe* can inhibit exhalation/often associated with TB
3. Invasive pulmonary aspergillosis
 - rare form - fungus wide-spread
 - usually opportunistic
 - pneumonia, fever, cough, pain
 - extensive X-ray
 - often in cancer patients with leukemia and lymphomas
 - may be chronic or sometimes fulminate
4. Disseminated
 - symptoms of acutely ill patient
 - lung> brain> kidney >heart>etc.
 - lung origin
 - hyphae in tissue dichotomously branched and nonsporulating
5. CNS mostly from iatrogenic invasion (drug addicts)
 - acute meningitis
 - rapidly fatal disease
6. & 7. Cutaneous & nasal (rare)
8. Iatrogenic - very common & often symptoms as with disseminated
9. Otomycosis = colonization of ear drum external surface (swimmer's ear), bacterial overgrowth common → much discomfort.
 - antibacterial treatment only gets rid of bacteria; fungal origin still there:. Can be treated with topical antifungals.

Aspergillosis - Prognosis & Therapy

Allergic - essentially benign; needs little attention or antiallergy treatments (steroids, desensitivation, Allegra™, etc.)

Colonizing

- colonizing may or may not require intensive antifungal therapy if in otherwise healthy patient
- need to minimize bronchial plugging (aspiration; lavage)
- surgical resectioning

Invasive:

- Amphotericin B; various azoles in use or in trial, itraconazole most promising
- Granulocyte Colony Stimulating Factor (G-CSF) therapy

Serology

CF, CIE, ID*

Factors for Successful Treatment of Aspergillosis*

1. Early recognition of disease
2. Prompt, aggressive therapy with FUNGIZONE^R (amphotericin B/Squibb)**
3. Supportive measures continued until granulocyte recovery

*Burch JA: J Clin Oncol 5 (12): 1985-1993, 1987

**Some patients included in this study also received flucytosine